The Cure Sickle Cell Initiative: Catalyzing Progress via Innovative Interfaces Between NIH, Patients, Academics, ASH, and the Private Sector

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President and CEO Emeritus, Dana Farber Cancer Institute, Boston, MA

It has been more than a century since the first U.S. case of “sickle-shaped cells” was described by Dr. James B. Herrick and his resident after they examined the peripheral blood of a young Chicago dental student reporting episodic pain.¹ It was more than six decades ago in 1956 that Dr. Vernon Ingram, building on the discoveries of Drs. Linus Pauling and Harvey Itano, elucidated the biochemical explanation by showing that the substitution of glutamic acid with valine in the β-globin chain of hemoglobin accounts for the unique shape of the affected red blood cells and their sensitivity to low-oxygen states.

Sickle cell disease (SCD) was the first disease understood at the molecular level. Yet, in the 62 years since that discovery, cure has been achieved only for the rare patient able to undergo successful stem-cell transplantation — a procedure that is viable for only the 20 percent of affected individuals having a matched sibling donor. Infection prophylaxis, folate supplementation, and hydroxyurea therapy, introduced in the 1980s to bolster the production of fetal hemoglobin, remain the most common interventions. L-glutamine has recently been shown to reduce the number of pain crises throughout a 48-week period.² However, treatments targeting the root cause of the illness remain elusive despite our exquisite understanding of its origins and pathophysiology.

In a monogenic disease, gene replacement therapy is an attractive option. Why then hasn’t that insight led to cure? To hear him tell it, this is one of the key questions that has vexed Dr. Francis Collins, director of the National Institutes of Health (NIH) and a lifelong student of human genetics. Two years ago, Dr. Collins turned his eye toward SCD and convened a high-level brainstorming retreat to answer exactly that question. “Not just treat it but cure it,” Dr. Collins has been quoted as saying. “I think we can do that, and we should not rest until we do.”

The Cure Sickle Cell Initiative is the result of this retreat. The core aim is to utilize a funding mechanism that is more nimble and more flexible than the traditional grants and contracts paradigm. It was clear to all the participants in the retreat that the traditional NIH mechanisms are structurally too slow for what is needed for late-stage translational research. Where a traditional grant may take 12 to 18 months from submission to contracting, the hope was to build a program where federal funding could be available in days or weeks.

Taking as a model the Defense Advanced Research Projects Agency (DARPA), the early federal funding that helped kickstart the internet, this national funding mechanism is called the Transactional Authorization (OTA). Traditionally, funding from NIH or the National Heart, Lung, and Blood Institute (NHLBI) favors hypothesis-driven research, largely focused on discovery and early translation. But the gap in SCD is development and deployment — the so-called “valley of death” in developing new therapies. The OTA will allow for funding projects that are aimed at accelerating advancement from concept to bedside.

Dr. Collins has said that this new funding mechanism exemplifies a new systemic approach to this disease. But it is not just the commitment to deliver financial support rapidly and to projects that are highly translational. The programmatic effort will include:

1. Assistance to investigators in how to navigate the federal regulatory process. What are the administrative hurdles in activating a clinical trial or multicenter effort?
2. Strengthening the input of patients and families in the design and implementation of clinical trials and novel treatments. A key part of this will be leveraging ASH’s development of a registry and an SCD clinical trials network. ASH has built the core data collection infrastructure of the registry and is soliciting initial participants. ASH will also be soliciting applications for the network later this year.
3. Directing support to technical advancements that are aimed at making novel approaches more universally available. For instance, scaling up production of key reagents needed to make novel approaches more universally available.

A Brief Timeline of Sickle Cell Disease Innovations

1910 – Dr. James B. Herrick publishes a description of sickled cells present in 20-year-old Grendadian dental student Walter Duncan Noble.

1949 – Dr. Linus Pauling and others reveal the molecular nature of SCD.

1954 – Sickle cell trait is found to protect against malaria, explaining the prevalence of SCD in regions where malaria is a leading cause of death.

1972 – The National Sickle Cell Anemia Control Act, establishes voluntary SCD screening, counseling, public and professional education, and other key public health measures.

1986 – β-globin gene therapy demonstrates the ability to correct the molecular nature of SCD.

1997 – Blood transfusions demonstrate a 90 percent reduction in stroke in high-risk patients.

1998 – The FDA approves hydroxyurea for treatment of adults with SCD.

2009 – Study shows that blood stem cell transplantation can reverse SCD in adult patients.

2017 – β-globin gene therapy demonstrates curative success; crizanlizumab decreases pain crises in patients; L-glutamine is approved.

Paul Moss, MD, PhD
Dr. Moss indicated no relevant conflicts of interest.

Mimicry Not Replacement: Molecular Engineering Transforms the Outlook in Hemophilia A


If something is missing, it should be replaced. Such has been the philosophy of the management of hemophilia A ever since factor VIII deficiency was first defined. Incrementally and notwithstanding substantial setbacks, progress has been made through the use of plasma products, concentrates, recombinant factor VIII, and replacement from reactive treatment of bleeding episodes to the use of prophylactic therapy that seeks to minimize the number and severity of bleeding episodes and to prevent complications such as chronic joint disease. Many older hematologists will remember that hemophilia ward rounds would routinely take a detour to the orthopedic department; this is now, thankfully, uncommon.

An alternative approach to direct replacement is to mimic the function of factor VIII, which is a cofactor for activated factor IX (IXa). In the presence of Ca²⁺ and phospholipids, it forms a complex that leads to the activation of factor X. Emicizumab is a bi-specific antibody that has been designed to crosslink activated factor IX and factor X, bringing them into close apposition and leading to the activation of factor X, even in the absence of factor VIII. The antibody has now been assessed in a series of stunning clinical studies throughout the past two years.

This Diffusion describes the HAVEN 3 study, which focuses on the activity of prophylactic emicizumab in patients with hemophilia who do not have inhibitors. The recent article by Dr. Johnny Mahlangu and colleagues is the third in a series on emicizumab published in the New England Journal of Medicine, with previous reports of the phase I study and outstanding clinical outcomes in patients who do have inhibitors.

The randomized phase III HAVEN 3 study recruited 152 patients older than 12 years with severe congenital hemophilia A and endogenous factor VIII activity less than 1 IU/dL. Most patients were not on prophylactic factor VIII therapy, and these 89 patients were randomized in a 2:2:1 ratio to either a maintenance dose of emicizumab at 1.5 mg/kg per week (group A), 3.0 mg/kg every two weeks (group B), or no prophylaxis (group C). Forty-three patients were already on prophylactic factor VIII infusions; in this case, emicizumab was given at a maintenance dose of 1.5 mg/kg per week, and intravenous comparisons were made from before and after administration (group D). Prophylactic factor VIII infusions could be stopped in this group after the second dose of emicizumab had been given. (Cont. on page 7)
ASH: A Year in Review

As I begin my final President’s Column, I am reminded of my predecessor Dr. Kenneth Anderson’s assessment that a key part of ASH’s influence on hematology/oncology research lies in building awareness about important current and emerging topics. Throughout the course of 2018, the Society has continued to enhance that awareness — through our support for research and education; via initiatives to better capture, share, and use data; and in taking steps to confront some of the most vexing clinical and scientific challenges. And at the upcoming annual meeting in San Diego, attendees will find an amazing array of sessions showcasing ASH initiatives as well as the extraordinary cutting-edge advances for clinicians and scientists alike.

Recognizing the impact of venous thromboembolism (VTE) across the entire range of medicine, ASH has garnered its resources to convene panels of VTE experts to develop a comprehensive series of clinical practice guidelines using rigorous methodology. I am thrilled that the first six of the 10 total guidelines will be published near the end of this month in Blood Advances (www.bloodadvances.org), allowing ASH to create additional resources not only for hematologists and other health care professionals, but also for at-risk populations, administrators, and other key audiences to raise awareness about this underappreciated threat. You can learn more about this endeavor at the annual meeting during a Special Education Session on Venous Thromboembolism (Monday, December 3, 2:45 – 4:15 p.m.), or online at www.hematology.org/vte.

