Ask the Hematologist

COMPENDIUM 2010-2015

This collection contains updated clinical information on malignant and nonmalignant hematology as profiled in The Hematologist.

Editor: Jason Gotlib, MD, MS
Ask the Hematologist Compendium

INTRODUCTION

A core feature of the ASH publication *The Hematologist: ASH News and Reports* is the department known as “Ask the Hematologist” (ATH). The aim of ATH is to provide clinicians with expert opinion about challenging diagnostic and management problems that span the areas of malignant and nonmalignant hematology. In some instances, the question posed in the ATH column is premised on a very specific patient scenario; in others, the question is intended to elicit a broader review of practice-changing diagnostic algorithms or therapeutic advances in hematology. ATH articles commonly touch on disease pathophysiology that helps anchor clinical explanations to the biologic underpinnings of disease. We have found that this translational mix of information has appeal not only to clinicians, but also to physician-scientists and basic researchers.

In this compendium, we have compiled ATH articles spanning the years 2010 to 2015. With the exception of some more recent works, we have asked authors to provide state-of-the-art updates to the content where applicable; to that end, authors either have rewritten their ATH articles or have provided an update/commentary that introduces their original piece. We hope that readers find the ATH compendium to be an easily digestible learning companion that serves as a “portable feast” for the practicing hematologist.

Jason Gotlib, MD, MS
Editor-in-Chief
# Table of Contents

## Malignant Hematology:

- 73-Year-Old Male with Stage 0 Chronic Lymphocytic Leukemia with Skin Involvement and No Evidence of Mantle Cell Lymphoma .................................................. 5
- Approach to Patient with a Bladder Tumor with Severe Hematuria and Hemoglobin Level of Eight with Associated Dyspnea .................................................. 6
- Recommendation of CHOP-Rituximab/More Intensive Regimen Such as Dose-Adjusted EPOCH-Rituximab for Cyclin D1 Expression in DLBCL .................................. 7
- FDA Approval of the JAK Inhibitor Ruxolitinib and the Management of Patients with Myelofibrosis .......................................................... 8
- Evaluation of Young Adult with Bone Marrow Failure .................................................. 10
- Standard of Care for Treating Older Patients with Chronic Lymphocytic Leukemia .................................................. 12
- Optimal, Upfront Management of Mantle Cell Lymphoma .................................................. 14
- Approach to the Diagnosis and Management of Mastocytosis .................................................. 16
- Assessment and Management of Patients with Chemotherapy-Induced Peripheral Neuropathy .................................................. 18
- Approach to the Evaluation of Patients with an IgM Monoclonal Protein .................................................. 20
- Treatment of Elderly Patients with Acute Myeloid Leukemia .................................................. 22
- Treatment of Relapsed/Refractory Hairy Cell Leukemia .................................................. 24
- Diagnosis of Immune Pathophysiology in Patients with Low-Risk Myelodysplastic Syndromes .................................................. 25
- Hematopathologic Overview of Lymphocytosis .................................................. 27

## Nonmalignant Hematology:

- Specific Thrombophilia Work-Up Approach .................................................. 30
- Recommendations for Thrombophilia Testing for Women before Oral Contraceptives are Prescribed .................................................. 31
- Treatment of Pregnant Female with Mesenteric Thrombosis and History of Spontaneous Fetal Losses .................................................. 32
- Factor Replacement for Surgery in 48-Year-Old Male with Factor XI Deficiency .................................................. 33
- Immune Thrombocytopenia with Pulmonary Embolism and Deep-Vein Thrombosis: Recommendations for Bone Marrow Aspirate and Biopsy .................................................. 34
- Heparin-Induced Thrombocytopenia Being Treated with Argatroban with Persistent Thrombocytopenia .................................................. 35
- Approach to the Diagnosis and Management of the Anemia of Chronic Inflammation .................................................. 37
- Approach to the Diagnosis and Management of Transfusion-Related Acute Lung Injury .................................................. 39
- Criteria for Selecting Patients with Sickle Cell Anemia for Allogeneic Hematopoietic Stem Cell Transplantation .................................................. 41
- Diagnosis and Management of Platelet Alloimmunization .................................................. 42
- Recommendation of Light Transmission Aggregometry as Part of the Evaluation of a Patient with a Suspected Bleeding Disorder .................................................. 44
- Anti-Phospholipid Antibodies and Pregnancy .................................................. 46
- Treatment Approaches to Castleman Disease with the Advent of Anti-Interleukin-6 Therapy .................................................. 48
- Treatment with Direct Oral Anticoagulants .................................................. 50
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MALIGNANT HEMATOLOGY

Ask the Hematologist
MALIGNANT HEMATOLOGY

30-Year-Old Male with Stage 0 Chronic Lymphocytic Leukemia with Skin Involvement and No Evidence of Mantle Cell Lymphoma – March/April 2010

The author has indicated that there has been no update regarding the content of this article since the original publication date in 2010.

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(Editor’s Note: The original question was submitted to Dr. O’Brien through ASH’s Consult a Colleague, a service for ASH members that helps facilitate the exchange of information between hematologists and their peers. She expanded her answer for print.)

The Question

I have been following a 73-year-old male with Stage 0 chronic lymphocytic leukemia (CLL) for two years. He has a normal hemoglobin and platelet count with a white blood cell count of around 15,000 and cytogenetics showing 13q deletion and trisomy 12. He recently had two small asymptomatic skin lesions removed from his arm and back. These consisted of a clonal population of B cells that expressed Bcl-2 diffusely and were CD20-positive, but CD5- and CD43-negative. This was similar to his original flow cytometry from peripheral blood. This case was interpreted by a referral lab as B-cell lymphoma. The patient is completely asymptomatic with no evidence of liver or spleen enlargement or adenopathy on CT scans. I’m not sure how to put this all together; is this atypical CLL with skin involvement? There is no evidence of mantle cell lymphoma.

My Response

This case presents two unusual aspects of CLL. The first is that this patient has small skin lesions that appear to be deposits of CLL. The second unusual feature is that this patient’s cells are CD5-negative. Looking at the whole picture, I would agree that this is most likely atypical CLL with skin involvement.

I will discuss the phenotype first. CLL is a B-cell malignancy that also expresses CD5. The other well-known lymphoid malignancy that expresses CD5 in addition to B-cell markers is mantle cell lymphoma, which can present in a leukemic phase. Typically, the morphology of mantle cell is significantly different from CLL, although in less classical cases, there may be some blurring of the morphology. CD23 is a useful marker to differentiate them, as this antigen is present on CLL cells and not present on mantle cells. However, in this case we have a patient who appears to have CLL but is CD5-negative.

Other B-cell lymphoproliferative disorders are usually CD5-negative, and the ones that could potentially overlap with CLL are prolymphocytic leukemia (PLL), marginal-zone lymphoma/leukemia (MZL), and follicular lymphoma in a leukemic phase. Again, morphologies differ between all these diagnoses, but there can be overlap. The most common overlap is between CLL and MZL. That’s because classically the diagnosis of marginal zone is, as the name implies, based on pathologic examination of lymph nodes. Patients presenting with leukemic disease without significant adenopathy render this diagnosis more difficult to ascertain. A group of investigators in France evaluated 165 leukemic patients with B-cell lymphoproliferative disorders selected on the basis of a score of ≤3 in the Royal Marsden Hospital scoring system, which implies atypical cases that don’t fit clearly into one diagnostic entity. Fifty-four cases were CD5-negative.

Morphological and phenotypical examinations were able to reveal the diagnosis in 24 of these, including the most common diagnosis of MZL in 11 cases. Thirty CD5-negative cases still could not be fully characterized after morphological and phenotypical examination. Only five of these patients had superficial lymphadenopathy, and in three cases where lymph node biopsy was done, the diagnosis of MZL was established. All in all, 14 were diagnosed as MZL, which was the most common diagnosis, and eight patients remained “unclassified.” These are likely the patients we would call atypical CLL.

From a practical point of view, the good news is that the approach to MZL is similar to that of CLL — namely watch-and-wait in early-stage asymptomatic patients. One difference, however, is in the approach to treatment. MZL cells have very strong expression of CD20 (as opposed to CLL cells), and these patients have dramatic responses to single-agent rituximab. In patients who need treatment, I generally use 375 mg/m² rituximab weekly for eight weeks and have had patients in complete remission for years after this single agent, whereas the efficacy of single-agent rituximab in CLL is much weaker. The reason I would diagnose CLL in this case is the presence of a 13q deletion and trisomy 12. These are well-known abnormalities seen in CLL, and, in fact, the presence of trisomy 12 is commonly associated with atypical features.

Skin involvement in CLL is quite rare. Probably the largest series to examine this came from a group of pathologists in Austria, who describe cutaneous infiltrates of CLL in 42 patients. The five-year survival of these patients was 67 percent, suggesting that they had a good, if not a more favorable, prognosis compared to those without skin involvement; there was no attempt to match them for comparable prognostic features to patients without skin involvement.

I’ve been following some patients for years with skin involvement. In particular, I’m thinking of one who has small deposits on both earlobes and has very indolent CLL that’s never required treatment. If these lesions are in a problematic area, low-dose radiation might be an option, but generally this is not an indication for systemic therapy, and it can simply be monitored.


Dr. O’Brien receives research support from Genentech.
I would like to re-state the concept that hemorrhage occurs within Virchow’s triad. To manage bleeding, one must identify and rank the pathophysiological factors affecting vascular integrity, blood flow, and hemostasis.

1) The most important cause of painless gross hematuria in anyone, even when it is self-limited, is vascular injury from bladder cancer. In a patient without known transitional cell carcinoma with painless gross hematuria, one must direct all interventions at getting tissue, and this usually begins with cystoscopy. Between 10 and 20 percent of these patients will be diagnosed with bladder cancer.1,2

2) Local hyperfibrinolysis contributes to hematuria in patients with urethral tumors, but systemic hyperfibrinolysis is unlikely in the absence of disseminated cancer. Recent data from liver transplant recipients indicate that thromboelastometry is two to four times more sensitive than thromboelastography (TEG) for identifying a systemic fibrinolytic state. TEG was 99 percent specific but only 23 percent sensitive, so it cannot be used to rule out systemic hyperfibrinolysis.3

3) Intractable hematuria from almost any cause – with or without systemic hyperfibrinolysis – should be treated with systemic antifibrinolytic therapy plus local measures, which could include intravesical instillation with formalin, alum, or prostaglandin PGF2α (best for low flow bleeding); arterial embolization; or hydrostatic pressure or urinary diversion (as a last resort). For patients with bladder cancer, hypofractionated radiotherapy or chemoperfusion with mitoxantrone often controls bleeding.4,5

4) Today, more than five and a half years since this case was first reviewed, there are no new data that recombinant activated factor VII (rFVIIa) should be used for massive hematuria from any condition other than acquired hemophilia or inherited hemophilia with an inhibitor. The therapeutic index of rFVIIa as a nonspecific hemostatic agent is unfavorable.5,6

The Question

A 78-year-old male with a bladder tumor had severe hematuria and a hemoglobin level of 8 g/dl, with associated dyspnea. Urologists were unable to evaluate the tumor secondary to severe bleeding in the bladder. Coagulation testing revealed a normal prothrombin time (PT) of 10 seconds, but his activated partial thromboplastin time (aPTT) was elevated at 108 seconds, lowering to 56 seconds when mixed with normal plasma. Levels of coagulation factors VIII, IX, X, XI, and XII were normal, although the report noted the possibility of an inhibitor. Von Willebrand factor (VWF) studies were normal, as were assays for anticardiolipin antibodies (ACA) and lupus anticoagulant (LA). The patient continues to bleed and his hemoglobin continues to drop. Should any other work-up be done? Given that he had no benefit from fresh frozen plasma infusions, should I give factor VII complex?

My Response

Bleeding is impaired hemostasis and therefore can be evaluated from the same perspective that Virchow organized for thrombosis — as dysfunction within the triad of blood (mainly soluble coagulation factors, thrombinogenic apparatus, or platelets), blood vessel (mainly its structural integrity or permeability), and/or blood flow (mainly the effects of ischemia or hyperperfusion). In most cases of bleeding, a simple, single explanation emerges. But in more complicated cases, like the one in question, I try to identify and rank the hemostatic elements that have broken down.

When I see bleeding from the bladder, I focus first on tumor-associated hemorrhage. This is because one must immediately direct therapy toward the cancer, if the fundamental pathophysiological element is tumor-erosive hemorrhage. But how does one establish the presence of the most common acquired inhibitor encountered in a bleeding patient: an acquired factor VIII inhibitor. It can emerge in patients with solid tumors,7 including bladder cancer.8 It almost always causes clinically significant bleeding that can be controlled with a pharmacological intervention such as rFVIIa.9 And the inhibitor itself (an auto-antibody to factor VIII that causes rapid clearance) is often reduced or eradicated with immunosuppressive therapy.10 To evaluate for this possibility, I suggest repeating the factor VIII assay and measuring the inhibitor titer in Bethesda units, which is the inverse of the dilution of the patient’s plasma that decreases factor VIII activity in control plasma by 50 percent. My speculation is that when this patient’s factor VIII level is repeated, it will be borderline low or low and that he will have an inhibitor level <5 units. If an inhibitor is identified, I would administer rFVIIa, although some would first try human factor VIII in cases of low titer acquired factor VIII inhibitors.4

Should one use rFVIIa under any circumstances? Assuming that the PT and platelet count remain satisfactory, I would first try bladder irrigation. If this or other urological maneuvers don’t work and everyone remains mystified by the pathophysiology, I would begin aminocaproic acid at an infusion rate of 1 g/h. If aminocaproic acid doesn’t work, I would then add rFVIIa, but only at 20 to 30 mcg/kg and beginning at four- or even six-hour intervals.11 This dose is prohemostatic but probably causes fewer thromboses than the conventional dose of 90 mcg/kg every two hours.10

Dr. Kroll is part of Eisai’s Speakers’ Bureau.

Dr. Kroll is part of Eisai’s Speakers’ Bureau.
Recommmended of CHOP-Rituximab/More Intensive Regimen Such as Dose-Adjusted EPOCH-Rituximab for Cyclin D1 Expression in DLBCL – March/April 2011

UPDATE/COMMENTARY

Since this article was originally published in 2011, limited additional data have emerged suggesting that cyclin D1 expression may have prognostic value, as patients with ABC-like GEPs have poorer progression-free survival. This finding is consistent with the recent publication of a large-scale, international, randomized trial comparing rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) to dose-adjusted EPOCH-Rituximab for patients with diffuse large B-cell lymphoma (DLBCL). Despite the early encouraging results cited in the original article, two recent randomized studies have failed to show a benefit of the inclusion of bortezomib in patients with ABC-type diffuse large B-cell lymphoma.1,2 We are still waiting on mature results from a third trial from the United Kingdom, which has now closed.

The Question

A previously healthy 72-year-old male presented with a new diagnosis of stage IV DLBCL with an antecedent involvement and involvement of multiple bony sites. His ECOG performance status was 0 and his International Prognostic Index (IPI) score was 3 based on his age, clinical stage, and involvement of multiple extranodal sites, all of which are adverse factors in the IPI. A biopsy from the maxillary sinus confirmed DLBCL by morphology and was positive for cyclin D1. Since cyclin D1 expression in DLBCL is reported to have a poor prognosis, should this patient be treated with R-CHOP or should he receive a more intensive regimen such as dose-adjusted EPOCH-Rituximab?

My Response

This clinical case raises several important questions regarding the management of advanced DLBCL, partly related to diagnostic criteria and to the optimal treatment regimen, but also regarding the broader issue of whether different immunophenotypic or molecular subtypes of DLBCL should be treated differently.

Cyclin D1 is a nuclear protein with a well-defined role as a regulator of cell cycle progression from G1. Its deregulation is central to the pathogenesis of some B-cell neoplasms, especially mantle cell lymphoma (MCL), where it is overexpressed in about 90 percent of cases, as well as in myeloma and hairy cell leukemia. In the vast majority of MCLs, cyclin D1 overexpression is associated with the t(11;14), whereas this association is much less common in other B-cell neoplasms.1

Reports of the expression of cyclin D1 in DLBCL have been conflicting, partly because different methodologies are used for detection of cyclin D1 and partly because the morphologic distinction between DLBCL and the blastic variant of MCL can be problematic, particularly since other immunophenotypic characteristics of DLBCL and MCL can sometimes overlap. Despite these challenges, there are several case reports and some larger series that describe the presence of cyclin D1 in cases of DLBCL that are negative for CD5 but have other classical markers of DLBCL, such as bcl-6 and MUM-1.2

As indicated by the questioner, there is a suggestion from the limited literature that patients with cyclin D1-positive DLBCL have a worse prognosis. In the largest published series, nine of 10 patients had died from progressive disease after a median of 29 months from diagnosis.3 However, these data are anecdotal, and if this represents a true clinicopathologic entity, there is insufficient data to indicate whether it has a meaningful difference from other prognosis of cases of DLBCL.

In contrast, other immunophenotypic and molecular features of DLBCL have been shown to have predictive and prognostic value. Examples include the adverse prognostic effect of bcl-2 expression and lack of bcl-6 expression, both of which can apparently be overcome by the addition of rituximab to standard chemotherapy regimens such as CHOP. Gene expression profiling studies have identified two major molecular subtypes of DLBCL; one has a gene expression profile (GEP) consistent with GCB (GCB-like), and one has a profile consistent with ABC (ABC-like). Molecular subtyping by GEP has also been shown to have prognostic value, as patients with ABC-like GEPs have poorer progression-free survival and overall survival rates independent of the IPI. This difference in prognosis is seen for patients treated both with CHOP and with CHOP-rituximab.1 The clinical utility of these findings has been limited by the lack of routine availability of these molecular parameters. As a result, several groups have explored the use of immunohistochemical (IHC) and molecular methods to assign GCB and ABC subtype.4 Since the correlation between cell of origin identified by IHC and IHC is high, these analyses are gaining widespread use as a method of risk stratification in clinical trials.

Although the prognostic significance of cell of origin (GCB versus ABC) in DLBCL is well established, the question of whether this or any other biologic predictor of outcome should be used to direct therapy for DLBCL is unknown. The dose-adjusted EPOCH-R regimen mentioned by the questioner uses infusional drug scheduling and pharmacodynamic dosing based on hematologic toxicity to exploit tumor proliferation as a target mechanism. Phase II studies of this regimen have shown impressive results and, interestingly, no difference in progression-free or overall survival according to GCB or non-GCB cell of origin. As a result, this regimen is now being compared directly to CHOP-rituximab in a randomized, prospective intergroup study led by the CALGB, which includes an analysis of cell of origin by GEP. The results of this study will not be available for several years, so for now, CHOP-rituximab remains the standard regimen for first line therapy of DLBCL, irrespective of cell of origin or expression of other biomarkers.

Early results from some recent studies suggest that this is likely to change. Two recent studies have suggested that the addition of bortezomib to standard chemotherapy-rituximab combinations for DLBCL produces improvements in response rates and progression-free survival rates, which may be restricted to patients with the ABC subtype.5,6 Additionally, data are emerging to suggest that some recently identified therapeutic targets such as Bruton’s tyrosine kinase (Btk) are differentially expressed in ABC versus GCB-like DLBCL, providing a rationale for limiting trials of these agents to those patients with specific molecular subtypes.

Future progress in the treatment of DLBCL is likely to emerge from further characterization of specific molecular targets. In the meantime, CHOP-rituximab should be regarded as standard, first-line therapy for all patients with DLBCL outside clinical trials. For further information, see the article by Stiller et al.1


Dr. Sweetenham indicated no relevant conflicts of interest.

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References


The Hematologist Compendium 2010-2015
**UPDATE/COMMENTARY**

Five-year follow-up data are now available for the COMFORT-I and II trials of ruxolitinib. In COMFORT-II, 53 percent of patients treated with ruxolitinib achieved a ≥35 percent reduction in spleen volume from baseline at any time during treatment. **1** Improvement in spleen size was maintained with long-term therapy, with the median duration of maintenance of spleen volume reduction being ≥3.2 years. The Kaplan-Meier probability of maintaining this reduction was 51 percent at three years and 48 percent at five years. Median OS was not reached in the ruxolitinib arm and was 4.1 years in the best available therapy (BAT) arm. There was a 31 percent reduction in risk of death with ruxolitinib compared with BAT (HR, 0.67; 95% CI, 0.44-1.02; p = 0.06). The probability of survival at five years was 56 percent with ruxolitinib and 44 percent with BAT. There were no new or unexpected adverse effects (AEs) with long-term ruxolitinib exposure. The most commonly reported AEs in patients who received ruxolitinib any time were thrombocytopenia (52%), anemia (49%), diarrhea (36%), and peripheral edema (33%); grade 3/4 AEs included anemia (23%), thrombocytopenia (15%), and pneumonia (6%). There were similar rates of evolution to leukemia between the ruxolitinib (5.5%) and BAT (6.8%) arms. The long-term efficacy and safety results of COMFORT-I and II are very similar to COMFORT-II, and were presented at the ASCO annual meeting in June 2016 at the time of this writing.**2**

Ruxolitinib has immunosuppressive properties that are in part related to impairment of dendritic cell, NK-cell, and T-cell function.**3,4** Alkytal and/or opportunistic infections have been observed in MF patients treated with ruxolitinib, including reactivation of tuberculosis,**5** viral hepatit**5s**s,**6** and herpes zoster. Additionally, there have been case reports of toxoplasmosis and cytomegalovirus retinitis,**7** as well as pneumocystis and fungal pneumonias. Although there are no consensus guidelines regarding use of anti-infective prophylaxis (nor is the live vaccine vaccine recommended), treating physicians should perform risk assessments for these infections in patients before commencing ruxolitinib, with tailored laboratory screening where appropriate.

Phase III clinical development of another JAK inhibitor, fedratinib, was discontinued because of the development of several cases of Wernicke’s encephalopathy.**8** In vitro studies indicate that oral absorption of dietary thiamine update is inhibited by fedratinib, which blocks the human thiamine transporter.**9** Inhibition of the thiamine transporter does not appear to be an issue with the other JAK inhibitors currently being tested. Among JAK inhibitor, pacritinib, has been evaluated in two phase III clinical trials vs. BAT: PERSIST-1 (JAK inhibitor-naïve MF patients) and PERSIST-2 (prior JAK2 inhibitors treatment allowed and platelet count < 100 × 10⁹/L) required. In the PERSIST-1 trial, pacritinib produced reductions of spleen volume and symptoms and a 26 percent rate of red blood cell transfusion-independence with otherwise minimal myelosuppression.**1** However, in February 2016, the FDA placed a clinical hold on pacritinib due to an interim analysis of the PERSIST-2 trial which demonstrated a detrimental effect on survival in the ruxolitinib compared to BAT arm. Specifically, a relatively higher rate of intracranial hemorrhage, cardiac failure, and cardiac arrest was observed with ruxolitinib therapy.**1**

Molimotibim remains the only other JAK inhibitor currently in phase III clinical trial testing, with results expected soon from the SIMPLIFY-1 trial (molimotibim vs. ruxolitinib; 1:1 randomization; no prior JAK inhibitor therapy) and SIMPLIFY-2 trial (molimotibim vs. BAT; 2:1 randomization; a key inclusion criterion is anemia and/or thrombocytopenia with prior ruxolitinib treatment). Although a limited proportion of patients treated with ruxolitinib or the other JAK inhibitors may demonstrate a reduction in bone marrow fibrosis and/or JAK2 V617F allele burden over time,**1** disappearance of fibrosis or complete molecular remissions is exceedingly rare. More rigorous data need to be established on the long-term effects of JAK inhibitors on marrow fibrosis improvement or stabilization compared to conventional therapies. Meanwhile, phase II/III trials of ruxolitinib in combination with other therapies with different mechanisms of action are being undertaken to assess whether response rates and/or drug-related anemia can be improved. Such medications include immunomodulatory agents (e.g., lenalidomide; pomalidomide); hypomethylating agents (e.g., azacitidine; decitabine); phosphoinositol-3-kinase inhibitors (e.g., idelalisib; idelalisib); bortezomib (e.g., bortezomib; bortezomib); hedgehog pathway inhibitors (e.g., sonidegib); and agents to stimulate erythropoiesis (erythropoetin; danazol).**12** Phase II monotherapy trials of antifibrotics (e.g., PRM-151) and the telomerase inhibition (imetelstat) in patients with myelofibrosis (imetelstat) are in progress in intermediate or high risk MF patients who did not respond to, or did not tolerate ruxolitinib. Type II JAK inhibitors, which only inhibit mutant JAK2 (e.g., CHZ868), are in pre-clinical development and may offer the hope of more in-depth responses since currently available JAK inhibitors inhibit both wild-type and mutant JAK2.**1** Lastly, the role of ruxolitinib in the pre-and post-transplant setting is the subject of several ongoing clinical trials.

**ACKNOWLEDGMENTS**

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**The Question**

How does the recent FDA approval of the JAK inhibitor ruxolitinib influence your management of patients with myelofibrosis?