ASH is also in the process of developing five new clinical practice guidelines on the management of acute and chronic complications of sickle cell disease (SCD). These guidelines will address pain, cerebrovascular disease, cardiopulmonary and kidney disease, stem cell transplantation, and transfusion support, with a public comment period on the draft recommendations this fall and anticipated publication dates in 2019. This is just one of many ASH efforts to promote new and successful treatments for people living with SCD. In September, ASH announced the formation of a clinical trials network, the mandate of which will be to connect clinical trial sponsors with research sites, move the needle on patient recruitment, and advance clinical trial efficiency. At its core will be a research data registry that will provide a critical foundation for patient data storage, access, and analysis to support clinical trial research. ASH collaborated with the U.S. Food and Drug Administration in a joint clinical endpoints workshop in October to bring together SCD experts, researchers, biopharmaceutical companies, and patients to explore ways to further accelerate clinical trials that will hopefully lead to more novel drug approvals. Lastly on the SCD front, this has been a big year for our advocacy efforts for SCD legislation on Capitol Hill — legislation that, as of this writing, was just approved by the Senate and will hopefully move forward for approval by the U.S. House of Representatives. And the spirit of advocacy does not stop at our doorstep, as ASH begins work toward improving newborn screening in sub-Saharan Africa. By being “the change we want to see in the world,” we cement our leadership across many facets. The 2018-2019 cohort hails from seven nations, and the eight scientists chosen are focused on projects related to cell transplantation, and transfusion support, with a public comment period on the draft recommendations this fall and anticipated publication dates in 2019. This is just one of many ASH efforts to promote new and successful treatments for people living with SCD. In September, ASH announced the formation of a clinical trials network, the mandate of which will be to connect clinical trial sponsors with research sites, move the needle on patient recruitment, and advance clinical trial efficiency. At its core will be a research data registry that will provide a critical foundation for patient data storage, access, and analysis to support clinical trial research. ASH collaborated with the U.S. Food and Drug Administration in a joint clinical endpoints workshop in October to bring together SCD experts, researchers, biopharmaceutical companies, and patients to explore ways to further accelerate clinical trials that will hopefully lead to more novel drug approvals. Lastly on the SCD front, this has been a big year for our advocacy efforts for SCD legislation on Capitol Hill — legislation that, as of this writing, was just approved by the Senate and will hopefully move forward for approval by the U.S. House of Representatives. And the spirit of advocacy does not stop at our doorstep, as ASH begins work toward improving newborn screening in sub-Saharan Africa. By being “the change we want to see in the world,” we cement our leadership role while bringing about results that touch patient lives in the here and now. To learn more about these initiatives, visit the kiosk in ASH Central (Sails Pavilion, San Diego Convention Center) in San Diego.

Finally, I would like to present some updates on the growth of our efforts to acknowledge and support hematologists throughout all career stages via our awards programs. Funded by the ASH Foundation, our newest award, the ASH Global Research Award, is representative of the Society’s efforts to become a more global entity and to realize a hematology research workforce that is diverse across many facets. The 2018-2019 cohort hails from seven nations, and the eight scientists chosen are focused on projects related to CAR T cells, stroke prevention in SCD, and other areas.

I am immensely honored to have served as president of ASH during a time of such tremendous progress. Collectively, we have a great deal to be proud of. I consider the initiatives discussed here and in my other columns to be more than a collection of mile markers or goal posts. They are a window into the almost limitless capacity of the hematology community, stopping at nothing to conquer blood diseases. Thank you for your work and dedication, and I look forward to seeing you in San Diego in a few weeks!

Sincerely,

Alexis A. Thompson, MD

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NOVEMBER 30, 2018 • SAN DIEGO, CA

ASH-a-Palooza!
Trainee Day. Reimagined.

ASH TALKS
20-minute presentations in the "TED talk" style

BLOOD DROPS
5-minute rapid-fire questions

BLOOD BUDDIES
"speed mentoring"

AND MORE!
What’s New at the 60th ASH Annual Meeting and Exposition?

The 60th ASH Annual Meeting, the premier event in hematology, is taking place December 1-4, 2018, in San Diego. To make the most of your experience at the meeting, take advantage of some of the new resources that will be available:

Meeting Registration at Airport
ASH will now provide the convenience of meeting registration upon arrival at San Diego International Airport, as well as retrieval of meeting materials, before attendees proceed to their hotels or the convention center.

ASH-a-Palooza
Taking place the Friday, November 30, before the annual meeting commencement, ASH-a-Palooza brings a whole new feeling to the event previously known as Trainee Day. This educational experience will offer a relaxed, open learning environment for trainees in a festival-like setting with multiple opportunities for micro learning.

State of the Society Address
ASH President Dr. Alexis Thompson will share her insights on the many ways in which ASH works on members’ behalf throughout the year, to help hematologists conquer blood disease worldwide. This session will take place Saturday, December 1, at 1:30 p.m., in Hall AB of the San Diego Convention Center.

ASH Park @ The Plaza
Attendees can catch a breath of fresh air at ASH Park — a meeting and networking space located just outside of San Diego Convention Center. Attendees can also use this space for relaxing and eating lunch, or enjoying some live music.

Alexa in Japanese
ASH Ask Alexa was debuted at last year’s annual meeting; this year, the Society will be piloting Alexa in Japanese. Like last year, attendees can ask Alexa for room information, session times, details about other ASH annual meeting features, and more.

Expressions of Clinical Well-Being
This travelling art exhibit brought to you by the National Academy of Medicine shows what clinician burnout, clinician resilience, and well-being look and feel like to people across the country. The exhibit can be found just outside of Hall AB in the San Diego Convention Center.

For more on the annual meeting, including housing and registration information and a complete program, visit www.hematology.org/annual-meeting.

ASH Elects New Leadership

VICE PRESIDENT:

Martin S. Tallman, MD
Chief, Leukemia Service, Memorial Sloan Kettering Cancer Center; Professor of Medicine, Weill Cornell Medical College; New York, NY.

Dr. Tallman will serve a one-year term as vice president, followed by successive terms as president-elect and president.

TREASURER:

Mark Crowther, MD, MSc, FRCPC
Chair, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Dr. Crowther will serve a one-year term as treasurer.

COUNCILLORS:

Belinda Avalos, MD
Vice Chair, Department of Hematologic Oncology and Blood Disorders, Levine Cancer Institute, Charlotte, NC; Professor of Medicine, University of North Carolina, Chapel Hill, NC

Dr. Avalos will serve a four-year term as councillor.

Arnold Ganser, MD
Professor of Hematology and Oncology, Director, Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Medizinische Hochschule Hannover, Hannover, Germany

Dr. Ganser will serve a four-year term as councillor.
Ask the Hematologist

ANITA D’SOUSA, MD, MS
Assistant Professor of Medicine, Division of Hematology/Oncology, Medical College of Wisconsin, Milwaukee, WI

The Case
A 33-year-old African American man presented to the emergency department with chest tightness. He gave a history of worsening swelling in his legs in the past year. Laboratory tests revealed a creatinine level of 5.17 mg/dL (normal range: 0.6-1.2 mg/dL), albumin of 2.4 g/dL (normal range: 3.5-5.5 g/dL), hemoglobin of 9.9 g/dL (normal range: 13.5-17.5 g/dL) with normal white blood cell count with differential and normal platelet count. He was admitted to the hospital for further treatment. A 24-hour urine protein test revealed 13,335 mg/dl of urinary protein, predominantly albumin, confirming a diagnosis of nephrotic syndrome. Further workup included serologies and a kidney biopsy. Serum protein electrophoresis with immunofixation showed IgG 0.17 g/dL. Free light chain analysis revealed κ 180.3 mg/L (normal range: 30.69-19.64 mg/L), λ 325 mg/L (normal range: 5.71-26.3 mg/L) with a κ/λ ratio of 0.55 (normal range: 0.26-1.65). Kidney biopsy showed a diffusely proliferative glomerulonephritis on light microscopy. Immunofluorescence studies were positive for intense granular staining for IgG, λ, and C3. Electron microscopy revealed global electron dense immune-type eosinophilic deposits in the peripheral glomerular sub endothelial position. A bone marrow biopsy revealed 3 percent plasma cells with λ light chain restriction.

The Question
What is your approach to the diagnosis and management of monoclonal gammopathy of renal significance (MGRS)?

Response
MGRS is defined as a renal disease caused by a B-cell or plasma cell clone resulting in the deposition of the secreted monoclonal immunoglobulin, or a fragment thereof, without evidence for overt lymphoma or myeloma.1 This is a fairly recently described clinical entity and warrants recognition and differentiation from the more common clinical plasma cell disorders, monoclonal gammapathy of undetermined significance (MGUS) and multiple myeloma (MM). The diagnosis of MGUS requires the monoclonal protein in serum to be less than 3 g/dL, bone marrow plasma cells to be less than 10 percent, and an absence of end-organ damage (e.g., anemia, hypercalcemia, lytic bone lesions, or renal failure) attributable to plasma cell proliferation.2 Patients with MGUS have a percent-per-year risk of progression to malignancy, which includes blood cancers such as MM, light chain amyloidosis and lymphoproliferative disorders. While renal failure is a defining feature of MM, this is driven by cast nephropathy or hypercalcemia, which is secondary to a high tumor burden. This is not MGRS.

The underlying pathologic lesion in MGRS is due to deposition of the monoclonal immunoglobulin fragment, with distinct localization and pattern of ultrastructural organization.1 Histologic features vary between MGRS subcategories, but all of the entities are linked by the presence of monoclonal immunoglobulin in the kidney, indicating the presence of any underlying clone of the pathologic immunoglobulin-producing lymphocytes or plasma cells.4

The suspicion of MGRS is usually based on finding a monoclonal gammopathy in conjunction with renal symptoms. It is imperative to rapidly assess the characteristics of the monoclonal gammapathy, carefully search for extrarenal manifestations (which can be common and critical in patients with light chain amyloidosis who frequently have multiorgan involvement, and where early diagnosis is critical for good outcomes), and gauge the type of nephropathy. In most cases, a kidney biopsy with immunofluorescence, and electron microscopic studies to identify the deposit composition and pattern of organization are needed. The spectrum of MGRS encompasses a variety of renal lesions and may be associated with extrarenal manifestations (Table).

Laboratory Diagnosis of MGRS
Following a diagnosis of MGRS, a search for the underlying clonal disorder needs to be undertaken. These tests include a serum protein electrophoresis, urine electrophoresis, serum and urine immunofixation, and the free light chain assay. A peripheral blood flow cytometry can be helpful in identifying a B-cell clone. Further, a bone marrow aspirate and biopsy helps direct detection of the underlying clone. Lastly, a whole-body scan using computed tomography (CT) scan or 18-fluorodeoxyglucose positron emission tomography (CT) is helpful in cases where the bone marrow is negative, and there is high suspicion for lymphoma to identify lymphadenopathy. In this setting, a lymph node biopsy may be warranted to identify the underlying clonal pathology. While among most cases the underlying clone is associated with the same light chain restriction as the renal pathology, in rare cases there may be a discordance between the clonal type in the bone marrow and the renal pathologic deposits.

Treatment of MGRS
Recent years have seen the development and approval of many therapies to treat B-cell and plasma cell cancers. These clone-directed therapies are also effective in eradicating the underlying clone of MGRS, but clinicians must still pay attention to the toxicity profile of agents, particularly toward the kidneys, and any dose reductions that may be warranted.

Proteasome Inhibitors
Bortezomib, carfilzomib, and ixazomib are U.S. Food and Drug Administration (FDA)–approved proteasome inhibitors used in MM. Bortezomib is also approved in some subtypes of lymphomas. It is the preferred agent in MGRS as it has 1) no renal toxicity, 2) does not need dose adjustments for renal insufficiency, and 3) has a good tolerance profile. Recently, there has been concern for drug-induced thrombotic microangiopathy with proteasome inhibitor therapy,5 which should be recognized and considered in the right setting.

Monoclonal Antibodies
Rituximab, a monoclonal antibody directed at CD20, is effective in B-cell clones. It has a favorable toxicity profile and can be given at full dose in renal failure. Daratumumab is a monoclonal antibody directed at CD38, and it is effective in B-cell clones. It has a favorable toxicity profile and can be given at full dose in renal failure. Daratumumab is a monoclonal antibody directed at CD38 and is approved for treatment of relapsed MM. There is an ongoing clinical trial testing daratumumab in the treatment of MGRS (NCT03095118).

Cytotoxic Chemotherapy
Alkylation agents such as cyclophosphamide, bendamustine, and melphalan can target both B-cells and plasma cells. Cyclophosphamide and bendamustine have a safe renal profile. Purine analogs such as fludarabine and pentostatin also have excellent activity against B cells and may be used in combination with other drugs such as antibodies or alkylators; however, they can have more toxicities related to myelosuppression and are not recommended in the setting of an estimated glomerular filtration rate lower than 30 mL/min.

Table . Monoclonal Gammapathy of Renal Significance Lesion Type and Associated Renal/Extrarenal Manifestations

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Underlying Clone Type</th>
<th>Type and Location of Renal Deposit</th>
<th>Renal Manifestations</th>
<th>Extrarenal Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ig light chain, heavy chain, and heavy and light chain amyloidosis</td>
<td>PC, CLL, NHL</td>
<td>Fibrillar, glomerulus (tubulointerstitial and perivascular involvement common)</td>
<td>Proteinuria, NS, CKD</td>
<td>Common: heart, peripheral and autonomic nervous, soft tissue, liver</td>
</tr>
<tr>
<td>Immunostained GN/GOMMID</td>
<td>NHL, CLL, PC</td>
<td>Microtubules, glomerulus</td>
<td>Proteinuria, NS, CKD</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Type 1 cryoglobulinic GN</td>
<td>PC, LPL</td>
<td>Microtubules, glomerulus</td>
<td>Proteinuria, NS, CKD, microhematuria, hypertension, nephrotic syndrome</td>
<td>Common: skin, peripheral nerves, joints</td>
</tr>
<tr>
<td>Light chain proximal tubulopathy</td>
<td>PC</td>
<td>Crystals, tubules</td>
<td>Fanciuri syndrome, tubular proteinuria, slowly progressive CKD</td>
<td>None</td>
</tr>
<tr>
<td>Crystal-storing histiocytosis</td>
<td>PC, LPL</td>
<td>Intratubular eosinophilic crystalline inclusions within interstitial histiocytes, proximal tubular cells and podocytes</td>
<td>CKD</td>
<td>Common: bone marrow, liver, spleen, LN, skin, cornea, lung</td>
</tr>
<tr>
<td>Monoclonal immunoglobin depositoin disease</td>
<td>PC, LPL</td>
<td>Granular deposits/inclusions, glomerulus</td>
<td>Proteinuria, NS, CKD, microhematuria, hypertension</td>
<td>Heart, lung, liver</td>
</tr>
<tr>
<td>Proliferative GN with monoclonal immunoglobin deposits</td>
<td>PC, NHL</td>
<td>Granular deposits/inclusions, glomerulus</td>
<td>Proteinuria, NS, CKD, microhematuria, hypertension</td>
<td>None</td>
</tr>
<tr>
<td>C3 glomerulopathy with monoclonal gammapathy</td>
<td>PC</td>
<td>Granular deposits/inclusions, glomerulus</td>
<td>Proteinuria, NS, CKD, microhematuria, hypertension</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: CKD, chronic kidney disease; CLL, chronic lymphocytic leukemia; GN, glomerulonephritis; GOMMID, glomerulonephritis with organized microtubular monoclonal immunoglobulin deposits; LN, lymph node; NHL, non-Hodgkin lymphoma; NS, nephrotic syndrome; PC, plasma cell.
**Immunomodulatory Agents**

These agents, which include thalidomide, lenalidomide, and pomalidomide, are active against plasma cells as well as B cells. However, they need dose reductions when used in renal insufficiency and may be associated with more adverse effects. Consequently, these agents are not the first choice to treat MGUS.

**Stem Cell Transplantation**

High-dose melphalan with autologous hematopoietic cell infusion allows achievement of a deep hematologic response. In a series of four patients with dialysis-dependent monoclonal immunoglobulin deposition disease, all underwent kidney transplantation at a median of 2.6 years after stem cell transplantation (2 in complete response and 2 in partial hematologic response).5

**Other Agents**

Bortezomib is FDA-approved for CLL and multiple lymphoma subtypes. It is orally administered and has a generally favorable safety profile. There is no existing data supporting the use of bortezomib in MGUS. Corticosteroids are typically combined with other clone-directed therapies described here in most commonly used regimens.

**Patient Follow-Up**

This patient was discharged and referred to hematology to start treatment. He was started on cyclophosphamide with bortezomib and pomalidomide, are active against plasma cells and B cells. However, they need dose reductions when used in renal insufficiency and may be associated with more adverse effects. Consequently, these agents are not the first choice to treat MGUS.

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Dr. Christina Barrattau from the Lurie Children’s Hospital in Chicago, IL meets with Sen. Tammy Duckworth (D-IL).

**Mark Your Calendar for Policy and Practice Lunches at the 60th ASH Annual Meeting**

The ASH Grassroots Network Lunch, to be held Saturday, December 1, 2018, at 11:15 a.m., in the Marriott Marquis Ballroom G in San Diego, will provide a space for ASH leaders and colleagues to discuss the impact of a changing political landscape in Washington and how it affects hematology. Attendees will have the opportunity to learn about ASH’s advocacy efforts, including the Society’s communications with Congress and federal agencies, and how to become an effective advocate for hematology.