**My Response**

Myelofibrosis (primary and post-PV/ET MF) is a Philadelphia chromosome-negative myeloproliferative neoplasm that has a natural history characterized by thrombocytosis, spleen enlargement due to extramedullary hematopoiesis, and potential for evolution to acute myeloid leukemia (AML). Impairment of quality of life is due to both massive splenomegaly (e.g., early satiety and abdominal discomfort) and inflammatory cytokines, which mediate debilitating symptoms such as night sweats, fevers, muscle/bone pain, and cachexia. The activating JAK2 V617F mutation is present in 50 to 60 percent of patients, and the MPL mutation (W515L/K), resulting in ligand-independent activation of the thrombopoetin receptor, is identified in an additional 5 to 10 percent of individuals. It has become abundantly clear, however, that MPNs such as MF are more genetically complex. Molecular alterations in additional genes and dysregulation of the epigenetic machinery also contribute to disease pathogenesis.

Prognostic scoring systems based on clinical and laboratory factors obtained either at the time of diagnosis (IPSS) or during the disease course (dynamic IPSS, or DIPSS)**2** have been developed in order to estimate both overall survival and risk of progression to AML. The IPSS uses five adverse prognostic factors: age ≥65, hemoglobin ≤10 g/dL, white blood cell count >25,000/μL, constitutional symptoms, and peripheral blood blasts ≥1 percent. The DIPSS Plus refines prognostic assessment by incorporating three additional adverse risk factors: platelet count <100,000/μL, the need for red blood cell transfusions, and poor-risk cytogenetics. Using the IPSS as an example, patients can be stratified into one of four risk groups: low (score 0), intermediate-1 (score 1), intermediate-2 (score 2), or high (score ≥3), with a median overall survival among the groups ranging from approximately 11 years to just over two years.**3**

Age, performance status, and prognostic risk group drive decision making about treatment options. The Table illustrates this point using three patients. Patient 1 is a low-risk patient with excellent performance status, minimally abnormal blood counts and splenomegaly.
MALIGNANT HEMATOLOGY

The Hematologist 2010-2015

and no constitutional symptoms. Such patients do not warrant immediate treatment and a watch-and-wait approach may be undertaken. At the other end of the spectrum, Patient 3 is a younger, high-risk patient characterized by abnormal blood counts, marked splenomegaly, and poor-risk cytogenetics. The IPSS-Plus estimate of overall survival is 16 months, and the five- and 10-year leukemia rates are 18 and 31 percent, respectively.1 Given this patient’s younger age and relatively poor prognosis, evaluation for a potentially curative myeloablative hematopoietic stem cell transplant would be encouraged.

For patients who require treatment and are not candidates for transplantation, available therapies for MF-related cytopenias, splenomegaly, and symptoms are considered palliative. These options have included chemotherapy such as hydroxyurea; erythropoiesis-stimulating agents; immunomodulatory drugs such as thalidomide or lenalidomide, with or without corticosteroids; splenectomy; splenic irradiation; and clinical trials. In November 2011, only four years after commencing clinical trial evaluation, ruxolitinib became the first JAK inhibitor approved by the FDA for MF patients (intermediate- and high-risk).

The registration trials for ruxolitinib consisted of two large phase III trials: COMFORT-I was a randomized (1:1), double-blind, multicenter study comparing ruxolitinib 15 or 20 mg twice daily (dose stratified according to baseline platelet count) versus placebo,1 and COMFORT-II was a randomized (2:1), open-label, multicenter trial comparing ruxolitinib 15 or 20 mg bid versus BAT, investigator-selected including no treatment.1 Both trials met the primary endpoint of the percentage of ruxolitinib versus control patients achieving ≥35 percent reduction in spleen volume at week 24 (COMFORT-I: 41.9% vs. 0.7%) and week 48 (COMFORT-II: 28.5% vs. 0%). After 24 weeks in the COMFORT-I trial, the proportion of patients with ≥50 percent improvement in total symptom score (using the myelofibrosis symptom assessment form) was 45.9 percent versus 5.3 percent (ruxolitinib vs. placebo, p<0.0001). Anemia and thrombocytopenia were common ruxolitinib-related adverse events but rarely led to drug discontinuation, and the drug was otherwise well tolerated. In an updated analysis of COMFORT-I, there was a significant overall survival benefit with ruxolitinib; at a median follow-up of 51 weeks, there were 13 (8.4%) deaths in the ruxolitinib group and 24 (15.7%) deaths in the placebo arm.1 The implications of these short-term data are unclear since JAK inhibitors exert modest or no impact on fundamental disease-related features such as JAK2 mutant allele burden or marrow fibrosis.

Ruxolitinib’s potency as a “spleen shrinker” and “symptom mitigator” is shared by other JAK inhibitors currently in clinical trials (e.g., fedratinib [formerly SAR302503 and TG101308], momelotinib [formerly CYT387], pacritinib [formerly SB1518], etc.). Patients with or without the JAK2 V617F mutation respond similarly. Therefore, first-line treatment with a JAK inhibitor would be an ideal choice for Patient 2 described in the table and could be considered a bridging option for Patient 3 until a transplant is performed.

In an ad hoc analysis of the COMFORT-I and COMFORT-II trials, worsening of spleen size (≥below left costal margin by palpation) was considered a bridging option for Patient 3 until a transplant is performed. In an ad hoc analysis of the COMFORT-I and COMFORT-II trials, worsening of spleen size (≥below left costal margin by palpation) was considered a bridging option for Patient 3 until a transplant is performed. Given the rapid “on/off” action of JAK inhibitors, caution must be undertaken when stopping these agents because of the potential for return of symptoms in a short period of stopping. During therapy, disease “persistence” (incomplete regression or return of splenomegaly and symptoms) can occur and may be partly explained biologically by reactivation (phosphorylation) of JAK2 through heterodimerization with JAK family members JAK1 and TYK2. Future directions will therefore be focused on combination trials of JAK inhibitors with other targeted targets (e.g., histone deacetylase inhibitors, anti-fibrotics, PI3 kinase/AKT inhibitors) to improve the quality and duration of responses.

New Open-Access Peer-Review Journal, Blood Advances

The new bi-weekly journal from ASH, Blood Advances, will make its debut at the 58th ASH Annual Meeting in San Diego in December. Founding editor, Dr. Robert Negrin, describes the journal as “novel approaches for presentation of original content, including approaches that can only be performed using electronic format, including enhanced graphics, video, and discussion.” This journal will complement ASH’s flagship journal by publishing all new content not covered by Blood. For more information, visit www.bloodadvances.org.

Table. MF Patient Profiles

<table>
<thead>
<tr>
<th>IPSS Score/Risk Group</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
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<tr>
<td>0/Low</td>
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</tr>
<tr>
<td>4/High</td>
<td>0/2</td>
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Dr. Gotlib receives research funding from Incyte (manufacturer of ruxolitinib), Sanofi-Aventis (manufacturer of SAR302503), YM Biosciences (manufacturer of CYT387), and Celgene (manufacturer of lenalidomide).
Evaluation of Young Adult with Bone Marrow Failure

**UPDATE/COMMENTARY**

UPDATE BY DARIA V. BABUSHOK, MD, PhD AND TIMOTHY S. OLSON, MD, PhD

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**The Case**

The patient is a 29-year-old male who presented with a two-year history of progressive pancytopenia (WBC 2.2 x 10^9/L, ANC 0.83 x 10^9/L, Hb 9.9 g/dL; 2.9% reticulocytes; platelet count 25 x 10^9/L). He was of short stature with discrete facial dysmorphisms and mildly impaired cognitively. The family history was negative for BMF, but there was an extensive history of early cancer on the maternal side. Bone marrow examination revealed marked hypocellularity without dysplasia or excess blasts. The patient became transfusion-dependent, so an unrelated bone marrow transplant (BMT) had been recommended as definitive treatment, so an unrelated bone marrow transplant (BMT) had been recommended as definitive treatment.

**The Question**

How do you evaluate a young adult with BMF? What features suggest an underlying IBMFS as the etiology? How do you evaluate for these disorders, and why is it important?

**Our Response**

IBMFS is a collection of genetic disorders including FA, DC, DBA, Shwachman-Diamond syndrome (SDS), severe congenital neutropenia, and congenital megakaryocytic thrombocytopenia that are associated with insufficient blood cell production, congenital anomalies, and, in some cases, an increased risk of malignancies including MDS, leukemia, and certain solid tumors. IBMFS is not always inherited. Disease may also occur sporadically due to a de novo mutation, which may account for more than 50 percent of all cases for some of the IBMFS (e.g., certain genetic forms of DBA or DC). Sporadic appearance of disease may also be due to low penetrance of the causative mutation or genetic anticipation in which clinical phenotype becomes more severe in successive generations as observed in autosomal dominant DC. In this case, family members may carry the mutation but not have clinical symptoms (silent mutation carriers). IBMFS can affect one, two, or all blood cell lineages. Abnormal blood cell counts are frequently present at birth but develop during childhood, adolescence, or later in life. In some cases, BMF never becomes clinically manifest, and the affected individual may seek medical attention because of an unusually early onset of MDS, leukemia, cancer, or other non-hematologic manifestations associated with the condition, such as pulmonary fibrosis in individuals with DC. While once thought to be strictly the domain of pediatric hematologists, with improved insights into the spectrum of disease expression and genetic testing, IBMFS is increasingly being diagnosed and cared for in “adult” hematology clinics.

**When?**

For all patients presenting with BMF, the possibility of an underlying IBMFS should be considered. Such consideration is particularly relevant for patients in whom BMT is being considered as treatment. IBMFS should also be considered in children and young adults presenting with MDS or MDS/leukemia, as these clonal disorders are late complications of IBMFS and may be the first symptom of disease in about 20 percent of cases, typically in the young adult population. IBMFS, with disease onset in adults, often lack the classic physical stigmata, such as abnormal thumbs (FA) or dystrophic fingernails (DC), and other non-hematologic manifestations associated with the condition, such as pulmonary fibrosis in individuals with DC. Therefore, it is difficult to propose an age limit for the exclusion of an IBMFS, as these disorders may be diagnosed in old age. However, the therapeutic consequences are probably most significant when diagnosed in pediatric and young adult patients. The diagram above suggests the diagnostic genetic workup for a young adult with a suspected IBMFS or familial MDS/leukemia syndrome.
What?

Currently, there are more than 80 different genes that may cause BMFS. With the technology of whole-exome and whole-genome sequencing, the number of genetic abnormalities associated with BMFS is expected to increase dramatically, making it impractical to perform testing for every gene in every affected individual. Many of the mutated gene products fall into distinct biologic pathways (e.g., the FA DNA repair pathway, the maintenance of telomeres in DC, or ribosiose biogenesis in DBA). Some clinically available screening tests investigate the integrity of the affected pathway and, if abnormal, direct a focused and more economical approach to genetic testing. Given the important therapeutic implications associated with diagnosis and the availability of sensitive diagnostic tests, screening for FA and DC is recommended in every patient presenting with BMF or early MDS/leukemia. Due to abnormal DNA repair, chromosomes of dividing cells of patients with FA are hypersensitive to breakage induced by cross-linking agents such as deoxyphostibut (DEB) or mitomycin C (MMC), and this characteristic is the basis of the diagnostic test for the disease. The DEB/MMC sensitivity test uses patient lymphocytes in the analysis and is available in several major medical centers with a specific interest in FA. Telomeres of nucleated peripheral blood cells are excessively short in DC.

Clinical telomere length measurements by PCR, flow cytometry, or Southern blotting are available through several commercial laboratories. Results are usually provided as “percentile” in comparison to normal controls. The interpretation of the clinical significance of the measured telomere lengths can be difficult and often needs to be done in the context of disease manifestations. In general, telomere lengths within the normal distribution exclude DC to be the cause of BMF. In children and young adults with BMF caused by DC, the telomere lengths of total peripheral blood lymphocytes are usually 2 to 3 standard deviations below the telomere lengths distribution of age-matched healthy controls. Short telomere lengths in granulocytes are less specific for DC and can be short in a number of other BMFS. As telomeres get shorter with age, telomere length becomes less diagnostic for DC in older individuals. If one of these screening tests is abnormal, subsequent genetic testing should be pursued, as only the identification of a disease-causing mutation can confirm the diagnosis of an BMFS. More specific tests for other BMFS have to be chosen on an individual basis depending on clinical presentation, family history, and laboratory findings. For example, DBA may be considered in patients who present with macrocytic anemia, low reticulocyte count, and a bone marrow characterized by an isolated erythroid hypoplasia. An elevated erythrocyte adenosine deaminase activity may further support a diagnosis of DBA. A history of symptoms of pancreatic insufficiency in a patient with early-onset MDS may be suggestive for SDS. Genetic testing for mutations in the ribosomal proteins most frequently associated with DEA and for mutations in SBSD (the gene that is mutated in SDS) are available commercially. With wider applicability of novel sequencing technologies, genetic testing for all major BMFS genes using a single multiplex platform is likely to become available in the not-too-distant future. However, with the increased availability of genetic testing, the interpretation of results and consideration of their clinical significance will become more complicated, requiring management by an experienced team of physicians that includes geneticists, hematopathologists, and hematologists.

Why?

The natural history, response to treatment, and surveillance requirements differ significantly between patients with acquired BMF and BMFS. Patients with BMFS are typically not responsive to immunosuppressive therapies that may be used for acquired aplastic anemia. Furthermore, the presence of BMFS requires special considerations for BMF, both in terms of family member donor selection and choice of transplant conditioning regimen, as conventional conditioning regimens can be excessively toxic or fatal for some of the BMFS. The BMFS may require surveillance for long-term complications that may be accelerated by the choice of treatment (pulmonary fibrosis, osteopenia, MDS/leukemia, and other non-hematologic malignancies). Finally, the diagnosis of BMFS requires informed genetic counseling for both the affected individual and the family.

In the patient presented above, testing of peripheral blood lymphocytes revealed telomere lengths within the normal distribution, excluding DC as the cause of his progressive BMF. No increased chromosomal sensitivity to DEB was observed in his peripheral blood lymphocytes and only a mildly increased chromosomal fragility with the formation of few radials using MMC was observed. These findings were not sufficient for a firm diagnosis but raised our suspicion of FA and led to further testing of skin fibroblasts that demonstrated significant chromosomal breakage and numerous radial formations with both DEB and MMC. Together, these results suggested FA as the cause of the patient’s progressive BMF. Genetic reversion (the process by which a lymphohematopoietic cell undergoes spontaneous correction of an FA-causing gene mutation) and blood mosaicism are known to occur in about 15 percent of patients. This process is the likely cause of the ambiguous FA screening results from the peripheral blood lymphocytes in this patient.

...
The Question

Is there a standard of care for treating older patients with CLL?

Our Response

Despite recent progress in the understanding and management of CLL, the disease remains essentially incurable. Incidence of CLL is significantly higher in the elderly (those > 65 years old), as the median age at diagnosis is 72 and an estimated 70 percent of newly diagnosed patients are over 65. Despite the predominance of elderly CLL patients, this group has been under-represented in clinical trials because many have major co-morbidities or are perceived likely to tolerate therapy poorly. This omission leaves clinicians who treat CLL with definitive data on which therapy to choose for the large population of older adults.

At initial presentation, the clinical spectrum of CLL ranges from an asymptomatic patient, identified by routine blood work, to a symptomatic patient who experiences rapid progression to death from complications of CLL. Therefore, the first decision to make is whether or not treatment is required. Indications for consideration of treatment include: clinical symptoms (fevers, night sweats, weight loss, or painful lymphadenopathy or splenomegaly), non-immune-mediated cytopenias (hemoglobin < 11g/dL or platelets < 100 × 10^9/L), autoimmune hemolytic anemia, or thrombocytopenia (ITP) that is poorly responsive to standard therapies (hemoglobin < 10g/dL or rapidly enlarging lymph nodes, spleen, or liver). Isolated mild thrombocytopenia (platelets 70-100 × 10^9/L) often represents chronic ITP and is not a reason for treatment.

Treatment decisions can be informed by identifying factors that influence response rates, duration of response, and prognosis, including specific interphase cytogenetic abnormalities such as del(17p13.1) and del(11q22.3), complex cytogenetics (> 3 abnormalities) determined by stimulated metaphase karyotype, unmutated immunoglobulin heavy chain gene status, Rai stage III/IV, ZAP-70 expression in 20 percent or more of peripheral blood lymphocytes, and elevated serum β2-microglobulin concentration. Trials by the German CLL Study Group have factored in co-morbid features assessed by the Charlson-Deyo comorbidity index. Inclusion of co-morbidity indices into the risk strata of the Rai and Binet staging systems can improve prediction of outcomes in elderly patients with CLL.

Standard frontline therapy for younger patients with cytogenetic abnormalities other than del(17p13.1) or del(11q22.3) is the combination of fludarabine, cyclophosphamide, and rituximab (FCR) or fludarabine and rituximab. However, a subset of CLL patients age 60 or older in a large study of frontline therapy with FCR were more likely to require early treatment discontinuation due to myelosuppression and other non-hematologic toxicities, which likely limits the clinical benefit of the regimen in this population. In addition, Eichhorst et al. compared frontline CLL therapy consisting of either fludarabine or chlorambucil in a group of 153 patients 65 years. Although fludarabine improved the overall response rate (ORR), it improved the percentage of complete remissions (CR) and increased the time to treatment failure; there was no difference in PFS or overall survival (OS) between the two groups. Notably, the fludarabine group demonstrated a shorter median survival time and higher rate of toxicity, indicating that there is no major clinical benefit of using fludarabine over chlorambucil in the older population. These findings were confirmed by Woyach et al.
and colleagues \(^1\) who reviewed the experience of elderly CLL patients across all completed Cancer and Leukemia Group B trials and demonstrated no benefit for fludarabine treatment in patients \(\geq 70\) years. In contrast, patients of all age groups appeared to benefit from the addition of rituximab. Recently, Hillmen and colleagues published a phase II trial in which rituximab was combined with chlorambucil in 50 patients (median age \(\geq 70.5\) years). ORR was 84 percent, with infection and neutropenia being the most common adverse effects.\(^2\)

Therefore, for an elderly CLL patient without either del(17p13.1) or del(1q22.3), we recommend therapy with chlorambucil (10 mg/m\(^2\) orally days 1-7 of a 28-day cycle) +/- rituximab (375 mg/m\(^2\) day 1, cycle 1 and 500 mg/m\(^2\) day 1, cycles 2-6).

Patients with del(1q22.3) do not have favorable outcomes in the absence of fractionated alkylator-based therapy. For older CLL patients with del(11q22.3), we recommend therapy with FCR (pentostatin, cyclophosphamide, and rituximab) or bendamustine (70 mg/m\(^2\) days 1 and 2 of 28-day cycle) and rituximab (375 mg/m\(^2\) first cycle, 500 mg/m\(^2\) subsequent 5 cycles). Using the latter regimen, Fischer et al. reported an ORR of 90.9 percent in 117 patients (median age \(\leq 64\) years) with minimal major toxicities. A subgroup analysis of patients with del(1q22.3) showed a 90.5 percent ORR.\(^7\)

Treatment options are limited for older patients with del(17p13.1). Many propose the use of alemtuzumab, but we don’t recommend this therapy due to significant risk of infectious complications and limited response duration. Instead, we recommend rituximab (375 mg/m\(^2\) weekly for 12 weeks) in combination with high-dose methylprednisolone (1 g/m\(^2\) days 1-3 of each 4-week cycle). Using this regimen, James and colleagues reported that in a relatively small study of 28 patients (29% \(\leq 70\) the ORR was 96 percent (100% in the > 70-year-old subset) with CR observed in 32 percent (38% in \(\leq 70\) years). Adverse effects were found to be minimal.\(^8\) In general, for patients being treated with this regimen, we recommend hospitalization up to the first three days of cycle 1 as tumor lysis syndrome, metabolic aberrations, and fluid retention can occur.

For elderly, unfit patients without del(17p13.1), for whom we have concerns that therapy will be poorly tolerated, we typically recommend chlorambucil or rituximab alone or palliative supportive care. Elderly, unfit patients with del(17p13.1) are unlikely to respond to either of these therapies and should be directed to supportive care.

In summary, due to paucity of definitive data on management of the elderly CLL population, we encourage enrollment of these patients in clinical trials. However, when enrollment in a clinical study is not feasible, we use a treatment approach based on FISH/cytogenetic analysis together with our assessment of the individual patient’s capacity to tolerate therapy (Figure). The CLL treatment landscape is evolving rapidly. Promising new therapies that are currently undergoing clinical trials include lenalidomide, ibrutinib, and other studies, a carefully considered approach to the management of elderly patients is essential.

**References**


**Drs. Stephens and Byrd indicated no relevant conflicts of interest.**

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**Jennifer Woyach, MD**

Dr. Jennifer Woyach discusses the latest drug treatments for CLL patients in this video from the ASH Impact Series available on ASH On Demand. To watch this video and more, visit [www.ashondemand.org/FreeContent/Videos](http://www.ashondemand.org/FreeContent/Videos).
MALIGNANT HEMATOLOGY

Preliminary results of a randomized phase III trial comparing dose cytarabine, and cisplatin) followed by HDT and ASCR. The four- and 10-year PFS rates are highly encouraging at 73 percent and 55 percent, respectively.

Given the small number of randomized clinical trials in previously untreated patients with MCL, none of which have demonstrated an improvement in OS, the optimal initial approach to MCL has not been clearly established. Subsequently, patient participation in well-designed clinical trials is highly recommended. This article will focus on treatment strategies that have been shown to offer the best chance of prolonged remission.

A Watch-and-Wait Strategy Is Appropriate for a Subset of Patients

Young and Fit Adults with MCL

Although the addition of rituximab to conventional chemotherapy regimens has significantly improved prognosis in nearly all subtypes of B-cell non-Hodgkin lymphoma, its addition to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in MCL has not translated into improved outcomes. The German Low Grade Lymphoma Study Group found that, due to the short durability of the response, rituximab with CHOP (R-CHOP) compared with CHOP did not improve progression-free survival (PFS) despite an improvement in overall response rate (94% vs. 75%).

Given the disappointing outcome with R-CHOP therapy alone in younger patients, emphasis has been placed on intensification of induction therapies and consolidation strategies with high-dose therapies followed by autologous stem cell rescue (ASCR).

A randomized trial comparing myeloablative radiochemotherapy and ASCR versus maintenance interferon-α showed a clear OS benefit as well as less toxicity for patients receiving the intensified regimen. Preliminary results from a randomized phase III trial comparing six cycles of CHOP to R-CHOP/rituximab with DHAP, suggest both a PFS and OS advantage for patients receiving the intensified regimen. In terms of post-transplantation strategies, preliminary results from a randomized study from Europe demonstrated an improved three-year event-free survival of 88 percent versus 73 percent in patients receiving maintenance rituximab versus observation.

Another approach to increase the durability of remission in MCL patients uses intensified doses of chemotherapy including cytarabine without stem cell transplantation. A phase II trial of R-HyperCVAD (rituximab, fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) by the MD Anderson Cancer Center group showed a high complete remission rate of 67 percent and three-year failure-free survival of 64 percent. However, this therapy has significant toxicity, with 8 percent treatment-related mortality.

In general, we favor an intensive treatment approach consisting of an induction regimen followed by HDT and ASCR for patients who are 65 years or younger without significant comorbidity. The optimal induction chemotherapy has not been established, and options include standard or intensified R-CHOP with or without the addition of cytarabine-containing regimens. Post-transplant maintenance rituximab may be considered, but it is associated with neuropenia and risk of sinuspulmonary infections.

Older Adults with MCL

The use of dose-intensified, cytarabine-containing induction regimens followed by HDT and ASCR is not feasible for most elderly patients, due to excessive toxicity. Therefore, treatment strategies focus on regimens that improve PFS while minimizing toxicity. Results of a double randomized trial comparing R-CHOP versus R-FC (rituximab, fludarabine, and cyclophosphamide) in patients older than 60 years who were ineligible for HDT, with second randomization of responders (complete or partial response) to either maintenance rituximab or maintenance interferon-α showed a clear OS benefit as well as less toxicity for R-CHOP compared with R-FC. The remission duration was also doubled in the maintenance rituximab versus the interferon-α arm. Moreover, among patients who had a response to

Figure

Recommendations for Initial Management of Mantle Cell Lymphoma

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Therapy Recommendation</th>
</tr>
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<tbody>
<tr>
<td>Younger adults</td>
<td>( \text{R-CHOP} + \text{rituximab} )</td>
</tr>
<tr>
<td>Older adults &gt;65 years</td>
<td>( \text{R-Chemo} + \text{maintenance rituximab} )</td>
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<tr>
<td>Older adults &gt;65 years ineligible for HDT</td>
<td>( \text{R-chemo} + \text{maintenance rituximab} )</td>
</tr>
<tr>
<td>R-bendamustine</td>
<td>( \text{R-bendamustine} )</td>
</tr>
<tr>
<td>HDT and ASCR</td>
<td>( \text{HDT and ASCR} )</td>
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</tbody>
</table>

**KEY**
- HDT: High-dose therapy
- ASCR: Autologous stem cell rescue
- R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
- BR: Bendamustine and rituximab
- VR CAP: Boscham, rituximab, cyclophosphamide, doxorubicin, prednisone
R-CHOP induction, maintenance rituximab significantly improved OS when compared with maintenance interferon-α (4-year OS, 87% vs. 63%), while it had no influence in the group that received R-FC induction.11

Bendamustine is also a highly active drug in MCL. When compared to R-CHOP, bendamustine plus rituximab (BR) resulted in an improved PFS of 35 months compared to 22 months in a randomized study from Europe.13 In early results from a small study in the upfront setting, the combination of lenalidomide plus rituximab yielded overall and complete response rates of 92 and 64 percent respectively with a two-year PFS of 85 percent.14 In a randomized study comparing bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) to R-CHOP in transplant-ineligible patients, VR-CAP resulted in a superior median PFS of 24.7 months compared with 14.4 months in the upfront setting, the combination of lenalidomide plus rituximab yielded overall response and complete response rates of 92 and 64 percent respectively with a two-year PFS of 85 percent. 