Dr. Christina Barrattau from the Lurie Children’s Hospital in Chicago, IL meets with Sen. Tammy Duckworth (D-IL).
Targeting TP53 Mutations in Myelodysplastic Syndromes

The advent of next generation sequencing (NGS) has revolutionized management of pathogenic single nucleotide (SN) mutations (MDS). From these analyses, TP53 mutant MDS, accounting for 10 to 10% of de novo MDS and therapy-related MDS, represent a specific cohort with the worst outcome (median overall survival OS, 6-12 months). Specifically, these patients lack effective disease-modifying therapy compared to wild-type patients and display profoundly inferior OS with hypomethylating agent (HMA) therapy, which represents the standard of care in higher risk MDS.1,2 Furthermore, TP53 mutations are oncogenic single-gene mutation in all cohorts to predict inferior OS and minimal benefit from allogeneic hematopoietic stem cell transplantation.3,4 Additionally, we recently identified that TP53 variant allele frequency (VAF) is a key determinant of patient outcomes and further stratifies survival over binary mutation analysis and clinical prognostic models in MDS.1,5 Together, these studies highlight the profound negative clinical implications of TP53 mutations in MDS, and the urgent need for effective, biologically rational, targeted therapies.

Reactivation of Mutant p53
Clinical investigations in MDS are increasingly focused on exploiting biological consequences of specific somatic mutations as personalized therapeutic approaches, exemplified by IDH2/23 inhibiting the mutant enzyme.6 But what about targeting TP53 mutation? One option recently studied in a prospective trial uses a novel small molecule anti-cancer compound, APR-246, that reactivates mutated and non-functional p53 and targets the cellular redox balance, two Achilles heels of cancer cells.7 This small molecule pro-drug is a methylated derivative and structural analogue of p53 re-activation and induction of massive apoptosis (PRIMA-1).8 Notably, PRIMA-1 was able to restore DNA binding and wild-type configuration and function in both contact and structural mutants.9 APR-246 spontaneously releases the active drug, species, methylene quinuclidinone (MQ), at physiological pH. MQ forms a covalent bond with cysteine residues in p53—an event that thermodynamically stabilizes p53 protein, shifting the dynamic equilibrium away from the unfolded unfolded-misfolded state and toward the wild-type p53 conformation (Figure 1).10 Mutant p53 that achieves a wild-type conformation can then dimerize, and under conditions of cellular stress, form the tetrameric p53 species that drives transcription of targets that culminate in cell cycle arrest and apoptosis. A previous phase I study of APR-246 monotherapy that included patients with hematologic malignancy had on-target effects of p3 reactivation including induction of cell cycle arrest, apoptosis, and increased expression of p53 target genes (e.g., BAX, PUMA, and NOXA; Figure 1).10,11,12

In contrast to reactivating mutant p53, there has been substantial investigation of evaluating activation of wild-type p53 via inhibition of the critical negative regulators of p53 (i.e., MDM2 and its homolog MDMX (also known as MDM4)).13 Amplification of MDM2 and/or overexpression of MDM2/MDMX lead to blockade of p53 transcriptional activity and consequent tumor formation and/or progression. RG7112 is a small molecule MDM2 antiserin that blocks the p53 pathway. Notably, the MDM2 antagonist idasanutlin has yet to be resolved. Furthermore, understanding the downstream complex network of pathways that are impacted by transcriptional activation of p53 warrants investigation. It is notable that the clinical utility of these agents is likely in combination with other traditional and novel therapies, with unanswered questions focused on understanding how p53 reactivators can best synergize with these treatments. Personalized therapy in MDS has become possible through comprehensive understanding of the molecular architecture of an individual’s disease and optimally will translate into novel therapies for patients in the near future.

Conclusions and Unanswered Questions
As TP53 mutations represent the most common genetic alteration in cancer, occurring in approximately 50% of all invasive malignancies, developing targeted therapeutic strategies for mutant p53 proteins has far-reaching clinical applications. This is particularly relevant in hematologic malignancies in which TP53 has been identified as the most powerful negative prognostic covariate. Although mutant p53 historically has been considered an undruggable target, there are growing interests in compounds that reconstitute mutant p53 with APR-246, a notable advance in clinical development (Table). Defining the exact mechanisms of action of these agents with regard to restoration of wild-type function of p53 as well as impact on specific TP53 variants has yet to be resolved. Furthermore, understanding the downstream complex network of pathways that are impacted by transcriptional activation of p53 warrants investigation.

Therapeutic Targeting of Mutant TP53 in MDS
Current understanding of the care for higher-risk MDS is HMA, though those with TP53 mutations rarely achieve durable clinical benefit and need more OS.13 It is this population that is being targeted in a phase II/III combination study of sequential APR-246 and azacitidine in HMA-naive, TP53 mutant MDS and oligohematologic AML (≤ 30% blasts). The preliminary phase Ib results were presented at the 23rd European Hematology Association Congress in Stockholm, Sweden (Abstract 1155S ClinicalTrials.gov identifier NCT03162704). Five of six patients who received response evaluable, with one patient desconsuming treatment prior to the first disease assessment. Overall response rate by the 2006 International Working Group Criteria was 17 percent with 80 percent of patients (4 of 5) achieving complete remission (CR; 3 of 3 patients in dose level 2) and one minor CR (mCR). Patients who achieved CR had deep molecular responses, with a median VAF at minimum clearance of 0.8 percent. As nuclear p53 positivity by immunohistochemistry is strongly concordant with TP53 mutational status and provides a functional readout of accumulated misfolded protein,14 we are analyzing p53-IHC as a potential biomarker of response. Notably, all CR patients had high p53 positivity by IHC at baseline (35-70%), which normalized on serial assessment (<5%). These data are encouraging and provide early proof-of-principle of clinical efficacy of p3 reactivation in the treatment of patients with MDS.

Table. Novel Therapeutic Agents Targeting Mutant p53 Reactivation

<table>
<thead>
<tr>
<th>Class of Compounds</th>
<th>Agent</th>
<th>Novel Features</th>
<th>Patient Population</th>
<th>Stage of Development</th>
<th>ClinicalTrials.gov Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinolines</td>
<td>APR-246</td>
<td>Covalently bonds to mutant p53 to shift equilibrium to wt activity</td>
<td>HMA naive HR-MDS; R/R melanoma, ovarian, and esophageal cancer</td>
<td>Phase 1-3</td>
<td>NCT03072043; NCT02098843; NCT02998893; NCT03939105</td>
</tr>
<tr>
<td>Pyrazoles</td>
<td>PK7088</td>
<td>Reactivation of Y220C TP53 mutation</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>2-Sulfonpyrimidines</td>
<td>PK11007</td>
<td>↑ thermal stability of mutant p53 to wt activity</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Zinc metallochaperones</td>
<td>ZMC1</td>
<td>Reactivates p53 mutant proteins with impaired zinc-binding; ↑ ROS</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Thioserinobcarbene</td>
<td>COTI 2</td>
<td>↑ wt p53 conformation inhibits PKA/Akt/MTOR pathway</td>
<td>R/R gynecologic malignancies and head and neck SCC</td>
<td>Phase 1</td>
<td>NCT02433626</td>
</tr>
<tr>
<td>Small peptides</td>
<td>Peptide</td>
<td>Multiple mechanisms to wt properties</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HMA, hypomethylating agent; HR-MDS, higher risk myelodysplastic syndrome; NA, not applicable; ROS, reactive oxygen species; R/R, relapsed/refractory; SCC, squamous cell carcinoma; wt, wild-type.
The Novel Therapeutic Agents Targeting Mutant p53 Reactivation

2-Sulfonylpyrimidines

Pyrazoles

46, CDB3,

Multiple mechanisms

Inhibits PI3K/AKT/mTOR proteins with impaired equilibrium to wt mutant p53

wt p53 confirmation; thermal stability of wt

↑ ROS

head and neck SCC

R/R gynecologic R/R melanoma,

Phase 1-3

Identifier

COTI-2

APR-246

PK7088

Covalently bonds to

NCT03072043; NA


21. Welch JS, Petti AA, Miller CA, et al. TP53 and


2. Ingram VM. A specific chemical difference between the globins of normal


The Method to Our Movement

IFEYINWA (IFY) OSUNKWO, MD, MPH

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It is exciting to see so much traction in the field of sickle cell research in the past decade. The number of therapeutic clinical trials currently available for sickle cell disease (SCD) on clinicaltrials.gov has increased exponentially between 2008 and 2018. We have had the second FDA-approved drug for reducing pain episodes in sickle cell, L-glutamine, announced in July 2017. And for the first time, there was a new therapeutic, intravenous, cruizanumab, proven in randomized phase III clinical trials to be effective in preventing sickle cell vaso-occlusion for all sickle cell genotypes, including the often-forgotten double heterozygotes HbcG and SB+ thalassemia.

This is all good news for individuals living with SCD and for their treating providers. Curative therapies for SCD are no longer just whispered about and considered a pipe dream but are now front and center in the Sickle Cell Initiative. This bold initiative will catapult curative therapy to nearly every patient, using novel regimens and stem cell sources as well as gene editing technology. The role of the patient and the sickle cell community has also become more visible, and they are being truly engaged as equal partners in investigating therapeutic and supportive care options for persons living with SCD, including elderly adults who are now living well into their sixth decade and beyond.

A friend of mine living with homoygous SS recently shared her thoughts. "What about us ‘mature’ sickle cell adults? Why do... clinical trials have to cap at age 45 or 50? I am planning to live to be 99 years old with no teeth and a walker, so how long will I have to wait to benefit from therapeutic therapies that can help me?" Having benefited from past scientific successes that brought comprehensive care and hydrosaccs to the mainstream management of SCD she states, "I am ready for the future, but y'all researchers and clinicians need to keep up." This article by Dr. Benz brings visibility to the fact that clinicians, researchers, and funders are indeed trying to "catch up," borrowing a phrase from my dear friend. The Sickle Cell Initiative demonstrates a pragmatic approach to move the sickle cell research needle further and faster to keep up with the improvement in care outcomes we have seen in pediatrics. SCD is now considered an adult disease as patients are living longer. However, we are also seeing more of the long-term impact of chronic organ damage as adults with SCD age, and this forces us to not be complacent. It is not enough to show that we have improved infant mortality rates and that children are surviving 98 percent of the time into adulthood. We must take it a step further to ensure that every patient everywhere and at every time in their life trajectory has access to age-specific comprehensive care that includes shared decision making that gives the individual the ability to avail themselves of novel therapies to improve long term morbidity and mortality and yes, to cure their disease.

The Sickle Cell Initiative is also about timeliness of delivering these innovative interventions for SCD. As my friend said, her window of benefit from science to improve her long-term outcomes is "now," at age 62 years, so that she can safely and securely make it to age 99 years, "with no teeth and a walker."

Learn About a Groundbreaking Clinical Trials Network for SCD

On Monday, December 3, 2018, from 6 p.m.-7:30 p.m. at the 60th ASH Annual Meeting, ASH will host an SCD Clinical Trials Network (CTN) Q&A Reception in Room 2 of the San Diego Convention Center. This open event will provide information on the recently formed ASH Research Collaborative, which is now recruiting sites for its SCD CTN. Trial sites interested in joining the network will have a chance to have their questions answered directly by CTN leadership and receive an overview of the network and the research registry that will serve as its foundation from CTN Co-Chairs Drs. Charles Abrams and Edward Benz Jr., as well as CTN and registry staff. Dr. Benz indicated no relevant conflicts of interest.

The Cure Sickle Cell Initiative (Cont. from page 1)

4. Encouraging novel endpoints and clinical trial designs.

It has long been known that too often, only patients with the most advanced disease participate in higher-risk investigational endeavors. For example, most gene therapy or gene editing trials are likely to be undertaken in adults, yet those individuals are more likely to have organ dysfunction or comorbidities. How can we more rapidly and efficiently identify new therapeutic agents and/or strategies to treat patients before their disease makes them unlikely to benefit?

Dr. Collins will give a keynote talk at the Presidential Symposium taking place at the 2018 ASH Annual Meeting in San Diego, December 1-4, 2018, and is expected to outline the Initiative’s in his talk on "Accelerating Cures in the Genomic Age." Dr. Collins will describe not only how fundamental advances in understanding viral vectors, targeted cells, and genetic modification are advancing the field, but also what government entities such as NHLBI and NIH can do to foster these advances.

Skepticism might regard this initiative as lofty or even nonviable. Lofty, perhaps, but certainly realistic. After all, it is by envisioning a perfect outcome that one can devise a plan to get to that outcome.

A New Therapy for Sickle Cell Disease: FDA Approves Oral L-glutamine for Prevention of Acute Vaso-occlusive Events in Children and Adults


A cute vaso-occlusive events (pain or acute chest syndrome) are the hallmark of sickle cell disease (SCD), resulting in a vast number of pain events for individuals affected with the disease and in millions of dollars per year of preventable health care expenditures. Until now, the U.S. Food and Drug Administration (FDA) has approved only one therapy for the prevention of acute vaso-occlusive pain events – hydroxyurea therapy. In 2017, the FDA approved L-glutamine (an amino acid) twice daily for preventing acute vaso-occlusive events in children and adults with SCD. This article presents the results that led to this approval.

Artful clinical research and two decades of translational perseverance provide the study background. Red blood cells (RBCs) in individuals with SCD have increased concentrations of reactive oxygen species compared with normal RBCs. Prior work demonstrated that homoeosmia, asparagine, and glutamine inhibited sacking of erythrocytes at room temperature. In 1994, Dr. Yutaka Nihira and colleagues conducted a small clinical study in seven patients with SCD and demonstrated a subjective improvement in symptoms after treatment with L-glutamine. Most importantly, the team demonstrated evidence to support their hypothesis – namely, that oral L-glutamine can significantly increase the NAD redox potential and NADH level in sickle RBCs.

In 2005, Dr. Nihira and colleagues demonstrated that 30 g per day of L-glutamine reduced endothelial adhesion of sickle RBCs to human umbilical endothelial cells. Subsequently, in 2014, Dr. Nihira and colleagues conducted a phase II randomized double-blind placebo-controlled parallel-group multicenter study of 81 participants aged five years or older who were diagnosed with SCD or sickle β-thalassemia. The results were promising and demonstrated a significant decrease in the incidence of vaso-occlusive events (3 vs. 4 events; p=0.005) and hospital days (6.5 vs. 11 days; p=0.0045), with no increase in adverse events when compared with placebo.

Finally, this phase III double-blind randomized controlled trial has been completed and published. A total of 230 participants with SCD or sickle β-thalassemia (age range, 5-58 years) were randomly assigned in a 2:1 ratio to receive L-glutamine (152 participants) or placebo (78 participants) for a total of 48 weeks. The trial medication (active therapy or placebo) was self-administered orally twice daily at approximately 0.3 g per kg of body weight per dose (10 g, 20 g, or 30 g [maximum dose] per day). Participants were given packets containing 5 g of white unflavored powder. The participants were expected to mix the contents of the packet with a nonheated drink or food and consume immediately. To encourage adherence, participants received phone calls from research personnel. The participants in the L-glutamine group had significantly fewer pain episodes in the study period than those in the placebo group (p=0.005), with a median of 3.0 and 4.0 events, respectively, during the 11-month trial period. There were also fewer hospitalizations in the L-glutamine group versus the placebo group, with a median of 2.0 in the L-glutamine group and 3.0 in the placebo group (p=0.005). In both groups, hydroxyurea was prescribed in approximately two-thirds of the participants. Low-grade adverse events (nausea, noncardiac chest pain, fatigue, and musculoskeletal pain) were more common in the treatment group versus the placebo group.

Despite the success of the trial leading to an FDA-approved therapy, several questions linger about the results. The number of participants who completed the trial, designed to last 11 months, was significantly lower than expected. Only 63.8 percent and 75.6 percent in the treatment group and placebo group, respectively, completed all 11 months. Given the high dropout rate during the trial, imputation of the missing data was a key statistical approach to interpret the final clinical trial results. Furthermore, such a significant dropout rate in a clinical trial raises significant concerns about adherence outside of a clinical trial. Clearly, different strategies are required to improve adherence to this twice-a-day oral therapy. The trial excluded individuals with hemoglobin SCD and other compound heterozygotes with SCD. Presumably, compound heterozygotes with SCD will be prescribed L-glutamine therapy, but the relative benefits are unclear, particularly given the anticipated lower rate of acute vaso-occlusive events in this population. Very likely, children and adults with SCD prescribed hydroxyurea therapy will receive dual therapy, and for those who cannot tolerate or refuse to take hydroxyurea, L-glutamine may become the initial therapy to attenuate the incidence rates of acute vaso-occlusive events.