In early results from a small study in the United States is currently comparing BR with or without bortezomib followed by random assignment to maintenance rituximab with or without lenalidomide. Until these data are mature, we favor R-CHOP or BR maintenance after R-CHOP. An ongoing intergroup study in the United States is currently comparing BR with or without bortezomib followed by random assignment to maintenance rituximab with or without lenalidomide.

In a randomized study comparing doxorubicin, vincristine, and prednisone (DVP) to R-CHOP in transplant-ineligible patients, DVP resulted in a superior median PFS of 24.7 months compared with 14.4 months in the upfront setting, the combination of lenalidomide plus rituximab yielded overall response and complete response rates of 92 and 64 percent respectively with a two-year PFS of 85 percent.

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Dr. Devidze and Dr. LaCasce indicated no relevant conflicts of interest.
The World Health Organization (WHO) includes mastocytosis within the category of gastrointestinal tract. Flushing, diarrhea, anaphylaxis, and neuropsychiatric symptoms are associated with mastocytosis. Mastocytosis is characterized by the accumulation and proliferation of neoplastic mast cells. Defining Mastocytosis

Approach to the Diagnosis and Management of Mastocytosis

UPDATE/COMMENTARY

More attention is being focused on how to better capture the clinical heterogeneity within SM subtypes. For example, for patients with aggressive systemic mastocytosis (ASM) and increased numbers of neoplastic mast cells on a bone marrow aspirate (e.g., 5-19%), the term ASM (ASM in transformation) has been proposed to reflect the worse prognosis of these patients and higher risk of transformation to mast cell leukemia (MCL) compared to individuals with ASM patients with ≤5 percent mast cells on a marrow aspirate. Although the life expectancy of MCL is often less than six months, such patients may also exhibit variable clinical outcomes. The terms "acute MCL" (one or more signs of organ damage) and "chronic MCL" (no evidence of organ damage) have been proposed as variants that respectively denote relatively worse and better outcomes within the spectrum of MCL.

However, retrospective and prospective data are needed to confirm whether the absence of presence of organ damage adequately discriminates prognosis between these two MCL subgroups.

The Question

What is your approach to the diagnosis and management of mastocytosis?

Defining Mastocytosis

Mastocytosis is characterized by the accumulation and proliferation of neoplastic mast cells in one or more organs (e.g., skin, bone marrow, spleen, lymph nodes, liver, and gastrointestinal tract). Flushing, diarrhea, anaphylaxis, and neuropsychiatric symptoms resulting from mast cell release of bioactive molecules such as histamine, leukotrienes, and various inflammatory cytokines can impose a significant burden on a patient’s quality of life. Indeed, mediator symptoms may be triggered by physical stimuli, exercise, alcohol, NSAIDs, opioids, insect stings, or certain foods. In advanced disease, mast cell infiltration of tissues can lead to organ damage and shortened survival.

The World Health Organization (WHO) includes mastocytosis within the category of myeloproliferative neoplasms (MPN) and divides these disorders into clonal and systemic forms. The diagnosis of systemic mastocytosis (SM) is based on consensus diagnostic criteria (Table) and requires one major plus one minor criterion or three minor criteria. Clinically, mastocytosis is further subclassified into SM and indolent SM which has been primarily based on case reports and small series.

Recent data from Dr. Celalettin Ustun and colleagues have provided more clarity on the role of hematopoietic stem cell transplantation (HSCT) in advanced SM which heretofore has been primarily based on case reports and small series. In a large, multicenter retrospective analysis published in 2014, Dr. Ustun and colleagues evaluated the outcomes of 57 SM patients (ASM, n=38; ASMD, n=7; and MCL, n=12) who underwent allogeneic HSCT. Responses were observed in 70 percent of patients, including a 16 percent complete response rate. The remaining 30 percent of responses were split between stable disease (21%) and primary refractory disease (9%). All 38 patients with SM-AHNMD achieved CR of the AHNM component, but 10 subsequently relapsed with AHNM, and half of these patients died. The median overall survival for all patients at three years was 57 percent, for all patients, consisting of 74 percent for patients with SM-AHNMD, and 43 and 17 percent for ASM and MCL patients, respectively. The strongest risk factor for worse overall survival was a diagnosis of MCL. Additionally, lower survival was observed in patients undergoing reduced intensity vs. myeloablative conditioning. These data suggest that transplantation can provide extended survival in selected patients, particularly for patients with SM-AHNMD.

In the fully accrued global trial of the multikinase/KIT inhibitor midostaurin in 89 evaluable patients with advanced SM (ASM, SM-AHNMD, and MCL), the overall response rate was 60 percent; 45 percent of patients achieved a major response, of response was 24.1 months. Median overall survival was 28.7 months and 90 percent for ASM and MCL patients, respectively. The strongest risk factor for worse overall survival was a diagnosis of MCL. Additionally, lower survival was observed in patients undergoing reduced intensity vs. myeloablative conditioning. These data suggest that transplantation can provide extended survival in selected patients, particularly for patients with SM-AHNMD.

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MALIGNANT HEMATOLOGY

Diagnosis
In addition to a high index of suspicion, obtaining the expertise of a cadre of subspecialists (hematologists, dermatologists, and allergists/immunologists) as well as hematopathologists versed with the nuances of mast cell disease is important in establishing the correct diagnosis. A combination of clinical, morphologic, immunophenotypic, and molecular studies is required to establish the diagnosis of SM and its subtype. Bone marrow mast cell burden is best quantified by morphologic analysis, and use of the aforementioned IHC stains on the core biopsy is essential. The major criterion for SM requires demonstration of multiclonal mast cell aggregates in the bone marrow (or other extracutaneous organ), of which ~25 percent are atypical, often spindle-shaped mast cells. In MCL, mast cells account for ~20 percent of nucleated cells on the BM aspirate and form a diffuse infiltrate on the core biopsy with or without circulating mast cells. Multi-parametric flow cytometry of the BM aspirate can also be used to quantify mast cell types in the marrow and complements morphologic evaluation. The overwhelming majority of SM patients (~80%) carry the activating KIT D816V mutation, which should be obtained from the bone marrow aspirate or from a core biopsy that is preserved in formalin to avoid degradation of DNA for PCR analysis. Determination of KIT D816V mutation status is critical to the diagnostic evaluation of SM, but it also guides treatment decisions. Although KIT D816V is an imatinib-resistant mutation, this tyrosine kinase inhibitor has been reflexively misapplied and overused in the treatment of SM. However, a small minority of patients (~5%) may exhibit juxtanuclear KIT mutations, which exhibit sensitivity to imatinib in vitro as well as in clinical practice. Such cases illustrate that sequencing the remainder of the KIT gene in SM patients who are negative for codon 816 mutations may prove fruitful. Total serum tryptase levels generally reflect the increased burden of mast cells in patients with SM. A serum tryptase level >20 ng/ml is an additional minor criterion for the diagnosis of SM. Although not always concurrent, it is the most useful blood marker to assess changes in mast cell burden in response to cytotherapeutic therapy. In advanced disease, staging studies include CT of the abdomen to assess hepato/splenomegaly, lymphadenopathy, and changes in mast cell burden in response to cytoreductive therapy. In advanced disease, multi-parametric flow cytometry of the BM aspirate can also be used to quantify mast cell types in the marrow and complements morphologic evaluation.

Treatment
Individuals with symptomatic skin-only disease or SM with mediator symptoms are educated to avoid known triggers and are encouraged to carry an Epipen®; particularly those with a history of anaphylaxis or anaphylactoid symptoms. Antihistamines (H1- and H2-blockers) serve as the foundation for symptom palliation; leukotriene antagonists (e.g., montelukast) and mast cell stabilizers (e.g., cromolyn sodium) are typically used for refractory mediator symptoms. Osteoporosis is treated with conventional approaches, and radiotherapy and/or IV bisphosphonates may be used to treat osteolytic or pathologic fractures. Patients with advanced SM exhibit shortened survival, and cytotherapeutic therapy is used in an attempt to reverse organ damage. Interferon-α with or without corticosteroids and 2-chloro-deoxyadenosine demonstrate overall response rates in the range of 30 to 60 percent, including major responses denoting normalization of organ dysfunction. Intensive chemotherapy has been used in MCL with modest benefit, and there is a paucity of published data regarding the utility of stem cell transplantation for advanced SM. The generally short-lived responses and tolerability of these approaches have reinforced the need to enroll patients in clinical trials evaluating novel agents. The tyrosine kinase inhibitors dasatinib and midostaurin exhibit in vitro activity against D816V-mutated KIT, with the latter demonstrating encouraging activity in an ongoing international, multi-center clinical trial. In patients with SM-AHNMD, the clinical approach for such patients has been to treat the SM component as if the myeloid neoplasm were not present and to treat the myeloid neoplasm as if SM were not present. However, in clinical practice, priority should be given to treating the disease component that is contributing to the most urgent clinical concerns. Because KIT D816V or other pathogenic abnormalities may reside in both the abnormal mast cell and associated myeloid clonal cell populations, the future availability of agents that inhibit shared therapeutic targets may make the distinction between the two disease compartments less relevant. Next-generation sequencing approaches of sorted cell populations should inform this approach. The recent identification of CD30 expression on neoplastic mast cells also provides an opportunity for testing anti-CD30 antibody approaches (e.g., brentuximab vedotin) in advanced SM.

Table

<table>
<thead>
<tr>
<th>Major criterion</th>
<th>Minor criteria</th>
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<tbody>
<tr>
<td>Multifocal dense infiltrates of mast cells (~15 mast cells in aggregates) detectable in sections of bone marrow and/or other extracutaneous organs</td>
<td>a. In biopsy sections of bone marrow or other extracutaneous organs, &gt;25% of the mast cells in the infiltrate are spindle shaped or have atypical morphology or, of all mast cells in bone marrow aspirate smears, &gt;25% are immature or atypical.</td>
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<tr>
<td></td>
<td>b. Detection of an activating point mutation at codon 816 in KIT in bone marrow, blood, or another extracutaneous organ</td>
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<tr>
<td></td>
<td>c. Mast cells in bone marrow, blood, or other extracutaneous organs express CD2 and/or CD25 in addition to normal mast cell markers</td>
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<tr>
<td></td>
<td>d. Serum total tryptase persistently exceeds 20 ng/ml (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid)</td>
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*Requires a major criterion + 1 minor criterion or 3 minor criteria.

B Findings
- Presence of 2 or more B findings
- Bone marrow biopsy showing >30% infiltration by mast cells (local, dense aggregates) and serum total tryptase level >200 ng/ml
- Signs of dyspnea or myeloproliferation in non-mast cell lineage(s), but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm (AHNMD), with normal or only mildly abnormal blood counts
- Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging (>2 cm)

C Findings (Organ Damage)
- Bone marrow dysfunction manifested by one or more cytopathies (ANC <1×10³/μL, or Hb <10 g/dL, or platelets <100×10³/μL)
- Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension
- Skeletal involvement with large osteolytic lesions and/or pathological fractures
- Palpable splenomegaly with hypersplenism
- Malabsorption with weight loss due to GI mast cell infiltrates

Dr. Gotlib is the chairman of the Study Steering Committee for the Nevatisa-sponsored global trial of midostaurin in advanced systemic mastocytosis. He also receives funding for administration of the clinical trial and payment for travel expenses from Novartis. Dr. Gotlib also serves as the principal investigator on, and receives funding for a trial of brentuximab vedotin in systemic mastocytosis.
The causes, presentation, and National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI-CTCAE) classification of disability from chemotherapy-induced neuropathy have not changed since the original publication of this article in 2014. Unfortunately, no new proven therapies have been identified. Herbal medicines are also ineffective. A pilot study of an electrical method (the ‘Scrambler’) was positive, and phase III trials are being planned.

The Case

The patient is a 54-year-old woman with IgA lambda multiple myeloma, receiving dexamethasone, lenalidomide, and bortezomib therapy. She was healthy before her diagnosis but had mild hypercalcemia and mild renal insufficiency at diagnosis, both of which have resolved with treatment.

She is about to begin her third treatment cycle, but reports painful (pain score of 7/10) numbness and paresthesias in her fingers and feet. The former problem causes clumsiness when using her touch-screen tablet and phone because she cannot accurately feel her fingers touch the screens, and she needs the light on at night because she cannot reliably feel when her feet touch the floor. Her Zubrod (ECOG) performance status is 1. She had similar, but less severe, symptoms at the beginning of her last chemotherapy cycle, but she did not mention them to anyone for fear that treatment would be delayed or discontinued.

During her exam, she was anxious, alert, and oriented. She denied both spine pain and bowel or bladder incontinence. Her exam was unremarkable except for the neurologic findings.

The NCI-CTC for Neuropathy

NCI-CTC for Peripheral Sensory Neuropathy

Grade 1: Asymptomatic or loss of deep tendon reflexes or paresthesia

Grade 2: Moderate symptoms limiting instrumental ADL

Grade 3: Severe symptoms limiting self-care ADL

Grade 4: Life-threatening consequences; urgent intervention indicated

Peripheral Motor Neuropathy

Grade 1: Asymptomatic clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate symptoms limiting instrumental ADL

Grade 3: Severe symptoms limiting self-care ADL, assistive device indicated

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death

The patient under discussion had grade 2 sensory neuropathy by these criteria, which underestimated her disability and functional losses. The NCI-CTC are not as sensitive to patient-reported symptoms or functional loss as are some other scoring systems, but no consensus has yet been reached on a standard for grading neurotoxicity. Quality-of-life scales may be more relevant (e.g., the CIPN 20 or FACT/GOG-NTx).

Treatment

Dose reduction or drug discontinuation is the only specific therapy for most CIPNs; patients may tolerate higher doses of bortezomib if the drug is given by a subcutaneous injection rather than by IV infusion. Symptomatic therapies for CIPN are limited (Figure 1). Of the adjuvant agents effective for patients with neuropathic pain, only duloxetine (30-60 mg/day) has clearly shown efficacy for the CIPN induced by taxanes and platinum. Despite the lack of proven efficacy of other agents in CIPN, insurance companies usually require that patients first fail a trial of gabapentin or pregabalain before authorizing duloxetine. Occupational therapy or physical therapy is recommended for patients with a grade 2 sensory or motor toxicity to improve function and quality of life. Patients should also be assessed for depression, which often accompanies uncontrolled chronic pain.

While vitamin E, vitamin B6, magnesium, calcium, acety-L-carnitine, glutamine, glutathione, n-acetyl cysteine, omega-3 fatty acids, alpha lipoic acid, and cannabinoids each have shown efficacy in non-randomized, non-placebo-controlled trials, none can recommend yet as standard therapy.

Amitryptiline does not prevent or ameliorate chemotherapy-induced neuropathy from vinca alkaloids, platins, or taxanes. Venlafaxine, gabapentin, the N-methyl-d-aspartate (NMDA) receptor antagonist dextromethorphan, the oral aesthetics memantine and mexiletine, and low-dose continuous capsaicin treatment are also ineffective.

Opioids are recommended for CIPN patients with severe pain. Patients will usually require a long-acting agent to provide basal pain relief (e.g., sustained-release morphine or a fentanyl patch) and short-acting opioids for breakthroughs. Methadone (Figure 2) is particularly helpful for basal pain relief. Methadone includes d- and l-isomers that act as opioid-receptor agonists and NMDA receptor antagonists. Because NMDA antagonizes the activity of the opiate receptors, blocking NMDA receptors enhances the analgesic effect of externally administered opioids. Methadone also inhibits the reuptake of serotonin and norepinephrine; therefore, it functions as a serotonin-norepinephrine reuptake inhibitor (SNRI).

Methadone is usually given orally bid to tid. Dose adjustment is needed for hepatic failure but not for renal failure. The steady-state is not reached until 72 hours after the initial dose or after a dose increase. Therefore, short-acting opioids should be used to control symptoms in the interim. If pain level falls to ≤ 3 within the first 24 to 48 hours of initiating methadone, reduce the dose by half immediately to avoid excessive sedation and respiratory depression that may otherwise occur in the next 24 hours. This delay in reaching steady-state plasma levels, along with potential cardiac toxicity (prolongation of the rate corrected QT [QTc] interval) and its interactions with inducers and inhibitors of the cytochrome P450 system, CYP1A2, CYP3A4, and CYP2D6 make using methadone safely somewhat complex. Palliative care specialists can be helpful in managing initiation
Evidenced-Based Algorithm for Evaluation and Symptomatic Treatment of Patients with CIPN

**Figure 1**

- **Correct**
  - Pain relief acceptable?
    - Yes: Continue and monitor
    - No: Add opioid?
      - Yes: Duloxetine
      - No: Continue and monitor
  - Pain relief acceptable?
    - Yes: NCI-CTC Grade ≤3?
      - Yes: Continue and monitor
      - No: On platinum or taxane?
        - Yes: Continue and monitor
        - No: Add methadone?
          - Yes: Continue and monitor
          - No: Pain relief acceptable?
            - Yes: Continue and monitor
            - No: Add methadone?
              - Yes: Continue and monitor
              - No: Pain relief acceptable?
                - Yes: Continue and monitor
                - No: On drugs than prolong QTc?
                  - Yes: Continue and monitor
                  - No: Methadone 5 mg po bid
                    - Wait 72h
                      - Yes: Continue and monitor
                      - No: Methadone 2 mg po bid
                        - Wait 72h
                          - Yes: Continue and monitor
                          - No: Methadone 5 mg po tid
                            - Continue and monitor
                            - No: Methadone 2 mg po tid
                              - Continue and monitor

**Figure 2**

- Add methadone?
  - Yes: QTC > 450?
    - Yes: Replace Ca. Mg. £
    - No: Low Ca. Mg. £
      - Yes: On drugs than prolong QTc?
        - Yes: Continue and monitor
        - No: Methadone 5 mg po bid
          - Wait 72h
            - Yes: Continue and monitor
            - No: Methadone 2 mg po bid
              - Continue and monitor

**Conclusion**

The patient continued therapy, but bortezomib delivery was switched from IV infusion to SQ injection. Her pain symptoms fell to tolerable levels on 2 mg tid of methadone such that she was able to work, and her functional level was further enhanced by participation in an occupational therapy program.

Methadone's drug interactions are listed on websites including www.drugs.com or www.qtdrug.org. Fluconazole, voriconazole, fluoxetine, and fluvoxamine raise methadone levels. Common drugs used in hematology patients that also prolong the QTc include the quinolone antibiotics (especially levofloxacin), typical and atypical antipsychotics (such as haloperidol and olanzapine), selective serotonin reuptake inhibitors (SSRIs) (but not SNRIs), and metoclopramide.

Dr. Abrahm receives royalties from her book, *A Physician's Guide to Pain and Symptom Management in Cancer Patients*, 2nd edition, 2005, from Johns Hopkins University Press. She is the paid section editor for UpToDate on the topic of pain in palliative care patients. She also receives expense reimbursement and honoraria from Knowledge to Practice for her lectures on palliative care.

Since this article was published there has indeed been a very important development in multiple myeloma (MM) that has implications for IgM monoclonal proteins. Historically, MM was defined by the presence of "CRAB" criteria (elevated calcium, renal insufficiency, anemia and bony disease). However, three additional criteria have now been added to this definition as endorsed by the International Myeloma Working Group, published in late 2014.14

These three criteria include clonal bone marrow plasma cell percentage of a 60 percent; involved/uninvolved serum-free light chain (FLC) ratio > 100 (involved FLC level must be 100 mg/L); and more than one focal lesion on magnetic resonance imaging (MRI) studies (at least 5 mm in size).

Each of these criteria was validated by at least two large databases. They do reflect a change in the concept that one must have "established end organ damage" to be treated for myeloma; this is important, as patients with these three criteria have pending organ damage, and if untreated, that damage may be permanent. It has therefore shifted a small subset of smoldering myeloma patients to active myeloma warranting treatment. I recommend that we sacrifice three criteria with <90 percent plasma cells; more than 100 light chains involved/uninvolved; MRI evidence of one or more focal lesions) now creating the overall acronym SLiM CRAB for multiple myeloma.

This new definition of MM, therefore, affects my approach to IgM monoclonal proteins; in the algorithm, I ask the question, "does the patient have end-organ damage attributable to the IgM monoclonal protein?" Instead of only considering CRAB criteria, one should now consider SLiM CRAB criteria, as that would invoke the IgM myeloma diagnosis if present, as opposed to IgM monoclonal gammapathy of undetermined significance (MGUS).


The Question
What is your approach to the evaluation of patients with an IgM monoclonal protein?

My Response
Benign monoclonal proteins were first described by Dr. Jan Waldenström in 1960 after he detected abnormal serum hypergammaglobulinemia bands in serum protein electrophoresis (SPEP) samples from healthy individuals.1 The term MGUS was coined by Dr. Robert Kyle in 1978 to describe an asymptomatic plasma cell dyscrasia characterized by a monoclonal protein of <3 gm/dL, bone marrow plasma cells <10 percent, and the absence of end-organ damage commonly associated with MM.2 MGUS is a relatively common condition with a prevalence of three to five percent in the adult population over the age of 50 years.3 SPEP is a frequently performed laboratory test ordered by primary-care physicians evaluating patients with anemia, by nephrologists evaluating patients with renal insufficiency (possibly with associated proteinuria), and by neurologists evaluating patients with peripheral neuropathy. When the SPEP reveals a monoclonal protein, referral to a hematologist usually follows. Therefore, it is part of routine practice for hematologists to see patients with monoclonal proteins that are initially identified as the result of screening assessments. The hematologist must then decide which additional diagnostic studies are warranted, and based upon those results, develop management and follow-up plans.

Although it accounts for only 15 to 20 percent of MGUS cases (that also include IgG-MGUS, IgA-MGUS, and light chain-MGUS), IgM-MGUS poses a unique diagnostic challenge because of the association of monoclonal IgM proteins with B-cell lymphoproliferative disorders (particularly Waldenström macroglobulinemia [WM], amyloidosis, and peripheral neuropathy).4 This review is intended to provide the practicing hematologist with a focused diagnostic approach to patients with a monoclonal IgM protein that takes into account its associations with other disease processes.

MGUS

Three distinct classes of MGUS are recognized: Non-IgM MGUS (essentially IgA-MGUS or IgG-MGUS as both IgM-MGUS and IgE-MGUS are fleeting rare), light chain-MGUS, and IgM-MGUS.5,6 Figure 1. Distinguishing among these subgroups is important, as doing so directs both the diagnostic plan and the follow-up recommendations, facilitates identification of diseases associated with MGUS, and impacts on management recommendations and prognosis. Although the majority of patients with IgM-MGUS will have a benign course, it is critical for the clinician to rule out a concurrent associated disease and to monitor for progression or transformation into a distinct entity that requires specific therapy.

The Risk of MGUS Progression

Unstratified patients with non-IgM MGUS have approximately a one percent per-year risk of their disease transforming into MM; however, the risk of transformation is double in patients with IgM MGUS. Risk for transformation can be more precisely stratified based on three parameters: IgG subtype versus non-IgG subtype, monoclonal protein concentration <1.5 gm/dL versus ≥ 1.5 gm/dL, and normal versus abnormal serum free light chain ratio. Stratification of risk can help guide the diagnostic evaluation and follow-up recommendations.

IgM MGUS not only has a higher risk of transformation than non-IgM MGUS, but also the spectrum of diseases associated with IgM-GUS transformation is broader than that of non-IgM MGUS. Whereas non-IgM MGUS can progress into smoldering and active MM and AL amyloidosis, IgM MGUS can transform into WM, AL amyloidosis, and less commonly, IgM smoldering myeloma or IgM-MM. For this reason, patients with IgM-MGUS require closer follow-up than patients with non-IgM MGUS, and from a conceptual perspective, IgM MGUS may be thought of as a “lymphoproliferative” MGUS while non-IgM MGUS behaves as a “plasma cell proliferative” MGUS.