Dr. Nihira, his colleagues, and the study participants and their families are to be congratulated on a job well done. The SCD community is grateful for completion of this trial and for establishing a new treatment option for children and adults with SCD. We look forward to the next iteration of research to better define other benefits of L-glutamine for SCD and to identify strategies for improved adherence to this therapy.
Mimicry Not Replacement: Molecular Engineering Transforms the Outlook in Hemophilia A

The New England Journal of Medicine

August 30, 2018

The dosing administration of emicizumab is straightforward. Four initial loading doses of 3 mg/kg are given weekly, then prophylaxis continues with either 1.5 mg/kg weekly or 3 mg/kg every two weeks. The half-life of the antibody is 30 days, which contrasts notably with the value of eight to 12 hours for factor VIII. It is important to remember that emicizumab is a prophylactic therapy, and as such, Factor VIII was given as required for breakthrough bleeding events.

The primary endpoint was beautifully simple and measured the difference in the rate of treated bleeding episodes (referred to as the "annualized bleeding rate") between the three groups. The results were truly remarkable. The annualized bleeding rate was 38.2 events in group C (no prophylaxis,) but was reduced to only 1.5 and 1.3 events in groups A and B. This equates to a 96 percent and 97 percent reduction, respectively. All patients in group A and B, respectively, did not have a single bleeding event, and more than 90 percent had at most three such events.

Outcomes in group D, in which patients had previously taken prophylactic factor VIII therapy, revealed an annualized bleeding rate of 1.8, and 56 percent of patients became entirely free of bleeding episodes. This was a particularly interesting group because the investigators could compare the annualized bleeding rate to that seen when patients were on prior prophylactic factor VIII therapy. This value was estimated at 4.8 events per year, showing that emicizumab led to a 68 percent reduction in bleeding episodes.

One of the huge advantages of emicizumab is that it is given subcutaneously every seven or 14 days, which is convenient for patient delivery. Remarkably, 84 percent of patients chose emicizumab therapy above traditional management with factor VIII. Of the 46 patients in group D who had had experience of both prophylactic factor VIII and emicizumab, all but one patient preferred emicizumab.

Treatment was well tolerated, and adverse effects were largely minimal and mainly related to injection site reactions, with only one patient stopping treatment due to factors that were thought to be related to the drug. There has been some concern that emicizumab can provoke thrombotic reactions in patients undergoing concurrent treatment with activated prothrombin complex concentrate (APCC), but no microangiopathic or thrombotic microangiopathy events were observed in this trial. This observation does have a logical explanation as factor VIII and emicizumab compete for their activity and do not have "additive" coagulation potential, whereas the combination of emicizumab and APCC could have synergistic activity in thrombin generation.

The U.S. Food and Drug Administration has already granted breakthrough therapy designation to emicizumab for the treatment of patients with hemophilia A without factor VIII inhibitors, on the basis of the HAVEN 3 trial. Emicizumab is emerging as a genuine game changer in the treatment of hemophilia A and may come to represent a standard form of prophylaxis, with a subsequent huge reduction in usage of factor VIII. Ironically, its major threat may ultimately come from the introduction of gene therapy to "cure" the condition. These findings are evidence, indeed, of a truly remarkable transition in the management of this disorder.


The Hematologist: ASH News and Reports

Paul Moss, MD, PhD
Dr. Moss indicated no relevant conflicts of interest.
Can We Vaccinate Our Way Out of Multiple Myeloma Progression?


T he fundamental idea that the immune system has antitumor potential can be traced back to 1893 when Dr. William B. Coley reported on 10 carcinoma cases treated with injections of killed cultures of Streptococci and Bacillus prodigiosus producing erysipeloid infection and inducing immune-mediated tumor regression. More recently, the therapeutic potential of the immune system has been appreciated due to the curative impact of allogeneic hematopoietic stem cell transplantation, such as the graft-versus–multiple myeloma (MM) effect.1 Profound immune dysfunction in MM has been demonstrated,2 therefore the therapy targeting the suppressive tumor microenvironment has gained a lot of attention. Antiviral vaccination aims to overcome inadequate endogenous cellular antitumor immunity by stimulating effector cells to target myeloma cells. While early vaccine therapy studies were shown to be safe with minimal toxicity and to induce immunogenicity, clinical efficacy has been uncertain or limited.3,4 Critical issues to address in myeloma vaccine therapy include low mutational burden that results in lower numbers of neoplastic epitopes, unique fusion protein targets generated by chromosomal abnormalities, and ineffective T-cell responses of clonal populations with decreased immunogenicity upon immune editing of malignant clones.5

Dr. David Avigan and colleagues recently discussed key hurdles to overcome for a successful and effective antitumor vaccine. In addition to finding the optimal antigenic target for MM, alternative vaccine platforms are necessary to overcome the functional and phenotypical deficiencies of endogenous antigen–presenting cells in the tumor microenvironment. Determining the appropriate setting for vaccination to maximize T-cell activation and prevent exhaustion and defining optimal combination therapies that enhance the vaccine’s effect are essential in driving clinically effective antitumor vaccines. Furthermore, early immunotherapeutic interventions in smoldering MM (SMM) are attractive, not only because the rate of progression to MM is substantially greater versus monosclerotic gammopathy of undetermined significance, but also because disease progression is associated with loss of myeloma-reactive clones in the T-cell repertoire, thereby limiting the immune response. This is an area where we have observed in myelomas and is a clinical reality that a peptide-based vaccine was predominantly noted in patients with low disease burden (<10% blasts in the marrow).6

To address the feasibility of vaccine therapy in a stage of limited disease-related immune suppression, Dr. Ajay K. Nooka and colleagues conducted a phase 1/IIa nonrandomized clinical trial assessing the PVX-410 multivalent vaccine in SMM. Twenty-two patients with HLA-2 positive moderate- to high-risk SMM were randomized to one of three treatment cohorts, comprising monotherapy (n=9), combination monotherapy (n=9), or combination therapy (n=9) that consisted of biweekly subcutaneous vaccine injection along with three daily cycles of 25 mg oral lenalidomide. PVX-410 is an HLA-restricted multivalent peptide composed of four chemically synthesized myeloma antigen peptides: CD138, SLAMF7, and XBP1. These antigens were chosen based on in vitro T-cell reactivity to assess each antigen-specific effector response to myeloma cells resulting in cell proliferation, interferon-γ (IFN-γ) secretion, and cytotoxic activity in response to MM cells.7

Both PVX-410 monotherapy and combination therapy were well tolerated, with only grade 1 or 2 vaccine-related treatment-emergent adverse events such as chills, fatigue, myalgia and pruritis, and injection-site reactions. No patients experienced a PVX-410-related serious adverse event or discontinued treatment because of a treatment-related event. PVX-410 induced an immune response in 19 of 20 evaluable patients (10 of 11 monotherapy vs. 9 of 9 combination therapy) as measured by the increase in percentage of tetramer-positive CD8+ T cells (1.5-fold increase) and IFN-γ-producing T cells (twofold increase). Antigen-specific T-cell response was measured at baseline and after weeks 4 and 8 post-treatment. The addition of lenalidomide increased the immune response magnitude at weeks 4 and 8 post-treatment (p<0.001 for both).8,9 Both therapies significantly increased effector memory CD8+ T cells, suggesting durable immune responses. Monotherapy resulted in stable disease (SD) with five of 12 patients progressing within 12 months, while combination therapy led to SD in four patients and some minimal response in four patients. Those who did not progress had a greater immune response; specifically, patients showing more than tenfold response at more than two time points were more likely to demonstrate a clinical response or SD.

Although clinical response was modest, the safety, tolerability, and efficacy of the PVX-410 vaccine in SMM remains promising. The complex nature of immune dysfunction and the low mutational burdens in SMM supports the use of combination therapy. Lenalidomide induces antitumor immunity and potentiates vaccine therapy in MM,10 and it therefore seems a logical choice for combination therapy. Moreover, other strategies to potentiate antitumor vaccination are currently being studied by adding hypomethylating agents (NCT02886605), targeting earlier disease stages (NCT03591614), and developing a personalized ‘measocan’ vaccine (NCT03561043). Could the answer be as simple as a vaccine to prevent progression to MM? There are still roadblocks to a cure for myeloma; however, it is of no surprise that therapy targeting the suppressive tumor microenvironment has gained a lot of attention. Antigen-specific T-cell response was measured at baseline and after weeks 4 and 8 post-treatment. The addition of lenalidomide increased the immune response magnitude at weeks 4 and 8 post-treatment (p<0.001 for both).8,9 Both therapies significantly increased effector memory CD8+ T cells, suggesting durable immune responses. Monotherapy resulted in stable disease (SD) with five of 12 patients progressing within 12 months, while combination therapy led to SD in four patients and some minimal response in four patients. Those who did not progress had a greater immune response; specifically, patients showing more than tenfold response at more than two time points were more likely to demonstrate a clinical response or SD.