Special Concerns for IgM MGUS

a. Association with neuropathy – Neurologists routinely screen patients with peripheral neuropathy for the presence of a monoclonal protein, and approximately five to 10 percent of such patients will be found to have a monoclonal protein by SPEP. A causal relationship between MGUS and peripheral neuropathy is supported by association of peripheral neuropathy with other plasma cell dyscrasias including WM, MM, AL amyloid, and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammapathy, skin changes). The peripheral neuropathy of MGUS is classically bilateral, peripheral, and sensory with electrophysiologic studies showing a demyelinating pattern; and in patients with progressive, debilitating disease, biopsy may reveal axonal loss. Although peripheral neuropathy can occur with all forms of MGUS, it is most commonly associated with IgM MGUS. Demonstration of IgM anti-myelin-associated glycoprotein (MAG) antibodies supports a causal relationship between IgM MGUS and polyneuropathy but is not essential for the diagnosis. Because peripheral neuropathy can be caused by other processes that may co-exist with IgM MGUS, the clinician is often faced with the dilemma of whether to assign the neuropathy to MGUS, and if so, what to do about it. The decision can be guided by the observations that the neuropathy associated with IgM MGUS is characteristically a relatively benign, slowly progressive sensory process (although some cases can be severe and debilitating). Management is challenging as effective therapy is lacking. A minority of patients respond to rituximab, and other immunomodulatory treatments are generally ineffective.7 As is the case with other plasma cell dyscrasia-associated neuropathies, the monoclonal protein concentration in IgM-MGUS-associated peripheral neuropathy does not correlate with disease severity, arguing against the use of myeloma-directed therapy to reduce the plasma cell burden as a treatment strategy for the neuropathy of IgM MGUS.

b. Association with AL amyloid – This complex disease can be associated with any form of myeloma, although usually one of the two processes dominates the clinical picture. That is to say that patients typically have either a myeloma-phenotype manifested by some combination of hypercalcemia, renal insufficiency, anemia, and skeletal involvement or an amyloid-phenotype characterized by organ (liver, heart, kidney) infiltration by the pathologic immunoglobulin light chain. AL amyloidosis is more commonly associated with IgM MGUS than other forms of MGUS. Thus, it is imperative that AL amyloid be carefully considered when evaluating patients with an IgM monoclonal protein.

c. Association with WM – The hallmark of this disease is an IgM monoclonal protein, lymphoedema, nephropathy, hepatosplenomegaly, and bone marrow involvement by plasmacytoid lymphocytes. Frank disease may be preceded by a relatively asymptomatic smoldering phase in which IgM MGUS is the only apparent clinical manifestation. The lymphoproliferative disorders associated with WM are the most common reason for patients with IgM MGUS to present. Patients typically present with significant peripheral or extremity edema, proteinuria, or nephrotic syndrome, or bone pain and tenderness, especially in the ribs. Paraproteinemia and bone marrow biopsy usually confirm the presence of a monoclonal IgM protein.

d. Association with other B-cell lymphoproliferative disorders – Although IgM MGUS is more commonly associated with WM, it can be observed in association with another B-cell lymphoproliferative disease such as CLL or non-Hodgkin lymphoma. Although the monoclonal protein may be discovered first as part of a laboratory evaluation, it is not usually the presenting clinical manifestation of lymphoproliferative diseases other than WM.
Suggested Approach to the Evaluation of Patients with an IgM Monoclonal Protein

The strategy that I use in the evaluation of patients with an IgM monoclonal protein is described below and illustrated in Figure 2.

1. History – This remains a critical aspect of the evaluation, as symptoms elicited from a careful history focus attention on specific issues that require further investigation. Indeed, even subtle symptoms become important when the differential diagnosis includes such a wide spectrum of disorders as amyloidosis, POEMS, MM, and lymphoma. Key symptoms to address include the following:
   a. Constitutional (weight loss, extreme fatigue) – Such symptoms suggest AL amyloid or lymphoma.
   b. Gastrointestinal – Upper GI bleeding, early satiety, and chronic diarrhea raise the possibility of GI amyloid.
   c. Cardiac – Progressive shortness of breath, presyncope/syncope, and chest pain are consistent with cardiac amyloid.
   d. Neurologic – Bilateral, sensory neuropathy is consistent with the neuropathy associated with plasma cell dyscrasias; and vision changes, headache, vertigo, or dizziness raise the possibility of hyperviscosity associated with WM.
   e. Skeletal pain – This symptom suggests IgM myeloma.
   f. Skin – Urticarial rash raises the possibility of Schnitzler syndrome.12

2. Physical Exam – The physical exam can be informative as patients with an IgM monoclonal protein and WM or other non-Hodgkin lymphoma may present with lymphadenopathy and hepatosplenomegaly. Patients with concurrent AL amyloid may have hepatosplenomegaly or macrocrania, while patients with IgM myeloma may have discrete sites of skeletal pain. A careful neurologic exam is essential for identifying and characterizing a concurrent neuropathy.

3. Labs
   a. The following lab studies should be obtained:
      i. CBC, serum calcium, creatinine, β2-microglobulin, LDH, liver enzymes
      ii. Serum protein electrophoresis with immunofixation electrophoresis
      iii. Serum free light-chain assay
      iv. Quantitative immunoglobulins
   b. Other laboratory tests that should be considered based on the clinical circumstances:
      i. Cardiac function biomarkers (NT-proBNP and troponin) for suspected amyloid
      ii. Anti-MAG antibodies in patients with a sensory neuropathy
      iii. Peripheral blood flow cytometry for suspected CLL

4. Radiologic and Other Diagnostic Testing
   a. Skeletal survey (radiographic or MRI myeloma protocol) is recommended for patients with bone pain and for patients in whom IgM MM is a consideration.
   b. Other diagnostic studies that may be considered based on clinical circumstances:
      i. Abdominal US to assess for hepatic amyloid
      ii. Echocardiogram and ECG to assess for cardiac amyloid
      iii. Abdominal/pelvic CT to assess for non-Hodgkin lymphoma including WM
      iv. PET scan to assess for lymphoma

5. Bone marrow evaluation – Although many patients with MGUS do not require this procedure, in higher-risk cases (monoclonal-protein concentration >1.5 gm/dL and IgM-MGUS), bone marrow aspirate and biopsy is recommended and may also include cytogenetics, myeloma FISH, flow cytometric analyses, and targeted gene sequencing.11,12 In a small number of patients, conventional cytogenetics, and myeloma FISH. However, recommended bone marrow analysis for all patients with a monoclonal protein. Specifically, I may defer bone marrow analysis in the very elderly, in those in whom the monoclonal-protein concentration is low (<0.5 gm/dL), and in patients with an inflammatory condition, as low-risk MGUS is relatively common in these settings.
   a. Myeloma FISH and targeted gene sequencing – Recommended if marrow findings are consistent with MM or lymphoma. Finding t(11;14) by cytogenetics or FISH suggests IgM MM, and mutant MYD88 supports a diagnosis of WM.
   b. Flow cytometry – This analysis is informative in patients suspected of having a B-cell lymphoproliferative disorder including CLL, non-Hodgkin lymphoma, or WM.

6. Fat pad aspirate – I do not routinely subject patients to this procedure; however, if there is clinical suspicion of AL amyloid, fat pad aspirate with congo red staining is an excellent screening tool. I have a slightly higher index of suspicion for AL amyloid when the IgM monoclonal protein is lambda-restricted. If the fat pad aspirate is negative for AL amyloid but suspicion remains high, targeted organ biopsy with congo red staining is warranted.

Follow-Up

If after the initial evaluation a patient is diagnosed with IgM MGUS, regular surveillance is imperative as risk of progression/ transformation is a continuous variable. I recommend that patients be seen twice annually with a clinical assessment, along with the following laboratory studies: CBC, comprehensive metabolic panel, SPEP, serum-free light-chain assay, and quantitative immunoglobulins.14 I do not recommend repeat imaging or bone marrow analysis unless there is suspicion of progression.

Conclusion

Monoclonal IgM is associated with a diverse set of diseases that range from a generally benign process requiring no specific therapy (IgM-MGUS) to overt disease requiring a specific management plan. Approaching the initial evaluation systematically and comprehensively will enable the clinician to accurately characterize the disease process.

1. Waldenström J. Studies on conditions associated with disturbed gamma globulin formation (gammopathies). Harvey Lect. 1903;56:211-231.
Treatment of Elderly Patients with Acute Myeloid Leukemia

The Question

What is your approach to the treatment of elderly patients with acute myeloid leukemia?

My Response

Acute myeloid leukemia (AML) is not a significant public health hazard, accounting for less than 2 percent of all cancers diagnosed yearly in the United States. The American Cancer Society estimates that 18,860 new cases of AML were diagnosed in 2014. Nonetheless, AML is second only to chronic lymphocytic leukemia as the most common subtype of leukemia in adults. The median age at diagnosis is 67 years, and more than 60 percent of newly diagnosed patients are older than 60 years. The management of elderly patients with AML poses unique therapeutic challenges. These individuals disproportionately account for greater than 75 percent of AML deaths yearly. In addition, recent data from the Surveillance, Epidemiology, and End Results (SEER) Program demonstrate that 50 to 60 percent of newly diagnosed AML patients older than 65 years do not receive any form of antileukemia therapy.

Definition of “Elderly” in Patients with AML

Older patients can be classified into three categories of chronological age: 1) young-old patients are 65 to 75 years of age; 2) old patients are 76 to 85 years of age; and 3) oldest-old patients are older than 85 years. In AML, clinical outcomes worsen with advancing age. Recognizing this relationship between older age and outcomes, contemporary AML treatment protocols have typically used an arbitrary cutoff of 55 to 65 years to distinguish between younger and older subjects. However, chronologic age by itself is not reliable in estimating life expectancy, functional reserve, or the risk of treatment complications. Comprehensive geriatric assessments (CGA) are multidisciplinary, in-depth evaluations designed to assess life expectancy and attendant morbidity and mortality risks in older patients. CGAs include tools to predict the functional age based on functional status, comorbidities, polypharmacy, nutritional status, and geriatric syndromes.

For this reason, pre-treatment CGAs or more focused geriatric assessment tools may replace chronologic age as an identifier of “functionally older” AML patients ineligible for aggressive treatment approaches.

AML and Non–AML-Related Factors Influencing Treatment Decisions

Recent studies suggest that age may be a suboptimal criterion for allocation to intensive AML treatment protocols, and that additional variables may improve the ability to predict toxicity and outcomes. Population-based data demonstrate that older age was only one of the several covariates (including history of antecedent hematologic disorder [sAML], higher comorbidity score, poor performance indicators, marital status, and lower household incomes) associated with lack of antileukemia therapy in newly diagnosed older patients with AML. A retrospective analysis showed that a pre-treatment geriatric assessment, focused on cognitive and physical function, improved the prediction of survival among older adults with AML treated with conventional induction chemotherapy. Two large retrospective studies have identified several AML and non-AML covariates that predict early outcomes, such as induction mortality and likelihood of complete remission, following intensive chemotherapy. In the first, investigators developed a simplified early death score with moderate discriminatory power that incorporates performance status at diagnosis, age, platelet count, albumin, sAML, white blood cell count, percentage of peripheral blood blasts, and serum creatinine (cstaging.fhcrc-research.org/TRM/Default.aspx). Interestingly, removal of age as a covariate had minimal impact on the predictive power of this model. Similarly, investigators from the Study Alliance Leukemia demonstrated that the risk of induction mortality and the chance of complete remission could be predicted in older patients with AML using a combination of pre-treatment covariates, including age, hemoglobin, platelet count, ferritin, type of AML, karyotype and limited molecular abnormalities at diagnosis (www.aml-score.org). These data suggest that age alone is a poor predictor of treatment intent and outcomes, and is likely a surrogate for other covariates associated with inferior prognosis.

Therapeutic Options for Elderly Patients with AML

In routine clinical practice, it remains challenging to know how to best utilize these data to inform patients and families on the optimal therapeutic approach for an individual with AML. Although these predictive models provide some guidance on the potential risks and benefits associated with conventional induction chemotherapy, treatment decisions regarding therapeutic intensity remain a highly individualized exercise. In my practice, I direct patients with low treatment-related mortality scores or favorable AML risk prediction scores to intensive or investigational therapy; conversely, I consider patients with high treatment-related mortality scores or unfavorable AML risk profiles for lower-intensity investigational regimens (Figure).

Results from population studies and randomized clinical trials add to the challenge of deciding optimal therapeutic intensity. Recent SEER-Medicare linked data showed that, after using a propensity score-matched survival analysis to account for all confounders, similar reductions in the risk of death were observed for elderly patients receiving either intensive chemotherapy or hypomethylating agents. Similar results have been reported in randomized clinical trials with similar overall survival between single agent hypomethylating agents (decitabine or azacitidine) and conventional care regimens.

The Future is Now: The Rise of Targeted Therapies

“...It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness...” This opening sentence from A Tale of Two Cities describes the sentiment of hematologists regarding the current state of management of AML in older patients. While our understanding of the molecular alterations responsible for leukemogenic transformation has flourished in recent years, none of these discoveries has yet translated into approved treatment strategies for patients beyond “7-5” conventional induction chemotherapy. However, characterization of the mutational landscape of AML has accelerated development of targeted therapeutics that may soon be within the reach of patients. Activating mutations in signaling pathways, including FLT3, KIT, RAS, and others, have been described in roughly 60 percent of AML patients. Clinical trials testing the activity of FLT3, KIT and MEK inhibitors (as single agents or in combinations) are available in most academic centers.
ters and may reshape treatment strategies for these patients. Mutations in the DNMT3A and TET2 genes have been linked to increased sensitivity to hypomethylating agents.\textsuperscript{12,13} Examples of novel agents in clinical development include small molecule inhibitors of mutant IDH1 and IDH2,\textsuperscript{14,15} DOT1L inhibitors for patients with MLL rearranged acute leukemia, novel epigenetic modifiers such as the bromodomain (BRD4) inhibitors, and development of second-generation anti-CD33 conjugated monoclonal antibodies. Also, addition of multikinase (sorafenib) or aurora kinase inhibitors to conventional induction chemotherapy is associated with promising antileukemic activity and improved survival. Finally, improved patient selection (genomic profile, AML-MRD, or adverse-risk karyotype) or combination with novel agents (pracinostat or pevonedistat) may optimize the clinical benefit of DNA methyltransferase inhibitors such as azacitidine.

At last, physicians caring for older patients with AML may say farewell to the age of foolishness when patients and physicians were painstakingly faced with choosing between nonspecific and toxic regimens or palliative care. Instead, they can usher in the age of wisdom, when patients and physicians were painstakingly faced with choosing between nonspecific and toxic regimens or palliative care. Instead, they can usher in the age of wisdom, when patients and physicians were painstakingly faced with choosing between nonspecific and toxic regimens or palliative care. Instead, they can usher in the age of wisdom, when patients and physicians were painstakingly faced with choosing between nonspecific and toxic regimens or palliative care. Instead, they can usher in the age of wisdom, when patients and physicians were painstakingly faced with choosing between nonspecific and toxic regimens or palliative care. Instead, they can usher in the age of wisdom, when patients and physicians were painstakingly faced with choosing between nonspecific and toxic regimens or palliative care. Instead, they can usher in the age of wisdom, when patients and physicians were painstakingly faced with choosing between nonspecific and toxic regimens or palliative care. Instead, they can usher in the age of wisdom, when patients and physicians were painstakingly faced with choosing between nonspecific and toxic regimens or palliative care. Instead, they can usher in the age of wisdom, when patients and physicians were painstakingly faced with choosing between nonspecific and toxic regimens or palliative care. Instead, they can usher in the age of wisdom, when patients and physicians were painstakingly faced with choosing between nonspecific and toxic regimens or palliative care. Instead, they can usher in the age of wisdom.


Dr. Medeiros indicated no relevant conflicts of interest.
MALIGNANT HEMATOLOGY

The Question

What is your management approach to patients with relapsed/refractory hairy cell leukemia?

My Response

Hairy cell leukemia (HCL) is an indolent B-cell malignancy, originally with a median survival of approximately four years. Single-agent purine analog therapy with pentostatin or cladribine achieves complete remission (CR) rates of 70 to 90 percent and median relapse-free survival in excess of 15 years. However, minimal residual disease (MRD) often remains, and may be associated with relapse, particularly in younger patients with longer follow-up. Thus, in the past 25 to 30 years, many patients have neither died nor been cured, compelling the increasingly common question of how to treat relapsed and refractory patients. The answer requires accurate diagnosis, understanding the history of response and toxicity to prior agents, and a strategy for prioritizing options including exciting new targeted therapies.

Diagnosis of HCL and Recognition of Variant Disease

HCL diagnosis today is most accurately made by flow cytometry showing strong expression of B-cell antigens CD20 and CD22; strong CD11c; and positive CD25, CD103, and CD123. Bone marrow immunohistochemistry is positive for CD22, tartrate-resistant acid phosphatase (TRAP), annexin 1 (AnxA1), and for the V600E mutated form of BRAF. Variant HCL (HCLv) has a similar immunophenotype but lacks CD25, AnxA1, CD123, and TRAP. Additionally, BRAF is wild type. HCLv is more aggressive, with worse spleenomegaly, malignant lymphocytosis rather than cytopenias, and exhibits a poor response to single-agent purine analog; it also may require adding rituximab. Although classified in 2008 by the World Health Organization as a separate disorder, HCLv is also discussed here. Another aggressive variant is characterized by an immunophenotype of classic HCL, but with the IGHV4-34 type of immunoglobulin rearrangement that is more than 98 percent homologous (unmutated) to its germline sequence. Even with the classical immunophenotype, these patients resemble those with HCLv with malignant lymphocytosis, purine analog resistance, and wild-type BRAF. By shipping blood samples and unstained bone marrow slides to an expert center, accurate diagnosis is also possible without travel. Treatment should only be initiated after accurate diagnosis is established.

Treatment of Patients in First Relapse

With some exceptions, remission rates are lower after second-line versus after first-line purine analog therapy, however, if the length of the first remission is at least two to four years, many will recommend repeating the initial purine analog. The shorter the treatment-free interval, the greater the risk of overlapping toxicity. Patients relapsing after shorter intervals often receive the anti-CD20 MAb rituximab alone in four to eight weekly doses. While single-agent rituximab can achieve response without overlapping chemotherapy toxicity, response rates are relatively low in patients with prior purine analog therapy who have cytopenias requiring treatment. A more effective strategy is to combine a purine analog with rituximab. Elimination of MRD, detectable by immunohistochemistry of the bone marrow biopsy, as well as by flow cytometry of the blood or bone marrow aspirate, is possible with rituximab one month after cladribine.

We treat once-relapsed HCL/HCLv with rituximab, starting immediately with cladribine to effect synergy, or delayed at least six months so MRD status can be determined.

Therapy of Multiply Relapsed HCL

Several options are being tested for multiply relapsed HCL. In order to avoid chemotherapy toxicities, but to retain cytotoxic power, we use recombinant immunotoxins containing an Fv fragment of a MAb and a truncated form of Pseudomonas exotoxin. High CR rates in multiply relapsed HCL were reported in 2001 using the anti-CD22 recombinant immunotoxin BL22, included in the National Institutes of Health (NIH) protocol using rituximab. Mutations were made in the VH domain of BL22 that improve its binding to CD22, and the resulting affinity-matured recombinant immunotoxin moxetumomab pasudotox achieved CRs in approximately 50 percent of patients with multiply relapsed HCL, many without MRD. Another strategy to achieve MRD-negative CR is to use six cycles of either pentostatin plus rituximab, or bendamustine plus rituximab. Our protocol at the National Institutes of Health (NIH) prospectively evaluates and randomizes patients between both regimens and allows crossover to the other regimen if needed. Most can achieve MRD-negative CR, but with more toxicity than patients receiving non-chemotherapy approaches such as moxetumomab pasudotox.

Targeted Approaches in HCL

In the BRAF pathway of normal cells, BRAF phosphorylates MEK, MEK phosphorylates ERK, and phosphorylated ERK leads to cell proliferation. BRAF containing the V600E mutation, present in nearly all hairy cell malignancies, in lower percentages of other tumors, but in nearly all cases of classic HCL, exhibits uncontrolled phosphorylation leading to the malignant phenotype. Inhibition of this mutant BRAF with vemurafenib, or with dabrafenib combined with the MEK inhibitor trametinib, is approved for malignant melanoma and is currently being tested in HCL. Oral BRAF inhibitors in HCL can rapidly reverse severe cytopenias but have not yet been reported to clear MRD and prevent relapse. The oral agent trametinib, which targets the BRAF pathway, is also being tested in patients with HCL and HCLv. Though most patients achieve stable disease, this can have palliative benefit, particularly for patients with HCLv.

Figure HCL protocol treatment algorithm

Newly diagnosed HCL patients typically receive a purine analog, most commonly cladribine in five daily doses, less commonly pentostatin in six to 12 biweekly doses. Newly diagnosed or once-relapsed patients may receive repeat courses of single-agent purine analog, but at MD Anderson and the NIH, are also eligible for protocol treatment with rituximab and cladribine (CDAR). At the NIH, multiply relapsed HCL/HCLv patients eligible for moxetumomab pasudotox receive that option (also available in other centers), while ineligible patients may receive LMB-2, BRAF inhibitor, rituximab, and BRPR (bendamustine-rituximab vs pentostatin-rituximab) in that order of priority. Common off-protocol options for multiply-relapsed HCL include repeat courses of single-agent purine analog, single-agent rituximab, and pentostatin-rituximab. Splenectomy and even splenic radiotherapy can have palliative benefit at least for a limited period of time.

Summary and Algorithm for Treatment Approach to Patients with Relapsed/Refractory HCL

The Figure shows our algorithm for prioritization of clinical trials for relapsed HCL; additional options can be used off-protocol. Patients with once-relapsed HCL after purine analog can be retreated with the same or different purine analog as a single-agent, particularly if the remission duration was long, but we prefer combining cladribine with rituximab on study to eliminate MRD. For patients with multiply relapsed HCL, moxetumomab pasudotox is our preferred option due to its unique ability to achieve MRD-negative CR without chemotherapy toxicities. For patients who responded to anti-CD22 recombinant immunotoxin (BL22 or moxetumomab pasudotox) but need additional therapy, we target CD20 with recombinant immunotoxin LMB-2. For patients ineligible for moxetumomab pasudotox or LMB-2, we use BRAF or MEK inhibitor, provided patients are able to handle toxicities and understand that remission durations may be limited if MRD persists. For patients with HCL/HCLv ineligible for these approaches, we prefer either the ibrutinib protocol or our protocol using rituximab combined with either bendamustine or pentostatin. Ibrutinib offers oral therapy without chemotherapy toxicity, while the rituximab-chemotherapy combination offers a likely path to high MRD-negative CR rates and the potential (as in patients after moxetumomab pasudotox) of not needing therapy for many years. Further follow-up and testing will be needed to determine the long-term benefit of these approaches and whether MRD-negative CR can translate into cure.

The Question

What is your approach to the diagnosis and treatment of patients with low-risk myelodysplastic syndrome (MDS) related to immune pathophysiology?

Case

A 53-year-old man was found to have pancytopenia during follow-up for hyperuricemia. The laboratory findings were as follows: WBC, 2.44×10^9/L with 26 percent neutrophils, 1 percent eosinophils, 8 percent monocytes, and 45 percent lymphocytes; RBC, 1.49×10^12/L, hemoglobin, 5.7 g/dL; mean corpuscular volume (MCV), 112.8 fL; platelets, 22×10^9/L; reticulocytes, 45×10^9/L; LDH, 195 IU/L. The patient’s bone marrow (BM) was normocellular with 2 percent blasts and showed signs of dysplasia in erythroid precursors and granulocytes without increased ring sideroblasts. The megakaryocyte count was decreased. The karyotype of the BM cells was 46,XY in 20 dividing cells. The patient was therefore diagnosed as having refractory cytopenia with multilineage dysplasia (RCMD) with an International Prognostic Scoring System (IPSS) risk group of intermediate-1 (IPSS-revised risk category: intermediate). His physician suggested that he receive red blood cell transfusions and possibly hematopoietic stem cell transplantation or azaclidine therapy if the pancytopenia progressed further.

My Response

Distinguishing Cases of Immune-Mediated BM Failure

Diagnosing MDS is often challenging in patients with pancytopenia or bicytopenia who do not show definitive poor prognostic markers, such as karyotypic abnormalities or increased blasts or ring sideroblasts in the BM, as in the present case. The differential diagnosis of such cases of gray zone BM failure includes refractory cytopenia with multilineage dysplasia, RCMD, idiopathic cytophenia(s) of undetermined significance, and moderate aplastic anemia (AA). It is generally difficult to make an exact diagnosis based on the established diagnostic criteria because these disease entities overlap, and each diagnosis relies on a subjective judgement of the cell morphology by physicians and/or pathologists. Giving a disease name to such an equivocal condition has virtually little value. Instead, it is clinically relevant to distinguish benign subsets of BM failure that are likely to respond to immunosuppressive therapy (IST) from cases of non-immune-mediated BM failure, including those associated with pre-leukemic features and inherited BM failure syndromes.

Difficulties in Evaluating BM Cellularity in Patients with BM Failure

BM aspiration and trephine biopsies are essential for obtaining the differential diagnosis of BM failure syndromes, and the detection of a hypocellular BM is a prerequisite for diagnosing AA. However, assessing BM cellularity in patients with BM failure is often difficult, particularly when the cytophenias are not severe. Even when the BM of a bone site is grossly replaced with fat tissue as a result of the immune-mediated destruction of hematopoietic stem cells (HSCs), some hematopoietic nests remain in other bone sites and may show hypercellularity due to increased BM activity that compensates for the decreased hematopoiesis. BM aspiration or biopsies of these hot spots can sometimes produce erroneous results. When pathological reports of BM examinations show hyper- or normal cellularity, the physician may not generally consider the differential diagnosis of AA. Hematologists should be careful with respect to cellularity when interpreting the results of BM examinations, considering that BM cellularity cannot be accurately determined based on BM biopsies of limited sites in the iliac bone. Magnetic resonance imaging (MRI) of the thoracolumbar spine can be used to supplement an assessment of cellularity with a BM biopsy. However, MRI often produces equivocal results in elderly patients owing to age-related fatty changes in the BM. Therefore, hematologists should keep in mind that BM hypercellularity does not necessarily preclude a diagnosis of immune-mediated BM failure.

Laboratory Markers Representing Immune Pathophysiology of BM Failure

The presence of predominant thrombocytopenia is the most fundamental feature of immune-mediated BM failure that should prompt further examinations of other laboratory markers. An increased percentage of paroxysmal nocturnal hemoglobinuria (PNH)-type cells, which can be detected using high-sensitivity flow cytometry (FCM), represents a reliable marker of immune pathophysiology. The usefulness of detecting increased PNH-type cells for predicting the response to immunosuppressive therapy (IST) in AA patients was confirmed in recent prospective studies utilizing high-sensitivity FCM-based methods that can precisely measure 0.01 percent or more PNH-type cells. Figure 1 shows the results of FCM in the current case, which revealed 0.126 percent of granulocytes and 0.001 percent of erythrocytes to be PNH-type cells. Such results can be obtained on the same day as the patient’s visit, and if those results are positive, physicians have the option of commencing IST shortly thereafter. The presence of HLA-DRB1*15:01 has been reported to predict a good response to IST in patients with MDS. However, in our previous study using a multivariate analysis of several factors, including the presence or absence of DRB1*15:01, only the detection of PNH-type cells was associated with a good response to IST in patients with AA. Therefore, DRB1 typing to clarify the immune pathophysiology of BM failure is unnecessary if high-sensitivity FCM is available and detects PNH-type cells.

Another solid marker of immune pathophysiology in patients with BM failure is the presence of HLAA allele-lacking leukocytes (HLA-ALLs) derived from HSCs that develop copy number–neutral loss of heterozygosity of the HLA haplotype owing to uniparental disomy of the short arm of chromosome 6 (6pUPD). Detecting 6pUPD(+) leukocytes requires a single nucleotide polymorphism array analysis, which takes several weeks. On the other hand, HLA-ALLs can be easily detected using monoclonal antibodies specific to HLA-A alleles with FCM if the patient is heterozygous for the HLA-A allele.

Another useful examination that does not require advanced techniques is measurement of the plasma thrombopoietin (TPO) level. Patients with MDS who have a TPO level of 320 pg/mL or greater (TPO(+)) patients) exhibit a high progression-free survival rate and good response to IST, similar to cases of AA. Virtually all patients having increased PNH-type cells or HLA-ALLs fall into the TPO(+)-group. Accordingly, if data for the TPO level are available, physicians may not need to examine the peripheral blood in patients with BM failure to determine the presence of other markers. The recent National Comprehensive Cancer Network guidelines recommend using hypomethylating agents for the treatment of MDS associated with thrombocytopenia; however, this option may be hazardous to TP53(+) patients, as BM failure in these cases is not based on the presence of abnormal stem cells with pre-leukemic features.
Figure 2 illustrates the mutual relationship of the markers that are potentially useful for diagnosing immune pathophysiology in patients who do not show any karyotypic abnormalities, increased blasts, or ring sideroblasts in the BM. The precise role of these markers in the management of gray zone BM failure must be evaluated in a large prospective study because the predictive values of HLA-LLs and plasma TPO levels have only been assessed in Japanese patients with BM failure. When deciding on treatment, physicians also need to take patient age and disease duration into account, both of which are known to affect the response to IST.11

Patient Follow-up
Based on the positive results for PNH-type granulocytes, we treated the patient with cyclosporine at a dose of 4 mg/kg/day. The pancytopenia gradually improved in response to this therapy, and the blood cell count seven months after the initiation of treatment was as follows: WBC, 3.0 × 10^9/L; platelets, 57 × 10^9/L; reticulocytes, 75 × 10^9/L. He continues to receive cyclosporine without any signs of significant toxicities.

References

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Joseph Michael, MD, Med, FRCPC
Dr. Joseph Mikhail recaps the “Social Media for Hematologist” session at the 2015 ASH Annual Meeting. Attendees discussed the professional benefits of social media and how it can be used by professional hematology research and clinical communities to promote conversations that could have a positive impact on patient outcomes. Watch the video on the ASH Youtube page. Learn about ASH’s social media presence at www.hematology.org/Newsroom/465.aspx.

Read an article by Dr. Mikhail in this Compendium on page 20.
ANCILLARY TESTS

A classic example of a pleomorphic lymphocytosis is infectious mononucleosis, where the most reactive lymphocytoses show a wide range of sizes and shapes in lymphocytes. The distinction between a lymphoproliferative disorder and a reactive lymphocytosis, respectively. Separating a monomorphic lymphocytosis from a pleomorphic lymphocytosis can help distinguish a lymphoproliferative disorder from a reactive lymphocytosis, respectively.

Reactive Lymphocytosis

Examining the Blood Smear

A slide review is appropriate in all patients with an unexplained lymphocytosis in order to confirm the automated cell counts or to perform a manual differential for leukocyte classification. In manually prepared blood smears, larger white blood cells tend to collect at the edges of the smear and in the feathered edge. Good practice for slide review requires assessments of all cell types (leukocytes, red blood cells [RBCs], and platelets) in both quantity and quality. It is not uncommon for fragile leukocytes such as in CLL, infectious mononucleosis, or acute leukemia to smudge on blood smears. In these situations, a few drops of albumin can be added to peripheral blood before preparing the blood smear. These “albumin smears” allow for proper identification of leukocytes and reduce the number of “smudge” or “basket” cells. However, examination of RBCs and platelets should still be performed on the original blood smear because the albumin can affect platelet and erythrocyte morphology.

Reactive Lymphocytosis

Separating a monomorphic lymphocytosis from a pleomorphic lymphocytosis can help distinguish a lymphoproliferative disorder from a reactive lymphocytosis, respectively.1 Most reactive lymphocytes show a wide range of sizes and shapes in lymphocytes. The classic example of a pleomorphic lymphocytosis is infectious mononucleosis, where the lymphocytes range in size from small and round, to intermediate with abundant cytoplasm (reactive lymphocytes), to frank immunoblasts. It is this spectrum of morphology that points to a greater likelihood that a patient has a reactive lymphocytosis; younger age is also a helpful clue. The causes of a reactive lymphocytosis are extensive and include infections (viral, bacterial, and parasitic), autoimmune disease, vaccination, drug hypersensitivity, endocrine disorders, stress (trauma, cardiac, extreme exercise), smoking, and malignancy.

While most of these reactive lymphocytes are pleomorphic, a few important exceptions are worth mentioning. The first is Bordetella pertussis, the causative agent of whooping cough. The leukocytes of B. pertussis are small and deeply clefted with mature chromatin as shown in Figure 1. As this is commonly seen in the pediatric and pregnant populations, clinical correlation will readily separate this from lymphomas, which can show similar morphologic features (e.g., follicular lymphoma or Sézary syndrome). The second exception is polyclonal B-lymphocytosis, which typically shows lymphocytes with distinct nuclear clefts but will demonstrate a spectrum of morphologic changes including nuclear lobation and binucleate forms. This uncommon disorder is found in young to middle-aged female smokers with a high association with human leukocyte antigen DR7, and several genetic abnormalities have also been documented.1 The final exception is a large granular lymphocytosis. Increased numbers of large granular lymphocytes (reactive lymphocytes with scattered azurophilic granules) are commonly seen with viral infections, malignancy, after bone marrow transplantation, and following chemotherapy. These populations of large granular lymphocytes will wax and wane. However, persistence of a large granular lymphocytosis with accompanying neutropenia and variable anemia should raise suspicion for large granular lymphocytic leukemia.2 This is typically T cell in origin, though a chronic lymphoproliferative disorder of natural killer cells is also well described. Flow cytometry is recommended in these cases, followed by either T-cell clonality or KIR analysis, if involving T cells or natural killer cells, respectively.

Neoplastic Lymphocytosis

Lymphoma cells tend to be monomorphic in appearance. While a blood smear may contain a subset of lymphoma cells, these cells will resemble one another and stand out against a background of normal bland lymphocytes. While CLL is the most common leukemia in adults in the western world and is frequently seen in peripheral blood (or its monoclonal B-cell lymphocytosis counterpart), peripheral blood involvement by bone marrow lymphoma is found in up to 30 percent of subjects in some studies.3 Lymphoma cells will show a wide variety of morphologic appearance, and this appearance raises a differential diagnosis as shown in Figure 2.4 Further identification of the type of lymphoproliferative disorder typically proceeds with flow cytometry. Although each laboratory has its own cocktail of antibodies used for flow cytometry, consensus guidelines have been published.5 While the results from flow cytometry narrow down one’s differential diagnosis to a short
The lymphocytes also lacked expression of CD200 by flow cytometry, another marker overexpressed in CLL as well as lymphoplasmacytic lymphoma, though few cases of the latter were tested. While the patient lacked splenomegaly, a diagnosis of marginal zone lymphoma with plasmacytic differentiation was considered. The patient is scheduled to receive ibrutinib.


Dr. George indicated no relevant conflicts of interest.
This collection contains updated clinical information on malignant and nonmalignant hematology as profiled in *The Hematologist*.

**NONMALIGNANT HEMATOLOGY**

Ask the Hematologist
Breast cancer is associated with an increased risk for venous thromboembolism (VTE). Among more than 13,000 women with breast cancer in four U.K. databases, the rate of VTE was 3.5 times that of age-matched controls.\(^1\) Similarly, among more than 100,000 patients with breast cancer in two California databases, the one- and two-year incidences of VTE were 0.9 and 1.2 percent, with the incidence greatest in the first six months after diagnosis.\(^2\) VTE incidence also increased while patients were receiving chemotherapy, in the month after therapy was discontinued, and during the initial three months of treatment with tamoxifen.\(^3\) Nonetheless, compared with cancers of the pancreas, stomach, ovary, lung, and kidney, as well as gliomas and lymphomas, this risk is relatively low.\(^4,5\)

There remains a paucity of data regarding thromboprophylaxis in ambulatory patients with cancer in general and with breast cancer in particular. One relevant study, TOPIC-1, was halted prematurely because of no difference in VTE incidence between ambulatory breast cancer patients treated with low-molecular-weight heparin or placebo.\(^3\) It is noteworthy that neither the American Society of Clinical Oncology,\(^6\) the American College of Chest Physicians,\(^7,8\) nor the European Society of Medical Oncology\(^9\) currently recommend thromboprophylaxis in ambulatory patients with any cancer, unless the individual patient is considered to be at high risk.

**Clinical Problem**

I have been treating a 54-year-old woman with a resected breast cancer with adjuvant docetaxel, cyclophosphamide, and trastuzumab. She developed a central line thrombosis during treatment and was treated with warfarin for three months, after which the central line was removed. I plan to discontinue the warfarin in the next several weeks, assuming it is safe to do so while she is receiving trastuzumab. Should the patient undergo a work-up for thrombophilia despite a negative family history, and should warfarin be restarted if she needs another central line to complete a one-year course of trastuzumab?

**My Response**

This is a common but complex situation. This patient has several predispositions to venous thrombosis, including breast cancer, chemotherapy, and an indwelling venous catheter. The thrombosis she experienced could have resulted from the cumulative effect of these factors, but I suspect the presence of the indwelling catheter was the major precipitating cause. As you know, cancers – in particular malignancies of the brain, adenocarcinomas of the lung and gastrointestinal tract, and hematologic malignancies – are associated with a sixfold to sevenfold increase in the risk for venous thromboembolism (VTE).\(^1\) Although this risk is greatest in the months following diagnosis and declines with time, the risk remains higher than in individuals without cancer even two years after diagnosis. Moreover, the risk for patients with metastatic disease is increased further compared to patients without. Although the risk for VTE in the first six months after a diagnosis of breast cancer is doubled to tripled for patients with the malignancies noted above, the cumulative incidence of VTE for patients with breast cancer approaches that of the others, because patients with breast cancer live substantially longer. This raises the question whether prophylactic anticoagulation in a patient with breast cancer would be beneficial. This issue was addressed in the most recent American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.\(^10\) After reviewing the available data, the authors of the guidelines concluded that the evidence does not support routine thromboprophylaxis for the primary prevention of VTE in ambulatory patients such as this one.

Chemotherapy administration and hormonal manipulation are also associated with an increased risk of VTE. Therefore, it is surprising that there is a paucity of studies addressing the efficacy of thromboprophylaxis in ambulatory cancer patients who are receiving chemotherapy or hormonal therapy. One widely cited study from 1994 reported that giving low-dose warfarin (INRs of 1.3-1.9) in patients with stage IV breast cancer receiving chemotherapy resulted in a significant reduction in VTE.\(^1\) However, these results were not replicated in subsequent studies,\(^2\) and thromboprophylaxis is not currently recommended for patients with cancer receiving chemotherapy or hormonal therapy.\(^3\) With specific regard to trastuzumab, after reviewing the prescribing information and searching the literature, I could not find evidence that VTE is a common adverse event related to the use of this drug.

As I mentioned earlier, I think the central venous catheter itself, as a foreign body in the circulation, was the proximate cause of the thrombosis in your patient. So, it would seem logical to ask whether prophylactic anticoagulation could prevent this from happening again. There have been a number of studies addressing this question. However, a recently reported meta-analysis of eight randomized controlled trials of thromboprophylaxis in patients with cancer and central venous catheters concluded that thromboprophylaxis had no significant effect on the risk of catheter-related thrombosis.\(^7\) Similarly, in the WARP study of warfarin thromboprophylaxis in cancer patients with central venous catheters,\(^8\) it was found that neither fixed-dose warfarin at 1 mg per day nor dose-adjusted warfarin to maintain an INR of 1.5 to 2.0 reduced the incidence of catheter-related thromboses. Thus, the available evidence does not support the use of prophylactic anticoagulation should the central line be re-inserted.

Although your patient has several recognized predispositions to thrombosis, the currently available evidence does not support the use of thromboprophylaxis for her clinical situation. Further, on the basis of this conclusion, as well her age and history, I don’t see the utility of a thrombophilia work-up.

**References**


Dr. Bennett indicated no relevant conflicts of interest.
The Question

A healthy 14-year-old girl presented with a hemoglobin of 2.9 g/dL, MCV 61 fL, and reticulocyte count of 0.9 percent. Pregnancy test was negative. Menarche began at age 11; periods were somewhat irregular and lasted five to seven days with clots. A diagnosis of severe iron deficiency due to menorrhagia was made and appropriately managed with transfusion and iron. Should an evaluation be done for an underlying bleeding disorder? What tests? What about such an evaluation if the anemia due to menorrhagia recur three years later?

The patient is now interested in contraception. A paternal aunt and maternal grandmother have a vague history of thrombosis requiring treatment. What form of contraception should be undertaken in this patient before contraception is prescribed? Indeed, should thrombophilia testing be recommended for all women before oral contraceptives (OCs) are prescribed? What form of contraception and medication for regularization of periods should be advised?

Our Response

This case represents a clinical situation encountered frequently by pediatric hematologists. Unfortunately, clinical management decisions for adolescents must still be largely extrapolated from published data and recommendations on and for women. However, in a 2015 Committee Opinion endorsed by the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists revised and updated their guidance on menstruation in girls and adolescents: menstrual cycle duration is typically 21 to 45 days; menstrual flow is seven days or less; and menstrual product use is three to six pads or tampons per day. Menorrhagia or heavy menstrual bleeding is defined as greater than 80 mL of blood per cycle and can be predicted on the basis of clots > 1 inch diameter or greater, low ferritin, and "flooding," defined as a change of pad or tampon more frequently than hourly.

In the case of the 14-year-old girl, heavy menstrual bleeding could be inferred on the basis of clots, cycles of up to seven days and severe iron-deficiency anemia in the absence of any other source of bleeding.

The causes of heavy menstrual bleeding include acquired abnormalities of the uterine cavity (polyps, adenomyosis; leiomyoma; malignancy and hyperplasia; other endometrial abnormality) ovulatory dysfunction; iatrogenic causes; (usually hormonal); causes not yet classified; and coagulopathy. However, in an adolescent, the cause is less likely to be an abnormality of the uterus and more likely to be ovulatory dysfunction, a hormonal cause, or possibly, an underlying bleeding disorder. A bleeding disorder may be the sole cause of heavy menstrual bleeding, or it may be a contributing cause. Consequently, an adolescent presenting with heavy menstrual bleeding requires a thorough evaluation that includes a thorough history and physical examination, an assessment of the uterus, an endocrine evaluation if there is anovulation or hypo-ovulation, and possibly, an evaluation for an underlying bleeding disorder. If anemia due to menorrhagia recurs three years later, a re-evaluation would be indicated.

Not only is heavy menstrual bleeding more prevalent among women and girls with bleeding disorders, but bleeding disorders are more prevalent among those with heavy menstrual bleeding. In adolescents who present with heavy menstrual bleeding, the prevalence of von Willebrand disease (vWD) has been reported to be 5 to 36 percent; the prevalence of platelet dysfunction (depending on how it was defined) was 2 to 44 percent; the prevalence of factor VIII deficiency was 8 percent; and the prevalence of thrombocytopenia 13 to 28 percent. Dr. Claire S. Philipp and colleagues reported on the importance of various signs and symptoms as predictors of a bleeding disorder in women with heavy menstrual bleeding. After administering a 12-page questionnaire of bleeding symptoms, the investigators were able to develop a screening tool that was considered to be positive if one of the following four criteria was met:

• Duration of menses greater than or equal to seven days and flooding or impairment of daily activities with most periods
• History of treatment of anemia
• Family history of a diagnosed bleeding disorder
• History of excessive bleeding with tooth extraction, delivery or miscarriage, or surgery

The screening tool alone had a sensitivity of 82 percent for bleeding disorders. Although the results would not be available at an initial visit, adding a pictorial blood assessment chart score > 100 increased the sensitivity of the screening tool to 95 percent. The patient in this case was positive for two of the criteria (7-day periods and anemia). Therefore, an evaluation for an underlying bleeding disorder would be indicated.

The laboratory evaluation for an underlying bleeding disorder would include a platelet count, mean platelet volume (MPV), and review of the blood smear to rule out thrombocytopenia and platelet morphologic disorders; prothrombin (PT), partial thromboplastin (aPTT), and thrombin times along with fibrinogen activity to screen for clotting factor deficiency; and a von Willebrand factor profile and platelet function studies. Additionally, specific factor activity levels would be performed if dictated by a prolonged PT or aPTT or otherwise suggested by high ethnic prevalence or an X-linked family history of a hemorrhagic diathesis. Any history or physical signs of connective tissue laxity should also prompt some consideration of collagen evaluation. If the bleeding is severe and the initial evaluation is negative, evaluation of the fibrinolytic system should be performed.

Hormonal therapy is a frequent and usually effective approach to treating heavy menorrhagia in women and adolescents. That this adolescent is asking for contraception makes this an ideal first-line therapy. The choice of hormonal therapy is made more complicated by the family history of thrombosis and raises the question of thrombophilia screening prior to prescribing contraceptives. The substantially increased risk of venous thromboembolism (VTE) with either thrombophilic risk factor(s) or OCs is synergistically amplified when underlying thrombophilia and OCs are combined. Nevertheless, with a low-baseline VTE risk in young women of 0.8 per 10,000 women years, even a 30-fold risk increase in young women with factor V Leiden on OCs would translate into a very low overall event rate, limiting the cost effectiveness of routine screening prior to initiating OCs.

Furthermore, the psychosocial consequences in adolescents of positive screening for thrombophilia or denial of access to OCs remain unexplored, but are probably significant.

In the absence of an effective predictive screening strategy, alternative approaches include counseling for risk-factor avoidance (especially smoking), intermittent thromboprophylaxis during periods of high thrombosis risk (immobilization, lower extremity injury, surgery), and minimization of risk through the prescription of less thrombogenic OCs. These conservative measures would be warranted for this patient. OC preparations containing low-dose estrogen and a second-generation progestin (levonorgestrel) would be preferred. Although there are limited data on their use in adolescents and women with bleeding disorders, combined hormonal contraception in the form of a ring or patch would likely be equally effective in managing heavy menstrual bleeding, but both the ring and the patch are associated with an increased risk of VTE compared to OCs. An alternative given this patient’s family thrombosis history would be a levonorgestrel-containing intrauterine device (IUD), which has been demonstrated to decrease menstrual blood loss in women with bleeding disorders, but does not increase the risk of VTE. Although this patient is quite young, there are reports of the levonorgestrel IUD’s successful use in controlling menstrual blood flow in adolescents. Hemostasis prophylaxis prior to IUD insertion should be considered in adolescents with severe bleeding disorders. Finally, for those adolescents with a specific bleeding diagnosis who fail gynecologic/hormonal management of heavy menstrual bleeding, hemostatic therapy at the time of menses would be the next step. Oral tranexamic acid is FDA-approved for this indication in adults, but has been used in adolescents as well.

In 2011, the question was posed concerning treatment of heparin-induced thrombocytopenia (HIT) during pregnancy. While there are no new treatment options for this patient, a couple of points are worth making. In terms of treatment, options are actually more limited for the acute setting, as the intravenous direct thrombin inhibitor lepirudin is no longer available. More data on the use of fondaparinux in treatment of HIT have been reported, and this remains a good option for treatment of outpatients and stable inpatients with HIT.13 The major caveats remain its renal clearance and long half-life without a reversal agent.

The patient presented had a history of both pregnancy loss and mesenteric vein thrombosis (MVT) during her prior pregnancy. The indication for anticoagulation in this pregnancy was the history of MVT. Since 2011, more data have been published showing that anticoagulation does not prevent pregnancy loss.13,14 The evidence is strong in women without documented thrombophilia. In women with thrombophilia, we await the results of an ongoing clinical trial; however, based on current data, if there is an effect on pregnancy loss, it is small.

While we have more oral anticoagulant options than in 2011, they remain without indication in pregnancy and, depending on the drug, animal data have demonstrated pregnancy loss and fetal harm.15 Dahigabrant crosses the placenta, and given that the other drugs are small molecules, they also would be expected to cross the placenta. Excretion in breast milk is unknown. There are accumulating data reported in women with some exposure during pregnancy,16 but they are not sufficient to assess safety, and thus these drugs (dabigatran, rivaroxaban, apixaban, edoxaban) should not be initiated during pregnancy.

My Response

HIT is uncommon during pregnancy. In a retrospective cohort study of 488 heparin-treated women (244 pregnant), there were no cases of HIT in the 10 pregnant women who became thrombocytopenic, but 10 cases in the 26 thrombocytopenic non-pregnant women.1 A study of 31 pregnant women receiving LMWH found that none were positive for anti-heparin/PF4 antibodies or developed antibodies when followed prospectively throughout their pregnancies.2 However, case reports and clinical experience document the occurrence of HIT with and without thrombosis during pregnancy. Although HIT may be less common in patients treated with LMWH versus unfractionated heparin (UFH), it can occur and must be considered in pregnant women receiving LMWH who have a > 50 percent decrease in the platelet count.

In choosing an anticoagulant for a pregnant woman with HIT, one has to consider the effects on both the woman and the fetus. Concerns with anticoagulants that cross the placenta include teratogenicity and bleeding. Data are limited and mostly reflect predictions based on drug characteristics and/or animal studies. Danaparoid, the drug with which there is the most experience in pregnancy, is unavailable in the United States. Fondaparinux, argatroban, and lepirudin have been reported in treatment of pregnant women with HIT.1,3 All are FDA Class B, indicating that animal studies have not shown harm in pregnancy, but there are no data from human studies. Outside the setting of pregnancy, fondaparinux, unlike argatroban and lepirudin, is not FDA-approved for HIT, but there are reports of its use in this setting.5 Patients who receive this drug may develop anti-anti-heparin/PF4 antibodies, but it is not clear that these are associated with the development of HIT.

Fondaparinux is a pentasaccharide that, with antithrombin, inhibits factor Xa. An advantage of this drug is its long half-life (~17 hrs.) allowing once-daily dosing. Disadvantages include managing a drug with a long half-life around delivery. Also, the drug has been detected in cord blood at concentrations unlikely to cause bleeding,6 and no adverse outcomes have been reported in infants. The short-acting direct thrombin inhibitors (DTI) argatroban, lepirudin, and bivalirudin require intravenous administration. Successful short-term use of argatroban and lepirudin has been reported in pregnant women with HIT.7 Based on their pharmacokinetic properties, little or no drug would be expected to cross the placenta, although one study showed minor transplacental passage of lepirudin.8

The patient presented above has a history of MVT in her prior pregnancy. Pregnancy is a known risk factor for splanchic bed thrombosis, and, in women with such a history, it is appropriate to provide at least prophylactic anticoagulation during subsequent pregnancies. The decision to test for additional conditions should be based on clinical and laboratory indicators of underlying disease. We would check a platelet count remotely from pregnancy, because essential thrombocythemia is associated with both pregnancy loss and splanchic bed thrombosis. It is unknown whether the JAK2 V617F mutation is associated with thrombosis in the setting of pregnancy.

When a pregnant woman develops HIT, the heparin should be discontinued; she should be evaluated for thrombosis by vascular ultrasound studies, and, unless contraindicated, alternative anticoagulation should be initiated. This patient needs continued anticoagulation because of the history of mesenteric vein thrombosis and her increased risk of thrombosis in the setting of HIT. As in non-pregnant patients, warfarin should be started in the setting of acute HIT. The patient could be transitioned to warfarin later after the acute HIT resolves. Teratogenic effects have not been demonstrated when warfarin is ingested after 12 weeks gestation; however, it does cross the placenta and complications related to fetal hemorrhage have been reported. Two new oral anticoagulants, dabigatran and rivaroxaban, will not be useful alternatives, as both demonstrated reproductive toxicity and excretion in breast milk in animals.9

Given the need for continued outpatient anticoagulation, it is reasonable to switch her to fondaparinux, recognizing the need to discontinue the drug in anticipation of labor given its long half-life. In a patient on prophylactic therapy without a recent thrombotic event, it may be possible to stop the drug three days prior to scheduled induction or cesarean section.