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Inherited Genetic Variants Increase the Likelihood of Developing Clonal Hematopoiesis: Something Akin to Pre-CHIP


Clonal hematopoiesis is commonly observed in persons without cancer or significant cytopenias, and its incidence increases with age. It is believed to be a normal variant of hematopoiesis. In this study, the authors assessed the association between clonal hematopoiesis and the risk of developing cancer. They found that an increased risk of developing a hematologic cancer (estimated at approximately 1% per year) and all-cause mortality is related to an elevated risk of cardiovascular events. Clonal hematopoiesis is a potential biomarker for the development of cancer, and the authors provide insights into various ways germline mutations favor the development of clonal hematopoiesis.

Acquired Clinical Resistance to IDH2 Inhibitors: Leukemia Finds Multiple Avenues for Escape


In approximately 20 percent of patients with acute myeloid leukemia (AML), an inhibitor of the enzyme IDH1 (AG-221) or IDH2 (ivosidenib or enasidenib) may be used to treat the disease. Despite initial response, peripheral blood counts improved and blast counts were reduced. However, treatment failure was common, and the authors found that the acquired resistance was due to the emergence of clones that harbored second-site mutations. These mutations allowed the emerging clonal populations to escape the pressure exerted by the IDH2 inhibitor.

Dr. Andrew M. Inteklof and colleagues studied serial samples from two patients with IDH2-mutant AML who had a clinical response to enasidenib followed by disease progression and a recurrent increase in circulating levels of 2-HG, an intermediate metabolite. Peripheral blood counts improved and blast counts were reduced. Consistent with previous observations, the authors discovered that the AML clones harboring IDH2-mutations, the variant allele frequency for the IDH2<sup>150L</sup> mutation did not substantially diminish, but remained at a level similar to those documented at the commencement of therapy. In both cases, new mutations were observed in the genomes of both patients at the time of acquired resistance. These missense mutations resulted in a substitution of glutamine 316 with glutamate (G316E) in the first patient and in substitution of isoleucine 319 with methionine (I319M) in the second patient. Nevertheless, these second-site mutations were detectable by highly sensitive digital droplet polymerase chain reaction assays prior to the initiation of enasidenib. Intriguingly, these mutations affected the other IDH2 allele (i.e., the previously wild-type allele of IDH2). These data suggest that the acquisition of the second-site mutation was a plausible event that occurred in the setting of acquired resistance to IDH2 inhibition. The authors proposed that these second-site mutations may occur early in hematologic malignancies, leading to a subpopulation of cells that are resistant to IDH2 inhibition.

In contrast to Dr. Inteklof and colleagues, Dr. Lynn Quek and colleagues did not find any examples of second-site IDH2 mutations at relapse in 16 patients treated with enasidenib. The investigation of the clonal basis of responses, and acquired resistance to enasidenib treatment provides insights into the mechanisms of treatment failure. Using sequential patient samples and applying advanced flow cytometric analyses, clonal culture, and next-generation sequencing, they determined the clonal structure of hematopoietic cell populations at different stages of differentiation. The authors found that in pretreatment samples, the ability of mutant IDH2 to impose differentiation block was dependent on the context of co-associated mutations within a leukemic clone. Response to enasidenib was associated with generation of primary mutations that were highly penetrant, suggesting that the risk allele confers a proliferative advantage in the homozygous state. Most notably, the CNN-LOH risk variants were highly penetrant, with a large fraction of carriers showing that the risk allele confers a proliferative advantage in the homozygous state. Other genes that encodes a DNA-dependent protein kinase can be associated with clonal hematopoiesis.

Acquired mutations in our DNA are often thought to occur randomly or as a consequence of exposure to DNA-damaging agents. This work contributes further to our growing understanding that our germline genome influences the development of acquired mutations. It also provides insights into the process of clonal hematopoiesis and provides additional information about the mechanisms involved in the development of clonal hematopoiesis.
Updates on Usefulness of HERDOO2 Score and on Direct Oral Anticoagulant Use in Antiphospholipid Syndrome


The original HERDOO2 score publication1 and subsequent validation study2 were discussed in the July/August 2017 issue of The Hematologist. Since then, further analysis of the latter study has been published, evaluating whether using D-dimer assays other than the originally tested VIDAS® D-dimer assay could lead to a change in anticoagulation at low risk for recurrent venous thromboembolism. The Table (available online only) shows the components of the HERDOO-2 score: Women with zero to one point can stop anticoagulation because of a low risk of recurrent VTE; women with two or more points should receive anticoagulation because of a high risk of recurrent VTE (HR, 9.4; 95% CI, 1.7-52.5). Three different assays were studied: 1) Innovance® β2-glycoprotein-I antibodies and lupus anticoagulant) and had a thrombotic event (arterial or venous). The primary study endpoint was the composite of recurrent thromboembolism, major bleeding, and vascular death. After enrollment of 120 patients, the study was prematurely terminated because of an excess of events in the rivaroxaban arm: 11 events (19%) in the rivaroxaban arm, and two events (3%) in the warfarin arm (HR, 6.7; 95% CI, 1.5-30.5; p=0.01). Thromboembolic events, all arterial (4 ischemic strokes, 3 myocardial infarctions), occurred in seven patients (12%) randomized to rivaroxaban, with no events in the warfarin group (time in therapeutic range, 67%). Major bleeding occurred in four patients (7%) in the rivaroxaban group (2%) and none in the warfarin group. The authors of this study concluded that in high-risk patients with APS the use of rivaroxaban was associated with an increased risk of events (thrombosis plus bleeding) and thus showed no benefit over warfarin, but instead demonstrated excess risks.

The results of the study appropriately caution the use of rivaroxaban in the very prothrombotic setting of triple-positive APS patients. A few things about this study need reiterating: 1) All thrombotic events in the Rivaroxaban arm were arterial. This is in keeping with patients’ and pathophysiologic evidence in the ongoing ASTRO-APS trial, which led to a protocol modification of that study.2 It is not clear why patients in the rivaroxaban group had a high rate of arterial thrombosis while thrombosis did not seem to be a problem in the warfarin group. As aspirin use was similar (approximate 50% in both groups, 19% use of aspirin), the finding cannot be explained on the basis of an aspirin use disbalance. It is possible that the different mode of action of rivaroxaban and warfarin leads to this discrepancy. 2) The arterial events in the rivaroxaban group occurred in patients with a previous arterial qualifying event (n=11, 19%), but also in patients with a previous venous qualifying event (n=10). Thus, rivaroxaban use is of concern in APS patients with a history of arterial, as well as venous thrombotic events. 3) Several of the arterial thrombotic events occurred several months after the patient had done well on warfarin – four (52%) of seven arterial events occurred eight to 23 months after randomization to rivaroxaban. This argues that, based on this study, one may want to change a triple-positive APS patient who is currently on warfarin and has done well for months to warfarin. 4) The study does not describe how long patients had been on an anticoagulant for their history of thrombosis and what anticoagulant drug they had been on before randomization and study enrollment. Given that patients with APS were enrolled and a diagnosis of definite APS can only be made once antiphospholipid antibody (APLA) tests have been repeatedly positive (at least three months apart), I assume that the enrolled patients had been on some anticoagulant for at least three months before they were found to be eligible for this study and enrolled. If I assume that this drug was typically warfarin, then it is possible that warfarin failure occurred during those three months before study enrollment, making such patients ineligible to be enrolled onto the TRAPS trial. This would have skewed the risk profile of enrolled patients toward those who were ineligible to be enrolled onto the TRAPS trial. Thus, this study would have skewed the risk profile of enrolled patients toward those who were eligible to be enrolled onto the TRAPS trial. The only conclusion one could then draw from the current study is that if a triple-positive APS patient is doing well on warfarin, do not switch to rivaroxaban. 5) Finally, the data from the current study of a high failure rate of rivaroxaban cannot be translated to APS patients who are not triple positive.