Dr. Konkle’s spouse has equity ownership in GlaxoSmithKline and Johnson and Johnson.

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Inherited deficiency of factor XI was first described in 1953 as a mild to moderate bleeding disorder. Factor XI deficiency exhibits an autosomal inheritance pattern with a variable clinical penetrance, as described below. It has been described in a wide variety of population groups but is most common in Ashkenazi Jews. In this particular group, it is estimated that one in eight individuals are heterozygous and one in 190 are homozygous for mutations in the factor XI gene.\(^1\)

Spontaneous bleeding, except for menorrhagia, is uncommon in patients with factor XI deficiency. Most bleeding episodes occur following surgical procedures or trauma. In contrast to patients with hemophilia A or B, the correlation between clinical bleeding and the baseline factor XI clotting activity is poor. For example, some patients with severe factor XI deficiency (factor XI level ≤ 10-20 IU/dL) exhibit no increase in hemorrhage, whereas other individuals with levels that are only moderately below the lower limit of the normal range develop bleeding complications after surgery.\(^5\)

Rates of hemorrhagic complication have also been shown to vary depending on the type of surgery being performed.\(^1\) In particular, procedures involving sites with increased local fibrinolytic activity, such as the oral mucosa, nose, and genitourinary tract, are more frequently associated with excessive bleeding compared to procedures involving tissues not expressing fibrinolytic activity, such as bones or muscles. This study included six patients who underwent trauma surgery and one total knee replacement, but none of the patients underwent an arthroscopic procedure. The implication from these observations is that conservative use of replacement therapy in patients with even severe factor XI deficiency undergoing certain types of surgery is possible.\(^6\)

Management of bleeding episodes and prevention of bleeding in relation to surgery is not straightforward and needs to be tailored to the individual patient.\(^1\) In many patients with factor XI deficiency, antifibrinolytic therapy alone may be sufficient to prevent bleeding in most surgical settings. Factor XI levels can be raised with fresh frozen plasma, but relatively large volumes may be required. The hemostatic level of factor XI activity to target is debated, but a level of 30 to 45 IU/dL is probably sufficient in patients with severe deficiency.\(^7\) Factor XI concentrates have been associated with an increased thrombotic risk in certain patients and are not available in the United States.\(^8\)

Good hemostasis helps to maintain arthroscopic visual clarity during surgery and is essential for the successful completion of the procedure. A variety of strategies have been used to control arthroscopic bleeding, including using electrocautery or a radiofrequency thermal probe, adding epinephrine to the inflow irrigation solution or increasing the irrigation fluid inflow pressure, and applying direct pressure via the shaver blade.\(^7\)

Relatively limited information is available describing therapeutic arthroscopy of the shoulder in patients with clotting disorders. A single case series describing the management and outcomes of five patients undergoing a total of six shoulder arthroscopic procedures included one patient with a mild factor XI deficiency (baseline level of 60 IU/dL) who underwent arthroscopic subacromial decompression.\(^7\) This patient was treated with a combination of intravenous and oral tranexamic acid without any bleeding complications.

Although shoulder arthroscopy is performed in a tissue not considered to have high fibrinolytic activity, the impact of even a minimal increase in bleeding during a surgical procedure in an enclosed space can be significant. The severely decreased factor XI activity level in this patient, and the fact that he had previously required antifibrinolytic therapy for periodontal surgery, are concerning for an increased bleeding risk. Consequently, it was recommended that the patient receive fresh frozen plasma to supplement the factor XI level prior to the procedure. Post-operatively, depending on the factor XI activity levels and clinical outcome of the procedure, additional fresh frozen plasma could be administered or antifibrinolytic therapy could be substituted instead.


Dr. Ortel indicated no relevant conflicts of interest.
In an article written for The Hematologist in 2011, I reviewed the results of several small series and population-based analyses that assessed the risk for thromboembolism in patients with immune thrombocytopenia (ITP). I concluded that "these studies provide evidence that the incidence of thromboembolism is increased in patients with ITP, even in the presence of very low platelet counts." Since that time, there has been no evidence presented to suggest that this conclusion is not accurate. Indeed, several additional analyses involving large numbers of patients with ITP support the conclusion that ITP is indeed associated with a small, but significant risk of thromboembolism.1,2

The management of thrombosis in thrombocytopenic patients with ITP is challenging and not addressed by current guidelines. Likewise, there are no evidence-based data on which to draw from recent studies. Most experts believe that thrombosis should be considered in the differential diagnosis of any patient with ITP who presents with signs or symptoms of intravascular coagulation or embolic events. The decision to perform a bone marrow aspirate and biopsy should be based on the presence of young, highly functional platelets, increased levels of plasma microparticles, or other factors. Surprisingly, recent studies have also demonstrated that patients with ITP have an increased risk of thrombosis. How often do you see ITP with pulmonary embolism (PE) and deep-vein thrombosis (DVT)? The data concerning ITP and thrombosis are derived from for recommendations. Many experts suggest that the risk of anticoagulation is acceptable for treatment of other significant thrombotic risk factors.

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Dr. McCrae indicated no relevant conflicts of interest.
The Question

How do you manage a patient with HIT being treated with argatroban who has persistent thrombocytopenia? The patient is a 45-year-old man with laboratory evidence of HIT (positive serotonin release assay) without thrombosis who has been treated with argatroban for 10 days. The platelet count was 52,000 per microliter at the time of diagnosis and increased to 95,000 per microliter during the first five days of therapy. However, over the past five days, no significant increase in the platelet count has been observed.

- Is there a platelet threshold at which you recommend starting warfarin? If so, what evidence supports that determination? Would your recommendation change if the patient had HIT?
- If the recommended platelet threshold is not reached, is there a point at which you feel it is safe to start treatment with warfarin? For example, in a patient who has been on argatroban for 10 days, is it acceptable to start warfarin even though his platelet count is less than 100,000 per microliter? Would your recommendation change if the patient had HIT?
- Does fondaparinux play a role in management of HIT in this setting?
- Is there a role for the new oral anticoagulants (dabigatran and rivaroxaban) in this setting?

My Response

HIT is a clinical-pathological syndrome that is typically characterized by the onset of thrombocytopenia (>50% fall from baseline) within five to 10 days of drug initiation. The mean platelet count in patients with this disorder is 60,000 per microliter. Thrombosis occurs in approximately 50 percent of patients and clusters in the first few days following onset of thrombocytopenia (termed HITT). It is mediated by antibodies against platelet factor 4 (PF4)-heparin complexes that activate platelets leading to excessive thrombin generation. Prompt recognition and appropriate treatment of HIT is required to reduce the risk of serious thrombotic events and complications including limb loss. Paradoxically, a major problem with HIT today is its under-diagnosis. Enzyme immunosassay (ELAs) for antibodies against PF4-heparin complexes are currently widely applied for making the diagnosis of HIT; while highly sensitive (>-95%), only some antibodies have strong platelet-activating properties in the serotonin-release assay, one of the “gold standard” platelet-activation assays used for diagnostic confirmation. As results of serotonin release assays are rarely available for clinical decision making early in the course of HIT, it is best not to order ELISA tests in patients with low pretest probability scores for HIT (4T score: Thrombocytopenia, Timing of platelet count fall, Thrombosis, Other causes of thrombocytopenia). Also, many labs do not report the optical densities (OD) of positive ELAs; in such instances, it is useful to request this information, as it can be useful diagnostically since the strength of a positive ELA (OD) predicts for a positive SRA.

After stopping heparin administration in patients with HIT, the median time to achieving platelet recovery or 21 days if there was acute thrombosis at study entry; this was followed by 20 mg daily. Among the 12 patients who proved to be HIT-positive, six had HIT with thrombosis (HITT) at study entry. Platelet recovery was seen in nine of 10 with thrombocytopenia; new thrombosis occurred in one, and one required limb amputation despite platelet recovery. This and other case reports suggest that direct oral anticoagulants such as rivaroxaban are effective in treating HIT.

The initiation of warfarin causes a rapid decline in protein C levels and a slower decline in the levels of longer-lived vitamin K-procoagulant factors (especially prothrombin) augmenting the preexistent hypercoagulable state due to HIT. This mechanism is contributory to the development of venous limb gangrene, which is estimated to occur in 12 percent of patients with HIT; its frequency is likely less in patients with isolated HIT. Fondaparinux, a synthetic pentasaccharide that selectively inhibits factor Xa after binding to its target, has been shown to have an attractive profile for the treatment of HIT based on in vitro studies; it is administered subcutaneously once daily. Small case series indicate generally favorable outcomes with initial use of this agent in HIT; in a recent retrospective series of 16 patients with the diagnosis confirmed by serotonin-release assay, nine of whom had thrombosis, none developed new or recurrent thrombosis. However, fondaparinux is not approved for this indication; it is approved in the United States for the prophylaxis of VTE following major orthopedic and general surgery and the initial treatment of VTE.

If the continuation of argatroban is the only reason for continued hospitalization, I would employ fondaparinux alone at this juncture provided the patient could self-inject the medication and drug acquisition was not a problem (i.e., inability to gain insurance approval or prohibitive out-of-pocket cost). The total duration of anticoagulant treatment has not been defined by prospective studies, but I would treat isolated HIT for a minimum of six weeks given the high risk of thrombosis within the first 30 days after diagnosis. The use of fondaparinux to complete treatment would obviate the use of warfarin entirely and the burden of INR monitoring with attendant dose adjustments. Alternatively, warfarin could be initiated after the platelet count had risen to more than 150,000 per microliter under the cover of fondaparinux overlap for a minimum of five days until the INR reached the target range of 2-3. This would also circumvent complexities relating to INR monitoring during argatroban therapy if this option were chosen.

For patients with HIT, I would treat with anticoagulation for three to six months.

It should be pointed out that the efficacy of non-heparin anticoagulants for HIT and their approval by the U.S. FDA was not based on prospective, randomized controlled clinical trials. Vitamin K antagonists have been used for the treatment of HIT for many years and adopted by evidence-based guidelines after initial treatment with a non-heparin anticoagulant, as they have up until recently been the only class of oral anticoagulants available. Based on our mechanistic understanding of venous-induced limb gangrene in HIT, a strong case can be made that we should be moving away from using warfarin in the initial phase of HIT (and HIT) treatment (up until 30 days after diagnosis) given that alternative oral anticoagulants that do not lower protein C levels are available.

These oral agents selectively target thrombin or factor Xa, have a rapid onset of action, and do not require coagulation monitoring; however, there is not yet any reported experience with these agents in this patient population, and they have no specific antidote. Dalteparin and rivaroxaban have gained FDA approval for stroke prevention in atrial fibrillation and rivaroxaban is
approved for the prophylaxis of VTE following total hip or knee replacement; they have shown promising results for the treatment of symptomatic VTE but have not yet been approved for this indication in the United States. Thus, caution should be exercised if either dabigatran or rivaroxaban is used in a patient such as this; if chosen, they should be used at therapeutic doses and limited to adult patients with satisfactory renal function (creatinine clearance > 30 mL/min). Furthermore, given that HIT can result in serious complications including limb loss and subsequent litigation against health-care providers, hematologists choosing to use any of the new anticoagulants (dabigatran, rivaroxaban, or fondaparinux) should carefully document in the medical record their rationale for choosing the new agent.

Both the infrequent occurrence of HIT confirmed by validated platelet-activation assays and the clinical heterogeneity of affected patients make it difficult to perform trials of new agents in HIT. It is therefore unlikely that the new oral anticoagulants will be studied in controlled trials so as to gain FDA approval for management of this disorder in the near future. Hopefully, the reporting of well-characterized cohorts of patients with HIT (or HITT) treated with these agents will lead to favorable outcomes that will improve, as well as simplify, management of this disorder.


Dr. Bauer has served as a consultant to GSK, Bayer Healthcare, and Johnson & Johnson.

The Hematologist Video Series

A new video series for The Hematologist titled “Conversations with Innovators” is available on YouTube; it features three videos by Dr. Omar Abdel-Wahab from Memorial Sloan Kettering Cancer Center, Dr. Neal Young from the National Heart, Lung, and Blood Institute at the National Institutes of Health (NIH), and Dr. Ann Mullally from the Brigham and Women’s Hospital and the Dana-Farber Cancer Institute. Dr. Abdel-Wahab discusses his lab’s efforts to understand the biology of mutations in components of the spliceosome with the goal of using them as therapeutic targets in the treatment of leukemias. Dr. Young covers his lab’s investigation of an improved treatment protocol for aplastic anemia involving immunosuppressive therapy in combination with eltrombopag. In the third video, Dr. Mullally talks about her lab’s study of mutant calreticulin in patients with myeloproliferative neoplasms. To watch all three videos and for more to come soon, visit www.youtube.com/ASHwebmaster under the playlist titled “The Hematologist: Conversations with Innovators.”
Approach to the Diagnosis and Management of the Anemia of Chronic Inflammation – March/April 2013

Since the publication of this “Ask the Hematologist” article, the role of inflammation in reduced renal erythropoietin (EPO) production has been better defined. With inflammation, renal EPO-producing fibroblasts have increased transforming growth factor-β1 (TGF-β1) and NFκB expressions that mediate their transformation to myofibroblasts, which no longer produce EPO.1-3 The potential restoration of EPO production in these cells by inhibition of specific hypoxic-inducible factor (HIF) prolylhydroxylases suggests a potential treatment for some patients with anemia of chronic inflammation (ACI).1,3-5 In a study of patients with unexplained anemia of the elderly (UAU) and age-matched normal controls, increases in serum ferritin and decreases in serum iron as well as increases in neopterin, a product of activated macrophages, correlated with the degree of anemia.1-3 Compared to controls, the UAE group had decreased renal function and similar EPO levels despite decreased hematoglobin values, suggesting that they had the restricted iron flux and decreased EPO found in ACI.

Introduction

ACI can be caused by many chronic inflammatory or infectious diseases, such as those shown in Table 1. These diseases are the result of a pathologic overproduction of inflammatory cytokines such as IL-6, TNF-α, and interferon-γ that directly inhibit the survival and differentiation of erythroid progenitor cells.1,4 Inflammatory cytokines suppress EPO production, decreasing plasma EPO concentration and increasing anemia of erythroid cells in the EPO-dependent stages of differentiation (Figure).5 Finally, the inflammatory cytokines IL-6 and members of the bone morphogenetic protein (BMP) family diminish serum iron concentration by inducing transcription of hepcidin, the master regulator of iron homeostasis.6 Hepcidin exerts its effects primarily through interaction with the cellular iron exporter, ferroportin, expressed on the basolateral surface of enterocytes and on reticuloendothelial cells. Binding to hepcidin induces endocytosis and degradation of ferroportin thereby restricting gastrointestinal iron absorption and impairing macrophage export and recycling of iron from phagocytosed senescent erythrocytes. The trapping of iron in reticuloendothelial cells accounts for the characteristic iron-laden macrophages observed in ACI bone marrow aspirates stained with Prussian blue. Because iron absorption and iron recycling are impaired, plasma iron concentration is low, and transferrin saturation is often subnormal (as in our case), resulting in a functional iron deficiency state with consequent suboptimal delivery of iron to maturing erythrocytes. Interpretation of transferrin saturation must also take into account the fact that transferrin is a negative acute phase reactant, and as such, the serum concentration is often subnormal or at the lower end of the normal range in patients with ACI (as illustrated in our case).

Diagnostic considerations

In most instances, ACI is normocytic, normochromic, but approximately one-third of cases fall into the microscopic, hypochromic morphological classification. In the latter cases, functional iron deficiency as a consequence of excess hepcidin production dominates the pathophysiology, and review of the peripheral blood film reveals features similar to other processes, such as iron deficiency or thalassemia, that affect production of heme or globin. ACI is typically a mild-to-moderate hypoproliferative process manifested as grade I or grade II anemia. If more severe, (grade III or worse, hemoglobin < 8.0 g/dL), the anemia is likely multifactorial with other processes, such as concurrent gastrointestinal bleeding contributing to the etiology. Blood loss and inflammation may coexist, especially in patients with renal failure on hemodialysis, in patients with gastrointestinal malignancy or inflammation, or in patients with arthritis treated with corticosteroids or non-steroidal anti-inflammatory drugs. In those cases, determining the relative contributions of absolute iron deficiency and functional iron deficiency can be challenging without performing a bone marrow analysis.
Serum ferritin concentration is less than 20 ng/mL in uncomplicated iron deficiency anemia. Although an as an acute-phase protein, the ferritin concentration can be driven into the normal range by the underlying inflammatory process, a ferritin concentration greater than 150 ng/mL is rare in ACI patients who have concomitant absolute iron deficiency. As noted above, low serum iron is characteristic of ACI, and low serum transferrin concentration and low transferrin saturation are also observed routinely in ACI.

Transferrin receptor (TfR) expression is regulated post-transcriptionally by intracellular iron concentration through the iron regulatory element (IRE)/IRE binding protein (IREBP) system. When intracellular iron concentration is low, the IRE/IREBP binding system stabilizes TfR mRNA, thereby increasing translation and protein expression. The effect of intracellular iron concentration on TfR production led to development of a clinical test of iron status. In this case, the concentration of TfR in plasma (soluble TfR or sTfR) serves as a surrogate marker of iron status (i.e., the concentration of sTfR is elevated in absolute iron deficiency). Subsequent studies suggested that the sensitivity of the assay in distinguishing absolute iron deficient states from inflammatory processes that affect iron metabolism can be improved by calculating the sTfR index by dividing the sTfR concentration by the log of the serum ferritin concentration. Another proposed method for identifying iron deficiency is to measure reticulocyte hemoglobin concentration (CHr) by flow cytometry. As the most recently produced 1 percent of erythrocytes in the blood, the reticulocytes are the subpopulation most affected by iron deficiency at the time the blood sample is obtained, and decreased CHr is a sensitive indicator of iron-restricted erythropoiesis. Combining CHr with sTfR index has been used to improve the identification of absolute iron deficiency in patients with inflammation.

While these studies may have value in some particularly problematic cases, their clinical utility is relatively modest. This interpretation is based on the fact that functional iron deficiency plays an important role in the pathophysiology of ACI, and patients with functional iron deficiency, without absolute iron deficiency, may benefit from supplemental iron. Therefore, the practical value of distinguishing functional iron deficiency from absolute iron deficiency is arguable because iron supplementation can be therapeutic in either case.

Treatment

Although many patients have mild anemia that does not require treatment, establishing a diagnosis of ACI is important as doing so implies an ongoing inflammatory process, the etiology of which should be investigated. Furthermore, effective treatment of the underlying disease results in improvement or resolution of the anemia. In some instances, however, the underlying disease may be resistant to therapy (e.g., poorly responsive malignancy or refractory connective tissue disease). In such cases, red cell transfusion support and therapy that targets the pathophysiologic mechanisms that underlie ACI (Figure) are the mainstays of management. ACI may respond to recombinant human EPO (rhEPO), but the response may be blunted by concomitant functional iron deficiency. Iron supplementation, with a goal of transferrin saturation of > 20 percent, may increase the effectiveness of rhEPO, and some patients respond to iron supplementation in the absence of rhEPO support. Infused iron rather than oral iron supplementation is often needed as hepcidin restricts gastrointestinal iron absorption. The desired response (increase in transferrin saturation) to iron supplementation, however, is relatively modest, and repeated iron infusion puts patients at risk for iatrogenic hemochromatosis because the high hepcidin prevents the recycling of this iron. Anti-TNF-α agents have been shown to increase hemoglobin concentration in patients with ACI independent of an effect on EPO concentration. Looking forward, suppression of hepcidin activity has been examined in animal models. In a mouse model of ACI, antibodies to hepcidin also required the concurrent administration of EPO to reverse the anemia, whereas inhibition of hepcidin transcription, by blocking BMP receptor activation or downstream signaling, prevented and reversed ACI without the need for exogenous EPO administration. As more therapeutic options become available, well-designed clinical studies will be needed to determine the optimal pharmacologic approach to the management of ACI.
The Question

What is your approach to the diagnosis and management of transfusion-related acute lung injury (TRALI)?

Our Response

Epidemiology

The blood supply in the United States is safe. Although non-life-threatening adverse events such as allergic and febrile transfusion reactions are encountered regularly by clinicians, transfusion-related fatalities are rare. From 2007 through 2011, 212 fatalities following blood collection and transfusion were reported to the FDA. Non-infectious complications pose the greatest mortality risk to the transfused patient with TRALI accounting for 43 percent of deaths and hemolytic transfusion reactions due to ABO (18%) and non-ABO (13%) incompatibility accounting for 23 percent. In comparison, 11 percent of transfusion-related deaths were due to microbial infections. Although usually associated with infusion of blood products containing high volumes of plasma (e.g., fresh-frozen plasma and platelets), TRALI has also been linked to red cell blood transfusions. Estimates of the incidence of TRALI may be influenced by factors such as transfusion policy. For example, the incidence fell from 2.57 to 0.81 per 10,000 transfusions concurrent with the reduction in the use of plasma from female donors.

Clinical Presentation and Diagnosis

The diagnosis of TRALI is made on clinical grounds, and no single laboratory or radiologic test definitively identifies or excludes this entity. We currently use the criteria and case definitions proposed by a Canadian Consensus Conference (Table). Thus, TRALI is an acute event presenting during a transfusion or within six hours of its completion. Characteristic signs and symptoms include fever, chills, dyspnea, hypoxemia, hypotension (or possible transient hypertension), and the new onset of bilateral non-cardiogenic pulmonary edema (e.g., chest x-ray showing bilateral alveolar and interstitial infiltrates in the absence of cardiomyopathy). TRALI is often associated with transient leukopenia or neutropenia. A diagnosis of “Possible TRALI” is made based on the same criteria as TRALI except that an alternative risk factor for acute lung injury is present concurrently (Table).

The differential diagnosis of TRALI includes the following: transfusion-associated circulatory overload (TACO), anaphylaxis, and sepsis. Distinguishing TACO from TRALI may be challenging because some of the signs and symptoms of the two entities overlap; in addition, the two processes can occur concurrently in a given patient. The key difference between these two conditions is the pathophysiologic origin of the pulmonary edema (i.e., cardiogenic in the case of TACO and non-cardiogenic in the case of TRALI). Thus, clinical improvement after treatment with a diuretic and/or an inotropic agent is characteristic of TACO, but not TRALI. Other findings suggestive of TACO include persistent hypertension, a post-transfusion brain natriuretic peptide (BNP) level of at least 100 pg/mL, and a post-transfusion pre-transfusion BNP ratio of >1.5. Although anaphylaxis can present with hypotension, cyanosis, and hypoxia due to bronchospasm and laryngeal edema, the absence of fever and pulmonary edema distinguish this process from TRALI. Although transfusion-induced sepsis, particularly after a platelet transfusion, typically presents with pyrexia and hypotension, respiratory distress is an infrequent complication. Other entities, such as myocardial infarction, pulmonary embolism, and other causes of acute lung injury share clinical features with TRALI and should be considered in the differential diagnosis.

The diagnosis of TRALI is particularly challenging in complex inpatients such as those encountered in the intensive care unit setting, given that such patients often have multiple medical problems and may exhibit some symptoms of TACO even before transfusion.

Pathophysiology

Although the exact mechanism of TRALI is uncertain, a “two-hit” process has been proposed. According to this hypothesis, the first “hit” is induced by an underlying condition, such as trauma or sepsis, which primes granulocytes and/or activates endothelial cells, thereby causing neutrophils to become sequestered in the pulmonary vasculature. The second “hit” results from passive infusion of donor antibodies in the blood product that recognize either human leukocyte antigens (HLA) on recipient endothelial cells or human neutrophil antigens (HNA) on recipient neutrophils. Alternatively (or in addition), infusion of biologic response modifiers (e.g., CD40 ligand) in the plasma portion of the donor product could induce the second hit. Together, these processes induce capillary endothelial damage, resulting in vascular permeability and pulmonary edema.

Based on this proposed mechanism, one might hypothesize that the incidence of TRALI would be higher for plasma-rich transfusion products and that the incidence would be lower when plasma derived from female donors (who have a higher prevalence of anti-HLA antibodies) is restricted; available data support these two hypotheses. In addition, recent studies indicate that circulating platelets are involved in TRALI pathophysiology, suggesting that anti-platelet therapy may be beneficial clinically.

Management

The first step in managing any suspected transfusion reaction is to stop the transfusion. Once the patient is stabilized, the episode should be reported to the transfusion medicine service so that a transfusion reaction evaluation can begin. Because hemolytic transfusion reactions are associated with significant morbidity and mortality, the transfusion medicine service will first perform a “clerical check” to ensure that the correct unit was transfused into the correct patient. Next, the ABO type of the patient and the transfused unit will be confirmed, the post-transfusion blood sample will be inspected for visible evidence of hemolysis, and an indirect and direct anti-globulin test will be performed on the post-transfusion sample to determine if circulating and/or red blood cell-bound antibodies are present. Additional laboratory tests to investigate for hemolysis, including a complete blood count, urinalysis, and plasma concentration of bilirubin, lactate dehydrogenase, and haptoglobin, are often needed. To diagnose TRALI, physical exam, chest x-ray, and arterial blood gas studies are recommended. In distinguishing TRALI from TACO, an echocardiogram may be useful in determining whether the observed pulmonary edema is of cardiogenic origin. Other causes of adverse events that share clinical features with TRALI (e.g., sepsis, myocardial infarction, and pulmonary embolus) should be promptly investigated.

Current management of TRALI consists of respiratory and circulatory support based on clinical severity. Oxygen supplementation is required in almost all patients; in severe cases, mechanical ventilation may be necessary. Hypotensive episodes can be treated with pressors. Corticosteroid treatment has not improved outcome. In theory, the non-cardiogenic pulmonary edema of TRALI should not respond to diuretics. Most patients improve within two to three days, but those who do not improve over this period typically have a protracted clinical course or a fatal outcome.

Patients who have experienced an episode of TRALI are not at greater risk for a second episode, assuming that the initial event was a consequence of infusion of donor antibodies that were present in the transfusion product and that subsequent blood products do not

Table 1: Canadian Consensus Conference on the Definition of TRALI

| TRALI: | 
| --- | --- |
| 1) Acute lung injury | 1) Acute lung injury |
| a. Acute onset | a. Acute lung injury |
| b. Hypoxemia | 2) No pre-existing acute lung injury prior to transfusion |
| i. Research setting: PaO2/FIO2 < 300 and/or SpO2 < 90% on room air | 3) During or within 6 hours of transfusion |
| ii. Non-research setting: PaO2/FIO2 < 300 and/or SpO2 < 90% on room air and/or other clinical symptoms of hypoxia | 4) No temporal relationship to an alternative risk factor for acute lung injury |
| c. Bilateral infiltrates on frontal chest x-ray | Possible TRALI: |
| d. No evidence of left atrial hypertension (i.e., no circulatory overload) | 1) Acute lung injury |
| 2) No pre-existing acute lung injury before transfusion | 2) No pre-existing acute lung injury prior to transfusion |
| 3) During or within 6 hours of transfusion | 3) During or within 6 hours of transfusion |
come from the initial donor. However, notification of the transfusion medicine service about a possible TRALI episode has important implications for the donor and the safety of the blood supply. If TRALI is suggested by both clinical presentation and laboratory results (e.g., finding anti-HLA and/or anti-HNA antibodies in the transfused blood product that match the corresponding antigens in the patient), the donor must be evaluated for consideration of their continued eligibility to donate. Indeed, many centers choose to exclude such donors permanently. That the product from a particular donor caused an episode of TRALI may be difficult to prove unequivocally, however, because patients often receive products from multiple donors.

Prevention

Approaches to reducing the risk of TRALI have included avoiding the use of plasma from female donors, using plasma derived only from males or from never-pregnant females, and testing female donors for anti-HLA antibodies. Although these measures reduce the incidence, they do not completely eliminate risk because TRALI can be induced by other blood products (e.g., red blood cells, platelet concentrates, cryoprecipitate). In addition to avoiding the use of high-risk blood products, conservative transfusion strategies and interventions that address the “first hit” could also help reduce TRALI incidence. Nonetheless, TRALI continues to be the most common cause of transfusion-related mortality, making rapid recognition and institution of appropriate supportive care imperative.


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The author has indicated that there has been no update regarding the content of this article since the original publication date in 2013.

The Question
What criteria do you use for selecting patients with sickle cell anemia (SCA) for allogeneic hematopoietic stem cell transplantation (HSCT)?

My Response
About 40 years ago, only half of the children born with SCA in the United States were expected to live long enough to reach adulthood. Now, however, as a result of the high quality of care available in comprehensive sickle cell centers, disease-related morbidity and mortality during childhood has been reduced to 1 to 2 percent.1,2 This remarkable improvement in survival stems mainly from interventions aimed at preventing early deaths from infection and splenic sequestration, as well as the greater use of disease-modifying therapies (e.g., hydroxyurea and chronic transfusions). No current U.S. statistics are available, but in a study published in 2001, the median lifespan for individuals with SCA in a Jamaican cohort was estimated to be more than 50 years.3 Not reflected in these improving survival data, however, is the burden of SCA-related chronic organ injury acquired in early childhood that becomes especially manifest in young adulthood, adversely affecting the quality and duration of the remaining life of the patient. The burden of morbidity and mortality in SCA has now simply shifted to adults, and the period after transition to adult medical care is associated with a particularly high risk of death, especially from acute chest syndrome and multi-organ failure syndrome.4

HSCT is the only available cure for SCA, and more than 500 transplants for SCA have been reported to international registries. Although usually successful and curative, the widespread use of HSCT is still limited by the lack of sufficient suitable donors and concerns about regimen-related morbidity and mortality. HSCT is safest when an HLA-matched sibling donor is available, but only about 10 percent of transplant candidates will actually have such a donor. Current estimates place regimen-related mortality for myeloablative transplantation using an HLA-matched sibling donor at about 5 percent, with a concomitant 9 percent risk of graft rejection and a 15 percent risk of chronic graft-versus-host disease (GVHD) (Table).5,6 There are additional late effects of transplantation not tabulated here, including infertility, endocrinopathies, premature cardiovascular disease, and possibly cancer. One can argue that SCA-related mortality during childhood (in patients cared for in comprehensive centers in developed nations) is now lower than the regimen-related mortality of HSCT, but this comparison does not integrate the lifelong risk of progressive morbidity, impaired quality of life, and early mortality due to SCA. Of course, there is no randomized comparison of transplantation versus no transplantation that accurately quantiles the relative lifetime risks of morbidity and mortality from SCA and HSCT, but life after a successful transplant — the event-free survival (EFS) of a full-sibling-donor myeloablative HSCT is approaching 90 percent (Table) — is arguably better than a life with SCA. An important caveat, however, is that the definition of EFS differs by study and often does not include chronic GVHD, which may be worse than SCA, so EFS rates that are meaningful to patients are usually lower than reported (70-80% vs. 90%, respectively).

Expert panels and professional societies provide differing sets of clinical indications for HSCT as a treatment option for SCA, but common recommendations include recurrent vaso-occlusive complications (acute chest syndrome and painful events), usually despite hydroxyurea therapy, and overt cerebrovascular disease. Other indications have been proposed and used, such as abnormal transcranial Doppler velocities and silent cerebral infarction, despite much less agreement among experts and very limited data. Some hematologists now also advocate that a diagnosis of SCA itself is an indication for HSCT, justifying a discussion of transplantation indications of SCA are often unpredictable, and many individuals with SCA will have progressively severe morbidity and early mortality. In my clinical practice, I do not compare a fixed list of indications for HSCT with an ongoing tabulation of the number and type of SCA-related complications experienced by the patient. Rather, I initiate (or continue) the discussion of HSCT in three main clinical scenarios.

The first usual scenario is planned. I ensure that all patients with SCA and their parents know about the possibility of cure by HSCT. I include discussion of the option of HSCT as part of the comprehensive, ongoing education about SCA starting with the very first visit after diagnosis (usually the result of newborn screening). I also recommend tissue typing of all unaffected full siblings, including those with sickle trait, to know if there is an HLA-matched donor. If there is a matched-sibling donor, I offer dedicated clinical visits for frank discussions about the risks and benefits of myeloablative HSCT compared with life with SCA, as well as the risks and benefits of hydroxyurea therapy and chronic transfusions. If there is continued interest in pursuing HSCT, then I arrange formal counseling with the patient and the SCA team. This multi-step process does not lead to HSCT for most patients, but they are at least aware and knowledgeable about the option, and I support them with decision-making.

The second scenario is a direct inquiry about HSCT by a patient or parent, often times as a result of something heard or read about on the Internet. Recent immigrants from Africa also tend to ask commonly about transplantation.

The third scenario occurs when a patient suffers a particularly serious complication, such as overt stroke. In these instances, I follow the same general process outlined above in counseling patients and their families about HSCT.

In essence, I consider every patient with SCA (here I include both HbSS and sickle-βthalassemia) who has an HLA-matched sibling donor to be a potential candidate for myeloablative HSCT. Honest discussions about the risks, benefits, and alternatives are needed, regardless of the “severity” of a patient’s disease, and the decision to pursue HSCT is a lengthy and patient- and family-centered process. Once a decision to perform HSCT is made, I recommend that it be done during early childhood. My opinions and practices are based upon the assumption that my patient’s HSCT will be performed in a center with substantial experience in transplantation for SCA and, ideally, as part of a clinical research study. The use of alternative donors (unrelated, mismatched, or haploidentical) and stem cell sources (unrelated umbilical cord blood) for children carries a much higher risk of transplant-related morbidity, mortality, and graft rejection and should be performed only as part of a carefully designed investigational study.

Adults with SCA tolerate myeloablative conditioning regimens poorly, likely because of the cumulative burden of chronic organ injury acquired during childhood. However, there is very promising early experience with a non-myeloablative conditioning regimen (including total-body irradiation, alemtuzumab, and sirolimus) in severely affected adults with SCA that can produce stable, mixed donor-recipient chimerism that effectively cures the disease.7 These outcomes have been achieved without chronic GVHD or mortality and with a low rate of graft rejection. The mixed chimerism appears to persist after discontinuation of immunosuppression.8 In the future, adults may no longer be summarily excluded from HSCT. Until then, all transplants in adults should be performed as part of a clinical research study with the indications being dictated by the eligibility criteria of the particular study.

While the experience with adult recipients and alternative donors matures, research needs to focus on reducing transplant-associated morbidity, especially sterility, in young patients undergoing reduced-intensity conditioning regimens. Ongoing studies will continue to expand access to HSCT for both children and adults, and the next “Ask the Hematologist” question on this topic might also include the option of gene therapy.

What criteria do you use for selecting patients with sickle cell anemia (SCA) for allogeneic hematopoietic stem cell transplantation (HSCT)?

Table. International Studies of Myeloablative HSCT for SCA Using Matched-Sibling Donors†§

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<tbody>
<tr>
<td>OSFI</td>
<td>93</td>
<td>94</td>
<td>100</td>
<td>97</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td>RRM</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>7</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>cGVHD</td>
<td>10</td>
<td>9</td>
<td>5</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rejection</td>
<td>20</td>
<td>12</td>
<td>6</td>
<td>13</td>
<td>22</td>
<td>36*</td>
</tr>
<tr>
<td>EFS</td>
<td>82</td>
<td>82</td>
<td>84</td>
<td>86</td>
<td>85</td>
<td>90</td>
</tr>
</tbody>
</table>

*Four of 11 patients had mild, chronic GVHD of the skin that resolved completely after steroid therapy.

†Data compiled from tables in Locatelli et al. and Lucarelli et al.

§Abbreviations: OSFI, overall survival; RRM, regimen-related mortality; cGVHD, chronic graft-versus-host disease; EFS, event-free survival.
Platelet refractoriness remains a clinical challenge associated with an increased risk of bleeding, prolonged hospital stays, and decreased survival. Poor one-hour post-transfusion increments typically represent immune platelet refractoriness, whereas an adequate one-hour increment followed by a suboptimal 18- to 24-hour count suggests peripheral consumption or sequestration. In the absence of a direct prospective comparison of the three strategies commonly used to support patients who have platelet alloimmunization—human leukocyte antigen (HLA) matching, HLA antibody avoidance, and platelet cross-matching—two recent reviews have concluded there is no definitive evidence that any of these strategies improves hemorrhage control or mortality.1,2,3 The provision of HLA-matched platelets can be very efficient in centralized transfusion systems as it has been in the United Kingdom.2,3

Apheresis platelets stored in additive solution, which contain 2/3 less donor plasma, have become available in the United States, with a longer track record in Europe. They are associated with lower platelet increments at one hour, but are less likely to cause allergic transfusion reactions or hemolysis, compared with standard platelets suspended in 100 percent donor plasma.2,3 Platelets that have undergone psoralen-UVA treatment to inactivate bacteria (and other infectious agents) are also known to produce lower post-transfusion increments. These considerations need to be taken into account when evaluating patients who seem to be refractory to platelet transfusion.

What is your approach to the diagnosis and management of platelet alloimmunization?

My Response

Platelet refractoriness occurs in 5 to 15 percent of patients who receive chronic platelet transfusions.1 The patient’s size and the number of platelets transfused should be factored into the assessment of refractoriness. For example, one measure, the corrected count increment (CCI), is computed as follows: CCI = ([platelet increment after transfusion]/pL) x (body surface area in m²) x (platelet dose x 10⁹). For the purposes of this calculation, assume that each single-donor apheresis unit contains 3 x 10¹¹ platelets or that each whole-blood-derived platelet concentrate contains 5.5 x 10¹¹ platelets. Using this formula, the if platelet count increased by 20,000/pL in a patient who had a body surface area of 2.0 m² and who received one apheresis unit of platelets, the CCI is 20,000/pL x 2 ÷ by 3 = 13,333/pL.

Refractoriness is defined as a CCI value below 2,500 platelets/pL at 18 to 24 hours post-transfusion or a value below 4,500 platelets/pL at 10 to 60 minutes post-transfusion4 on two to three consecutive platelet transfusion episodes. A less rigorous approach is to assume that, for an average size, non-refractory adult, the platelet count increment will be at least 10,000/pL at 20,000/pL one hour after the transfusion of either one unit of apheresis platelets or an equivalent dose of pooled platelets (5-6 combined random-donor platelet concentrates are equivalent to 1 apheresis unit), recognizing that the number of platelets per component unit may vary widely.

Non-immune causes of platelet refractoriness predominate.

Non-immune factors are present in the majority (72-88%) of transfusion-refractory patients, and immune causes are present in a minority (25-39%). Non-immune factors, most of which are prevalent in a high proportion of hematologic-oncology patients requiring prolonged platelet transfusion support, include splenomegaly, fever, infection, DIC, bleeding, and drugs such as vancomycin and amphotericin, which are associated with platelet refractoriness.2,3 The mechanism for refractoriness associated with various drugs is partially mediated by drug-dependent platelet antibodies, although specific testing for such is not widely available and unlikely to be of practical help.

Use of fresh ABO-matched platelets can improve post-transfusion response.

Platelets express blood group A and B antigens, but they are often transfused without ABO matching. Major ABO incompatibility (such as group A platelets transfused into a group O recipient) can decrease post-transfusion increments. A trial of fresh ABO-matched platelets can be a valuable temporizing measure while investigation of the basis of platelet transfusion refractoriness is ongoing.

A recent study in an animal model suggests that immune-mediated clearance of MHC mismatched platelets can occur in the absence of antiplatelet alloantibodies, in mice that are deficient in B cells. Allo-reactive CD8+ T cells appear to mediate antibody-independent platelet clearance.4,5,6 If this finding is corroborated in humans, immune platelet refractoriness may actually account for some refractory cases now presumed to be non-immune. A putative T-cell—mediated mechanism would also favor HLA matching over cross-matching as a management strategy.

Antibodies to HLA antigens account for the overwhelming majority of cases of immune platelet refractoriness, with antibodies to platelet-specific antigens being much less common. HLA alloimmunization may occur in response to prior pregnancies or to transfusions, although only a subset of alloimmunized individuals demonstrates immune platelet refractoriness.1,2 The TRAP study7 showed that filtration-removal of leukocytes and ultraviolet B irradiation to inactivate leukocytes were equally effective in the prevention of the development of platelet transfusion refractoriness, which occurred in 16 percent of control patients, compared with 7 to 10 percent of patients who received leuko-reduced or irradiated platelets. On the other hand, HLA antibodies developed in 45 percent of control patients compared with 17 to 21 percent of intervention patients. Outcomes were equivalent for filtered apheresis platelets and for filtered pooled platelets. In Canada, universal prestorage leuko-reduction of platelets has lessened the incidence of alloimmunized platelet refractoriness from 14 to 4 percent.8 Almost all apheresis platelet units and more than 80 percent of packed red blood cell units in the United States are leuko-reduced by filtration either at the time of collection or immediately prior to storage.

Use of irradiated platelets can also improve response.

Strategies to select platelets for refractory patients include HLA-matching, avoidance of known HLA antibody specificities, and platelet cross-matching.

For the purpose of platelet donor selection, a grading system (with designated categories A, B1, B2, C, D) is employed. A perfect four-antigen match (2 loci each at HLA-A and HLA-B) is grade A. In a B1 match, all of the donor’s HLA antigens are present in the recipient, but the donor lacks one of the recipient’s HLA antigens; in a B2-match, all of the donor’s HLA antigens are present in the recipient, but the donor lacks two of the recipient’s HLA antigens.

Strategies to select platelets for refractory patients include HLA-matching, avoidance of known HLA antibody specificities, and platelet cross-matching.
antigens; in a C-match, the donor has one HLA antigen that is not present in the recipient; in a D-match, the donor has more than one HLA antigen that is not present in the recipient. High-grade matched donors (grade A, B1, or B2) are specifically recruited to donate platelets for a particular patient, but transfusion with grade C or D “matched” units is unlikely to produce a clinically meaningful incremental increase in the platelet count. This grading approach to matching also allows for categorization of antigens into cross-reactive groups (CREG). For example, HLA-A1 and A36 are within the same CREG, so if a patient has the A36 antigen and no available donor platelet is A36 positive, then an A1 donor platelet – typically more prevalent in the Caucasian population – can be used in a grade B match. HLA Matchmaker is an epitope-based computer algorithm used in some centers to identify permissible donor platelets that are more likely to yield a high incremental platelet increase without being HLA matched. Despite the resources invested in the management of patients who are refractory to platelet transfusion, a recent review of the literature identified no studies that were adequately powered to detect an effect of transfusion of HLA-matched platelets on mortality or hemorrhage. Prospective studies utilizing current technology and examining clinical outcomes are needed to evaluate the effectiveness of HLA-matched platelet transfusion.

<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
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</thead>
<tbody>
<tr>
<td>HLA-matched platelets</td>
<td>HLA type may already be on file for allogeneic SCT candidates</td>
<td>Testing takes up to 1 week to complete.</td>
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<tr>
<td></td>
<td>One-time test per patient</td>
<td></td>
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<tr>
<td></td>
<td>Some haplotypes are relatively common such as A1 BB in Caucasians.</td>
<td>Perfect matches are rare.</td>
</tr>
<tr>
<td></td>
<td>Grade B matches or HLA Matchmaker increase the number of donor possibilities.</td>
<td></td>
</tr>
<tr>
<td>Avoidance of known HLA-antibody specificities</td>
<td>Many more donor possibilities compared with HLA matching.</td>
<td>Antibody testing takes several days.</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>Platelet cross-matching</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Testing takes several hours</td>
<td>Testing is repeated for each platelet search, labor-intensitive unless automated.</td>
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<tr>
<td></td>
<td>Applicable to apheresis or pooled whole-blood-derived platelets</td>
<td>Commercial kits have been temporarily unavailable in the United States.</td>
</tr>
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</table>

For management of the transfusion-refractory patient, available data argue that selection of donors with HLA antigens against which the recipient does not have antibodies is a better strategy than HLA matching. In one observational study involving 29 refractory patients and a database of more than 7,000 HLA-typed donors, a mean of 39 donors were HLA grade A or B matched, but a mean of 1,426 donors were identified as permissible by antibody screening. Post-transfusion platelet count increments were comparable for the two strategies. HLA antibody testing should be repeated at periodic intervals because antibody specificities may evolve over time.

Platelet cross-matching tests the patient’s serum against samples of available donor apheresis platelets using a solid-phase adherence assay or an ELISA. A recent study found a mean CCI of 7,000 at one hour in more than 400 cross-matched platelet doses transfused to 71 refractory patients. Platelet cross-matching can be done within a few hours compared with several days for HLA testing, but it does involve frequent repeat testing because the shelf-life of platelets is five days. Automated platforms are invaluable in making this approach efficient and practical.

A comparison of some of the advantages and disadvantages of the three strategies for dealing with refractoriness to platelet transfusion is contained in the table. Choice of method depends on local resources, and communication between the hematologist and the transfusion service is critical to ensure that donor selection is appropriate and that valuable resources are not wasted or used inappropriately.

### Anti-fibrinolytic agents can be a useful adjunct for mucosal bleeding

Other approaches to ameliorating the consequences of alloimmune platelet refractoriness include infusion of IVIgG, citric acid treatment of platelets to remove Class I HLA epitopes, and infusion of recombinant activated FVII in actively bleeding patients. Despite anecdotal reports of success, none of these approaches has been validated for clinical use. Use of family members as platelet donors for patients who are potential allogeneic SCT candidates is controversial, based on a theoretical concern for inducing alloimmunization that may jeopardize engraftment. Anti-fibrinolytic agents such as epsilon-aminocaproic acid and tranexamic acid, however, can be useful in platelet-refractory patients with oral mucosal bleeding.


Dr. Quillen indicated no relevant conflicts of interest.
The Question
When do you recommend light transmission aggregometry as part of the evaluation of a patient with a suspected bleeding disorder?

My Response
Light transmission aggregometry (LTA) remains the reference method for measurement of platelet function in patients with suspected platelet function disorders (PFDs). Remarkably, the core principles on which LTA is based have not changed since it was first described by O’Brien and Born more than 50 years ago. Platelet-rich plasma is stirred in a cuvette that is placed between a light source and a photocell. The plasma is cloudy due to suspension of platelets and allows relatively little light to pass through. Upon the addition of an agonist, platelets aggregate, and the sample becomes clearer, permitting greater light transmission. Transmission of light is detected by the photocell and recorded as a function of time (Figure). An enhancement of modern LTA is the capacity to simultaneously monitor ATP secretion from dense granules using a luciferin-luciferase reagent.1

When do I recommend LTA?
Rare PFDs such as Glanzmann thrombasthenia (GT) and Bernard–Soulier syndrome (BSS) are usually diagnosed early in life because of the severity of the bleeding phenotype. In syndromic PFDs, the presence of associated features (e.g., oculocutaneous albinism in Hermansky–Pudlak syndrome) may facilitate diagnosis. Far more common, however, are mild PFDs without associated syndromic features. Even with a detailed bleeding history, these disorders may be difficult to distinguish from normal variation due to the high frequency of mucocutaneous bleeding in the general population. In one study of healthy adults, epistaxis, easy bruising, and prolonged bleeding after tooth extraction were reported in 25 percent, 18 percent, and 18 percent of subjects, respectively; and 47 percent of menstruant women reported heavy menses.2

A bleeding history may be taken using either a conventional approach or a standardized bleeding assessment tool (BAT). Published BATs are effective in discriminating patients with bleeding disorders from healthy controls, but they have not proven effective in predicting the presence of PFDs among patients referred for a suspected bleeding disorder. A recent study investigated the utility of the International Society on Thrombosis and Haemostasis (ISTH)-BAT for this purpose. Twenty-one healthy controls and 79 patients with a suspected bleeding disorder were enrolled. A normal basic hemostatic work-up (platelet count, PT, APTT, fibrinogen, and von Willebrand panel) was required for study entry. The median ISTH-BAT score was significantly greater in patients than in controls (12 vs. 0). Among the patients who had a suspected bleeding disorder, however, there was no difference in score between the 41 who were diagnosed with a PFD by LTA and the 38 with a normal LTA (11 vs. 12).3

In my practice, I employ a conventional approach to the bleeding history. I query patients about spontaneous, mucocutaneous bleeding symptoms (location, frequency, severity, treatment); bleeding with hemostatic challenges (e.g., surgery, trauma, childbirth, menstruation); and family history of bleeding. I also ask about prescription and over-the-counter medications (e.g., anti-platelet agents) and comorbidities (e.g., liver disease, uremia) that could promote bleeding. I use data from the history to estimate the pretest probability of a PFD. I recommend LTA when I judge the pretest probability to be intermediate or high (i.e., >50%). My approach is likely to be highly operator-dependent and result in over-testing (only about half of the patients I refer for LTA have an identifiable defect). Although BATs hold promise for ameliorating these deficiencies, I have opted not to use BATs in my practice until they are shown to improve diagnostic accuracy compared with conventional approaches to assessment of bleeding.

Table. Characteristic LTA Patterns of Selected Platelet Function Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Primary ADP</th>
<th>Secondary ADP</th>
<th>Epinephrine</th>
<th>AA</th>
<th>Collagen</th>
<th>Ristocetin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inherited disorders</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>GT</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Normal</td>
</tr>
<tr>
<td>BSS</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Absent</td>
<td>Normal</td>
</tr>
<tr>
<td>Dense granule SPD</td>
<td>Normal</td>
<td>Decreased</td>
<td>Variable</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>Absent</td>
<td>Variable</td>
<td>Normal</td>
<td>Normal</td>
<td>Absent</td>
</tr>
<tr>
<td>Acquired disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>P2Y12 inhibitors (e.g., clopidogrel)</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Glycoprotein Ib/IIa inhibitors</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Uremia</td>
<td>Normal</td>
<td>Decreased</td>
<td>Variable</td>
<td>Decreased</td>
<td>Absent</td>
<td>Normal</td>
</tr>
</tbody>
</table>

GT=Glanzmann thrombasthenia; BSS=Bernard–Soulier syndrome; SPD=storage pool disorder; ADP=adenosine diphosphate; AA=arachidonic acid.

How is LTA interpreted?
A panel of seven platelet agonists – ADP, epinephrine, collagen, thrombin, thromboxane A2, mimetic U46619, arachidonic acid, and ristocetin – is recommended by an international consensus panel.4 Aggregation tracings (Figure) are evaluated with respect to a number of parameters including: shape change; length of lag phase; slope of aggregation; presence of a secondary wave of aggregation produced by weak agonists, such as epinephrine; maximal percent aggregation; and presence of deaggregation.
The pattern of aggregation and/or secretion defects observed with the agonist panel facilitates identification of a variety of hereditary and acquired platelet disorders (Table) and also helps to localize lesions to specific pathways. Classic examples include GT (caused by mutations in integrin αIIbβ3) and BSS (caused by mutations in the platelet glycoprotein Ib-IX-V complex), both of which have characteristic LTA signatures (absent aggregation to all agonists except ristocetin and absent ristocetin-induced agglutination, respectively).

In practice, LTA abnormalities often do not conform to one of the textbook patterns shown in the Table. Many of these “non-specific” abnormalities are of uncertain clinical significance and molecular pathogenesis. However, critical new insights are emerging from genotype-phenotype correlation analyses such as the United Kingdom Genotyping and Platelet Phenotyping (GAPP) study.\(^8\) GAPP is a multicenter study of patients with clinically suspected inherited PFDs. Results from the first 111 patients were recently reported.\(^9\) A defect by LTA was detected in 64 patients (58%). Most defects (84%) involved GPi (i.e., ADP and epinephrine) receptor signaling, thromboxane A\(_2\) receptor signaling, or dense granule secretion. Targeted genotyping subsequently identified novel mutations in the P2Y\(_12\) ADP receptor, the thromboxane A\(_2\) receptor, and FLI1 and RUNX1, genes encoding transcription factors that participate in megakaryopoiesis and dense granule secretion.\(^8,9\)

Several limitations must be borne in mind in the interpretation of LTAs. First, some LTA “abnormalities” are observed in a small percentage of healthy volunteers. Clinical correlation is required, but not always conclusive, in distinguishing disease from normal variation. LTA cannot assess platelet function under flow conditions and may be influenced by a variety of preanalytic, analytic, and biologic variables.

### Which variables can confound LTA?

Many drugs affect platelet function in vitro. Drugs with reversible effects on platelets (e.g., NSAIDs) should be held for at least three days and drugs with irreversible effects (e.g., aspirin, clopidogrel) for at least 10 days prior to testing. An international consensus panel recommends a short rest period and avoidance of smoking and caffeine prior to blood collection to mitigate the effects of epinephrine release.\(^6\) Because chylomicrons in plasma can interfere with LTA, patients should be counseled to avoid fatty meals shortly before testing. Laboratories must adhere to meticulous specifications for sample collection and processing to avoid in vitro platelet activation. The platelet count in platelet-rich plasma should be measured. Results may be inaccurate when the platelet count is < 150 × 10\(^6\)/L. Studies should be completed within four hours after blood collection.\(^6\)

### Conclusion

As they have for decades, a detailed bleeding history and LTA form the backbone of the diagnostic evaluation of patients with suspected PFDs. These approaches are not without shortcomings. The bleeding history has relatively poor specificity because of the frequency of mucocutaneous bleeding symptoms in the general population. LTA is labor-intensive, requires considerable expertise and a fresh blood sample, is not well-standardized, and shows overlap between normal variation and pathology across certain parameters. Continued development of BATs and improved methods for measuring platelet function are needed to overcome these limitations. Genotype-phenotype correlation studies are elucidating novel defects, are providing new insights into platelet function in health and disease, and may ultimately pave the way for more exacting approaches to diagnosis.


Dr. Cuker indicated no relevant conflicts of interest.
Anti-Phospholipid Antibodies and Pregnancy – July/August 2014

The authors have indicated that there has been no update regarding the content of this article since the original publication date in 2014.

The Question

What is your approach to a patient with laboratory evidence of anti-phospholipid antibodies who is pregnant or considering pregnancy?

Our Response

Antiphospholipid antibody syndrome (APS) is a heterogeneous autoimmune disorder characterized by arterial and venous thromboembolic events and obstetric complications (especially recurrent fetal losses) in association with persistent laboratory evidence of anti-phospholipid antibodies (aPL). The aPL associated with the disease include the lupus anticoagulant (LA), anti-cardiolipin (aCL), and anti-β2-glycoprotein-1 (anti-β2 GP-1). APS and aPL can occur in isolation (i.e., primary) or in association with other disease processes (i.e., secondary) including connective tissue diseases, most commonly systemic lupus erythematosus (SLE).

Diagnostic Criteria for APS

The presence of aPL alone does not constitute APS. The international classification criteria for APS (the Sapporo criteria) were introduced in 1998 and revised in 2006. To make a definitive diagnosis of APS, the presence of at least one clinical feature (thrombosis or pregnancy morbidity) and one laboratory abnormality must be observed, and the laboratory abnormality must be present on two or more occasions at least 12 weeks apart. Laboratory parameters are as follows: IgG and/or IgM aCL or anti-β2 GP-1 in moderate to high titre (i.e., a titre > 40 for IgG or for IgM or a titre > the 99th percentile), or documentation of the LA. Further details about the diagnostic criteria for APS can be found in the Journal of Thrombosis and Haemostasis.

Maternal and Fetal Morbidity

The pathogenesis of an aPL-related pregnancy morbidity is incompletely understood. For a pregnant woman, APS (and perhaps the presence of aPL) raises the possibility that she is at increased risk for thrombotic events and/or obstetric complications such as recurrent pregnancy losses, preeclampsia, eclampsia, intra-uterine growth restriction, and Hemolysis, Elevated Liver enzymes, Low Platelets (HELLP) syndrome. In a European referral cohort of 1,800 patients with APS (many of whom had a connective tissue disease), 188 pregnancies were documented over 10 years; among patients in this group, early pregnancy loss (16.5%), intra-uterine growth restriction (26.3%), and prematurity (48.2%) were common. A systematic review found that lupus anticoagulant was associated with preeclampsia (OR 2.34), intra-uterine growth restriction (OR 4.65), and late (after 10 weeks of gestation) fetal loss (OR 4.73); however, numerous case-control studies were included in this analysis. When the analysis was restricted to cohort studies, late fetal loss was the only outcome associated with the aPL. Catastrophic APS (CAPS), a rare but devastating form of this syndrome, has been associated with pregnancy and the peripuerium with 0.9 percent of the pregnancies from the aforementioned cohort being complicated by CAPS.

Laboratory Diagnosis of aPL

The laboratory identification of aPL can be problematic because of variability in the sensitivity of assays and reagents, high false-negative and false-positive detection rates, lack of standardization of assays, and lack of adherence to established guidelines. To address these issues, guidelines for laboratory detection of aPL were published in 2009 by the Scientific Standardization Subcommittee (SSC) of the International Society of Thrombosis and Haemostasis (ISTH) and by the British Committee on Standards in Hematology. The Clinical Laboratory Standards Institute (CLSI) has also prepared guidelines for laboratory testing for LA that are to be published soon. Before counseling a patient about risk or recommending therapy, we suggest that the hematologist ensure that aPL testing is not only confirmed on more than one occasion but also performed by a hematologist experienced in the management of thrombophilic conditions is recommended. APS patients on chronic anticoagulation should be informed about the potential teratogenic effects of warfarin, and oral anticoagulation should be switched to a therapeutic dose of low-molecular-weight heparin (LMWH) either before or very shortly after conception.

Pregnancy with aPL or APS – Clinical Management Scenarios

1. Pregnant women with positive evidence of aPL who do not fulfill the diagnostic criteria for APS

There are no robust data to guide management of pregnant women in this cohort. Dr. Anne Lynch et al. measured aPL in early pregnancy in 451 low-risk nulliparous women and found that 24.4 percent had aPLs.1 The rate of fetal loss in this cohort was higher than those without aPLs (15.8 vs. 6.5%), but the rate of adverse maternal outcomes was similar in both groups. We usually recommend low-dose ASA because it is easy to take and there is a reasonably high quality of evidence that it reduces the risk of preeclampsia; however, the significant uncertainty about the benefit of any antepartum, antithrombotic therapy in women who do not meet criteria for APS means that decisions should be individualized. The role of post-partum thromboprophylaxis in this patient group is not established.

2. Women with adverse obstetric outcomes plus aPL, but no history of thrombosis

In three meta-analyses of randomized trials in women with APS, the combination of APS with prophylactic heparin significantly reduced pregnancy loss (RR 0.46) or first-trimester loss (OR 0.39) and increased live births (RR 2.3).11,12,13 These analyses, however, have several limitations, including a small number of trials from which to draw evidence to define the optimal anticoagulant management of patients who desire regional anesthesia, communication with maternal-fetal medicine and anesthesiology is especially important. For a woman with prior thrombosis who has discontinued anticoagulation, we suggest LMWH be started upon confirmation of pregnancy; whether to use prophylactic/intermediate or therapeutic-dose LMWH would depend on the perceived risks of thrombosis during pregnancy. However, because the quality of evidence to support combination therapy over LMWH or ASA alone is not compelling, we suggest that the hematologist consider not only patient preferences, but also the recommendation of a maternal-fetal medicine specialist before choosing LMWH + ASA over LMWH or ASA alone. The optimal doses for LMWH and ASA have not been defined, but we suggest 75 to 100 mg of ASA per day plus prophylactic-dose LMWH (Table). For women with obstetric APS and no history of thrombosis, thromboprophylaxis during the postpartum period should be considered, but the net benefit is not well established.

3. Pregnant women with thrombotic APS

If a woman has APS and is anticoagulated for prior thrombosis, we suggest switching to therapeutic-dose LMWH before six weeks gestation. Full-intensity anticoagulation is important during the pregnancy and the postpartum period since these women have a significant, ongoing risk of thrombosis that is likely magnified by pregnancy. If a woman is on therapeutic-dose LMWH, delivery should be planned, and LMWH should be discontinued at least 24 hours prior to the procedure. Because there is no high-quality evidence to define the optimal anticoagulant management of patients who desire regional anesthesia, communication with maternal-fetal medicine and anesthesiology is especially important. For a woman with prior thrombosis who has discontinued anticoagulation, we suggest LMWH be started upon confirmation of pregnancy; whether to use prophylactic/intermediate or therapeutic-dose LMWH would depend on the perceived risks of thrombosis and bleeding. An elevated risk of thrombosis persists for up to 12 weeks following delivery.12 The absolute risk for thrombosis beyond six weeks, however, is small. Thus, thromboprophylaxis beyond the six-week mark of the postpartum period should be reserved for those patients with an especially high baseline risk.

Conclusion

Management of pregnant women with APS is challenging. Despite the imperfect data that are currently available, pregnancy outcomes in women with APS who are managed in centers that use a multidisciplinary approach, which includes input from clinicians experienced in thrombophilia management and fetal-maternal medicine, is often favorable.
Table. Overview of the Therapeutic Options Used in Antiphospholipid Syndrome Pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use</th>
<th>Evidence</th>
<th>Safety in pregnancy</th>
<th>Safety in breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Reduction of fetal loss. Prevention of eclampsia. Antiplatelet effect</td>
<td>No randomized controlled trials of aspirin for preventing VTE. Some evidence for aspirin use in improving pregnancy outcomes, specifically reduction in rates of preclampsia.</td>
<td>Will cross the placenta; human data inconsistent, but risk is likely low. Some first-trimester analyses have shown small increased risk of gastroesphagitis.</td>
<td>Does enter breast milk, but at low doses; should be safe</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Not recommended in pregnancy unless LMWH may be less effective (e.g., prosthetic heart valves)</td>
<td>Teratogenic between 6-12 weeks of gestation; switch to LMWH before 6 weeks of gestation.</td>
<td>Teratogenic.</td>
<td>Not excreted in breast milk</td>
</tr>
<tr>
<td>Unfractionated heparin (UFH)</td>
<td>May be used in event of massive pulmonary embolism. If rapid reversal of anticoagulation is needed during peripartum period or operative procedures</td>
<td>Most studies using UFH have been superseded by studies using LMWH.</td>
<td>Safe.</td>
<td>Not excreted in breast milk</td>
</tr>
<tr>
<td>LMWH</td>
<td>Drug of choice for women on warfarin, women who have had VTE or arterial thrombosis during pregnancy, women with previous pregnancy complications, or women who require thromboprophylaxis</td>
<td>Evidence for its role in preventing first-trimester loss remains controversial.</td>
<td>Does not cross placenta.</td>
<td>Does enter breast milk, but of little concern due to low bioavailability</td>
</tr>
<tr>
<td>Steroids (e.g., prednisone)</td>
<td>Little evidence for benefit in APS; used in immune thrombocytopenia associated with APS or SLE</td>
<td>Minimal evidence of therapeutic benefit. Benefit outweighed by its adverse effects (e.g., preclampsia, gestational diabetes, increased risk of preterm deliveries).</td>
<td>Cleft palate reported with first-trimester use.</td>
<td>Low concentrations in breast milk</td>
</tr>
<tr>
<td>Intravenous immunoglobulins</td>
<td>Used in a small number of women with APS as therapy for concomitant, immune-mediated thrombocytopenia</td>
<td>No additional benefit when added to conventional therapy with ASA and LMWH.</td>
<td>Crosses placenta after 30 weeks of gestation.</td>
<td>Excretion is unknown</td>
</tr>
<tr>
<td>Hydroxychloroquine (HCQ)</td>
<td>Used when women have coexisting SLE</td>
<td>Mild antithrombotic effects. Decreased risk of congenital heart block in women on HCQ in case-controlled studies.</td>
<td>No reports of fetal toxicity.</td>
<td>Considered safe despite excretion in breast milk</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>Reserved for treatment of catastrophic APS</td>
<td>Limited to case reports.</td>
<td>Rarely used in pregnancy.</td>
<td>Unknown</td>
</tr>
</tbody>
</table>


Future studies that expand our understanding of this complex disease, that clearly define obstetric and thrombotic risks, and that identify optimal antithrombotic regimens are needed.


Dr. Suryanarayan and Dr. Garcia indicated no relevant conflicts of interest.
The Question

What are your treatment approaches to Castleman disease with the advent of anti–interleukin-6 therapy?

Our Response

Castleman disease (CD) describes a group of heterogeneous lymphoproliferative disorders that share common histopathological lymph node changes. CD can present with localized (unicentric CD or UCD) or generalized lymphadenopathy (multicentric CD or MCD). MCD should be further divided into human herpesvirus 8 (HHV-8)–positive and HHV-8-negative MCD (Table). The latter is also referred to as idiopathic MCD (iMCD). UCD patients can exhibit a spectrum of clinical features from mild flu-like symptoms to sepsis-like multiorgan failure. It is important to distinguish these three entities since they require entirely different therapeutic approaches.

UCD

UCD presents with lymphadenopathy confined to one lymph node region, and many patients exhibit asymptomatic symptoms. UCD is usually due to compression of vital structures such as the trachea, blood vessels, or nerves. UCD occurs most frequently in younger females and is diagnosed when enlarged lymph nodes are found in the setting of HIV infection. Approximately 90 percent of UCD cases demonstrate the hyaline vascular (HV) subtype. The other 10 percent of patients with UCD demonstrate mixed cellularity or plasmacytic (PC) pathology and may have constitutional symptoms such as fever, fatigue, and weight loss. UCD is associated with HHV-8 or HIV infection. There is an increased association with lymphoma, which may be present at the same time, or the UCD may “transform” into lymphoma. The etiology of UCD is poorly understood, and there is usually no excess interleukin-6 (IL-6) secretion. Limited studies have demonstrated abnormal cytokine gene expression in anorectal cells, but the significance of these findings is unknown. Surgical extirpation is curative in 95 percent of UCD cases. Unresectable cases can be treated with rituximab and steroids, which may induce complete responses or shrink the mass sufficiently to make it resectable. UCD lymphadenopathy is highly vascularized, and embolization can be a further therapeutic option. Involution of lymphadenopathy after radiotherapy has also been reported. Difficult cases require a multimodal approach and are best managed at an experienced center.

HHV-8-Positive MCD

HHV-8-positive MCD presents with generalized lymphadenopathy and constitutional symptoms and can progress to multicentric failure leading to death. The disease is driven by the excessive release of viral IL-6, which is encoded by the HHV-8 virus and drives human IL-6, IL-10, and vascular endothelial growth factor (VEGF) secretion. HHV-8-positive MCD was first described in a single-arm study of 28 Japanese patients on tocilizumab demonstrated a high response rate in terms of symptoms, laboratory parameters, and reduction in hepatosplenomegaly. 11 Siltuximab has been evaluated in a double-blind, placebo-controlled, randomized study using a control arm of best supportive care including up to 60 mg of prednisone. The combined durable symptomatic and tumor response was 34 percent, and 50 percent of patients remained on drug for the duration of the study. This study provided the first placebo-controlled evidence for an iMCD therapy, and siltuximab is the first drug approved for iMCD by the U.S. Food and Drug Administration and European Medicines Agency. Both siltuximab and tocilizumab are safe and well-tolerated. 12 For patients that do not respond to anti–IL-6 therapy, immunosuppressants, immunomodulators, biologics, and cytotoxic chemotherapies, including cyclosporine, sirolimus, bortezomib, thalidomide, etoposide, have been reported to have some success in case reports or small series.

Table. Features of the Different Types of Castleman Disease

<table>
<thead>
<tr>
<th>Type of Castleman Disease</th>
<th>Type of Lymphadenopathy</th>
<th>Pathology</th>
<th>IL-6-Driven Inflammatory Syndromeb</th>
<th>Virologic Status</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unicentric</td>
<td>Localized</td>
<td>90 percent hyaline vascular</td>
<td>Typically not</td>
<td>Negative for HHV-8 by QPCR or negative LANA-1 stain</td>
<td>Complete excision</td>
</tr>
<tr>
<td>Multicentric HHV-8-Positive</td>
<td>Generalized ± hepatosplenoegenomal</td>
<td>Plasmacytic or plasmablastic</td>
<td>Yes</td>
<td>Positive for HHV-8 by QPCR or positive LANA-1 stain</td>
<td>Rituximab ± etoposide</td>
</tr>
<tr>
<td>Multicentric HHV-8-Negative</td>
<td>Generalized ± hepatosplenoegenomal</td>
<td>Mostly plasmacytic, but can be hyaline vascular or mixed cellularity</td>
<td>Yes, but variable clinical presentation from mild to very severe</td>
<td>Negative for HHV-8 by QPCR or Negative LANA-1 stain</td>
<td>Siltuximab ± etoposide</td>
</tr>
</tbody>
</table>

Hydroxyurea and interferon are used for patients that do not respond to anti–IL-6 therapy. Immunosuppressants, immunomodulators, biologics, and cytotoxic therapies are used in patients with one or more features of POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) syndrome, or a concurrent POEMS syndrome. 10 Patients with one or more features of POEMS often have less florid constitutional symptomatology.

The etiology of the pro-inflammatory hypercytokinemia in iMCD has not yet been identified. The pathologic cell and the responsible intracellular inflammatory pathway responsible for producing the IL-6 in these patients has also not been elucidated. Hypothesized etiologies include an unknown virus, a small population of malignant cells, or germline genetic mutations in the immune system. 13 No single gene causing iMCD has been identified, but systematic sequencing has not been performed. The disease may be influenced by ethnicity and genetic factors such as a polymorphism of the IL-6 receptor. 14 Asian patients may demonstrate violaceous skin lesions or intestinal pneumonitis usually not seen in other races. Currently, a diagnosis of iMCD can be made when patients have 1) histopathology typical of CD on excisional lymph node biopsy, 2) multiple regions of enlarged lymph nodes, 3) negative quantitative PCR for HHV-8 in the peripheral blood or negative LANA-1 staining of the lymph node biopsy, and 4) systemic exclusion of diseases known to demonstrate Castleman-like histopathology (e.g., systemic lupus erythematosus, Epstein-Barr virus, lymphoma, IgA-associated lymphadenopathy). Hence, both HHV-8-positive and –negative MCD are not purely pathologic diagnoses. Efforts are currently underway to establish international consensus around clinical, pathologic, and exclusion criteria for the diagnosis of iMCD. Although the PC variant predominates in MCD, HV and mixed pathology have also been reported.
Choice of Therapy for iMCD

In the authors’ opinion, patients with iMCD should first be treated with anti-IL-6 therapy approved in that region (siltuximab in North America and the European Union; tocilizumab in Japan). Patients with few symptoms or laboratory abnormalities suggestive of little excess IL-6 may not respond well to anti-IL-6 blockade and should be considered for rituximab and steroids. Patients with severe hypercytokinemia and organ failure may not respond sufficiently to anti-IL-6 targeting monoclonal antibodies, and they require combination chemotherapy or consideration of experimental treatment. Dosing intervals can be spaced out in selected patients responding to anti-IL-6 therapy. Progressive motor polyneuropathy suggesting coexistent POEMS does not respond well to rituximab or to IL-6–targeted therapy, and these patients require autologous stem cell transplantation as part of their treatment plan.

The Future

The introduction of rituximab has been a major advance in HHV-8-positive MCD, while therapy with IL-6-targeting monoclonal antibodies is an important innovation in iMCD. However, anti-IL-6 therapy is not effective for all patients, and it is not curative, as cessation of treatment results in relapse. In 2012, we co-founded the Castleman Disease Collaborative Network (CDCN; www.castlemannetwork.org) to accelerate research and elucidate the pathogenesis of MCD. In 2.5 years, we have assembled a 23-member Scientific Advisory Board representing seven countries; built a global community of more than 200 researchers and physicians worldwide; leveraged the community to establish and execute an international research agenda; and engaged patients throughout the entire process. We are currently finalizing plans to establish a global registry/natural history study, which we believe will be crucial for establishing diagnostic criteria and improving patient care. We also plan to launch viral discovery, serum proteomics, intracellular inflammatory pathway identification, and sequencing studies. We invite you to register on our website, attend our annual meeting that occurs during the ASH annual meeting, conduct research, contribute samples for research, and encourage your patients to enroll in our registry.


Dr. Van Rhee and Dr. Fajgenbaum indicated no relevant conflicts of interest.
The Question

Given the recent U.S. Food and Drug Administration (FDA) approval of edoxaban, the fourth direct oral anticoagulant (DOAC) to come to the U.S. market since 2010, what should I know about this class of medications, and what is their role in patient care? Are there patients for whom these medications are not (or possibly not) appropriate?

My Response

This is an exciting time for clinicians caring for patients with (or at risk for) thrombosis, but the amount of clinical trial data, not to mention the dosing peculiarities, relevant to the DOACs, can be difficult to digest. Here, I will try both to provide take-home points about safety and efficacy relative to other therapies as well as to address some of the practical management questions I am frequently asked about DOACs.

One or more of the DOACs has now been approved for three main indications: 1) the prevention of venous thromboembolism (VTE) at phase III clinical trials that included more than 100,000 patients show that, although no antidote was available, the likelihood of fatal bleeding was lower among the patients treated with DOACs than among those treated with vitamin K antagonists (VKAs). This potential advantage of the DOACs over VKAs may be overlooked because of the relative paucity of data on VTE prevention. 2) compared with warfarin, the DOACs cause 50 percent fewer intracranial bleeds and 3) the short half-life of the DOACs means that in many cases of major bleeding, no antidote or "reversal agent" is needed. These observations notwithstanding, antidotes and reversal agents in late-phase clinical development are likely to reach the U.S. market within the next two to three years. The DOAC antidotes that are furthest in the development process are andexanet (a factor Xa "decoy" molecule that is intended for patients on a FXa inhibitor) and idarucizumab (an antibody fragment targeting the direct thrombin inhibitor, dabigatran).

What should I do if consulted about a patient with DOAC-associated bleeding?

Many patients with DOAC-associated bleeding will be best managed with supportive care such as red blood cell transfusions and volume support; excellent renal perfusion will maximize the rate at which the anticoagulant effect dissipates. Unless a patient has compromised renal function, the plasma DOAC concentration (and corresponding drug effect) will have decreased by more than 50 percent six to 12 hours after the last dose. In the small minority of patients with DOAC-associated bleeding who require more aggressive efforts to counteract the anticoagulant effect immediately, one could consider prothrombin complex concentrates or recombinant activated factor VII. However, the thrombosis risk associated with these interventions is not trivial, and the rationale for their use is based entirely on animal and other preclinical models.

In which patients should DOACs be avoided?

In general, DOACs should be used only for approved indications. Because patients with mechanical prosthetic heart valves were not included in the phase III studies, and because dabigatran was inferior to warfarin in the only head-to-head comparison that has been done in this population,1 the DOACs should not be prescribed to patients with mechanical prosthetic heart valves. There are also subgroups of patients with (or at risk for) VTE where routine DOAC use should also be avoided pending further evidence. Because of their highly prothrombotic tendencies, patients with active cancer, heparin-induced thrombocytopenia, and bone fide antiphospholipid syndrome are other groups for whom I do not think DOACs should be a first option. Instead, we should work hard to enroll such patients in clinical trials that will provide evidence on which we can base future practice.

Conclusion

In summary, the DOACs offer hematologists and well-selected patients four oral alternatives to warfarin and other VKAs.23 Important ongoing trials will tell us more about how best to manage serious DOAC-related bleeding, whether DOACs can be safely used in patients with cancer-associated VTE, and what is the safest way to combine DOACs with antiplatelet agents (e.g., in patients with previous acute coronary syndromes). In the meantime, many patients for whom these medications are indicated (and for whom cost is not a barrier) will likely choose them over warfarin because of their convenience and impressive safety profile.

References


Dr. Garcia indicated no relevant conflicts of interest.

The Hematologist Compendium 2010-2015