The TRAPS study was discussed in the March/April 2018 issue of The Hematologist and has since been published. This randomized open-label trial compared rivaroxaban vs warfarin (target international normalized ratio, 2.0) in high-risk patients with antiphospholipid syndrome (APS) who were “triple positive” (i.e., positive for anticardiolipin and anti-β2-glycoprotein-I antibodies and lupus anticoagulant) and had a thrombotic event (arterial or venous). The primary study endpoint was the composite of recurrent thromboembolism, major bleeding, and vascular death. After enrollment of 120 patients, the study was prematurely terminated because of an excess of events in the rivaroxaban arm: 11 events (19%) in the rivaroxaban arm, and two events (3%) in the warfarin arm (HR, 6.7; 95% CI, 1.5-30.5; p=0.01). Thromboembolic events, all arterial (4 ischemic strokes, 3 myocardial infarctions), occurred in seven patients (12%) randomized to rivaroxaban, with no events in the warfarin group (time in therapeutic range, 67%). Major bleeding occurred in four patients (7%) in the rivaroxaban group (2%) and none in the warfarin group. The authors of this study concluded that in high-risk patients with APS the use of rivaroxaban was associated with an increased risk of events (thrombosis plus bleeding) and thus showed no benefit over warfarin, but instead demonstrated excess risks.

One clear benefit of the use of cDNTA for disease monitoring is the ease with which repeated sampling of disease can be performed. Given this, the authors then investigated whether dynamic changes in cDNTA levels might also predict disease response. They densely sampled plasma from the discovery cohort of 14 patients and noted that achieving 1) a two-log (i.e., -100-fold) decrease in cDNTA between pretreatment samples and post-treatment samples defined best responders. Since then, this study used CAPP-Seq, but alternative, commercially available methods for molecular monitoring in B-cell malignancies, including sequencing of immunoglobulin genes, should also be considered. Finally, these same threshold calls for implementation of clinical trials assessing the use of intensified therapy for patients with DLBCL who fail to achieve an EMR or MMP and have a high cDNTA level.

This study raises several points for future consideration. First, it builds on standardization of ethics and widely available assays for molecular monitoring in DLBCL. As mentioned earlier, this study used CAPP-Seq, but alternative, commercially available methods for molecular monitoring in B-cell malignancies, including sequencing of immunoglobulin genes, should also be considered. Finally, these same threshold calls for implementation of clinical trials assessing the use of intensified therapy for patients with DLBCL who fail to achieve an EMR or MMP and have a high cDNTA level.
A New Standard of Care for Children and Young Adults With T-cell Acute Lymphoblastic Leukemia


A multicenter, phase III, randomized clinical trial comparing two randomization assignments. Patients with TALL were randomized to standard-risk versus high-risk backbone therapy. The primary endpoint was event-free survival (EFS), with secondary endpoints including overall survival (OS) and relapse rates. The study enrolled 3,853 patients from 176 centers across the United States from 2007 to 2014.

Results:
- **EFS:** The median follow-up was 7 years. The 5-year EFS rate was 84.4% for the standard-risk arm and 86.4% for the high-risk arm (p=0.002).
- **OS:** The 5-year OS rate was 90.2% for the standard-risk arm and 92.3% for the high-risk arm (p=0.001).
- **Relapse Rates:** Relapse rates were lower for patients in the high-risk arm compared to the standard-risk arm.

Conclusions:
- The results of this study support the use of a high-risk backbone therapy for patients with TALL, suggesting that this approach may improve outcome compared to standard-risk therapy.
- The study highlights the importance of tailoring therapy based on risk stratification to improve outcomes for patients with T-cell leukemia.

The Hematologist: ASH NEWS AND REPORTS

Sapiens: A User's Manual for a Confused Species
By Yuval Noah Harari

I have recommended Yuval Noah Harari’s Sapiens to so many people, it was just a matter of time perhaps before Dr. Ash dealin invited me to pen my own “Sapiens.” It is a privilege to write about this particular work as I believe every human could benefit from reading it.

Dr. Harari is a historian who has connected multiple disciplines — anthropology, evolutionary biology, history, cultural studies, and philosophy — to weave them into a compelling story of our species. Homo sapiens. Sapiens is considered either a cultural history of our species or a product manual that explains some of our senseless behaviors (in essence, covenan biology and cognitive evolution of the past 10,000 years). Through his tight and elegant prose, Dr. Harari serves up massive amounts of data with wry humor to tell a gripping tale replete with delightful saliences and witty examples.

The past 70,000 years transformed us from an insignifi cant, small primate species eking it out in Africa (with no more environment significance than as a “firefly”) into the dominant, planet-shaping force that we are now. The four major processes that shaped our destiny including the cognitive, agricultural, and scientific revolutions, and the unification of humanity, are discussed in detail.

Mr. Harari’s take on some of humanity’s major achievements is rather unique. In fact, he questions whether they can actually be characterized as achievements. In a chapter titled “History’s Biggest Fraud,” he tackles the domestication of wheat, provocatively asking whether we domesticated wheat or were domesticated by it. Our species throughout the past few millennia transformed this “insignifi cant wild grass from the Middle East” into a ubiquitous plant species cultivated globally in an area 10 times the size of Great Britain. Homo sapiens broke rocks, tilled and irrigated fi elds, and destroyed wheat’s competitors, completely changing their own way of life from the ancient hunter- gatherer style to fi t into agricultural societies. It is hard to ignore the argument that wheat might have domesticated us (and not the other way around) — “a Faustian bargain between grains and humans.”

One of the chapters I fl nd most appealing describes the origins of large-scale human cooperation. The “mythical glue” that binds humans in large networks and allows them to cooperate on a broad scale is unique to our species and a product of our cognitive evolution. Mr. Harari expounds upon the imagined realities (i.e., social constructs or cultural myths) by providing us with intellectually satisfying examples such as the “legend of the twins.” These imagined realities that we all subscribe to in one form or the other — our own institutions, alma maters, sports teams, religions, the laws we obey, the idea of country, human rights, and justice — are all elements of an imagined reality and exist as signs of our species’ collective imagination. This insight on the nature of many things we hold dear has stuck with me. I fi nd it strangely comforting to think of the “dual reality” of our existence: that is, “the objective reality of trees and rivers and the imagined reality of gods, nations and corporations.” In his typically dry manner, Mr. Harari writes: “No one was more fl oored when … the UN demanded that the Libyan government respect the human rights of its citizens even though the UN, Libya and human rights are all fictions of our fateful imaginations.”

Another chapter that I have returned to many times deals with a comparison of Hammurabi’s Code and the Declaration of Independence — documents purporting to outline universal principles of justice. Mr. Harari reminds us that our imaginations of those principles and the myths we retell, there are no such concepts and immutable principles of justice. He comes up with a hilarious “biologically correct” version of the famous opening sentence from the

[Cont. on page 14]
Sapiens

(Cam. from page 13)

the Declaration of Independence, although some readers might take offense with his reductionism. One brilliant quote from the book: “History is something that very few people have been doing while everyone else was ploughing fields and carrying water buckets.”

One of the persistent arguments made throughout the book is that what we consider human greatness and evil. Realizing the artificiality of imagined realities can only be a positive step or happy. Was it when we lived in small bands of genetically related individuals hunting and gathering? Or was it when we learned the art of fire or when the wheel was invented? Or was it the moment in history when the first advent of writing allowed the preservation of knowledge? Or was it the moment in history when we started questioning the accepted wisdom and the status quo?

Ultimately, this is a book that creates a framework for introspection from which everyone can benefit. Can we spot wars predicated on disagreements over firmly believed imagined realities? Can we call our own imagined realities into question? Religion, caste hierarchies, partisanism, patriotism, and a whole host of other beliefs are drive what humans do to both greatness and evil. Realizing the artificiality of imagined realities can only be a positive step perhaps. As we stand on the threshold of manipulating our own genes and creating artificial intelligence, we must debate Harris’s question: “Can we trust covenants to be gods with unlimited power?”

Sr Francis Bacon said that only a few books could be chewed and digested thoroughly. Sapiens is certainly a book I wish all humans would chew, digest, and absorb.
While MRD status is well-established as a prognostic biomarker in B-ALL, not all MRD assays are the same, with a variety of established and emerging methodologies being worthy of further study. Most widely used are multiparametric flow cytometry MRD assays, which can identify a leukemia-associated immunophenotype in more than 95 percent of patients and detect one in 10,000 leukemic cells (analytical sensitivity of 10^-5).^{10} A less widely used and more laborious method for assessing MRD is the allele-specific oligonucleotide RT-PCR (ASO-PCR), which uses PCR primers designed for a patient’s individual immunoglobulin sequence. Using the ASO-PCR method, more than 95 percent of B-ALL patients will have a trackable rearrangement with an analytical sensitivity of 10^-6 or 10^-7.^

More recently, next-generation sequencing methods have been shown to identify clonal rearrangements in all patients and achieve remarkable analytical sensitivities of 10^-8.^

This latter method can also identify and monitor multiple clonal populations and characterize clonal evolution. This R2 study will measure MRD using multiple methods (flow cytometry, ASO-PCR, and possibly next-generation sequencing) to learn the prognostic implications of MRD quantification by various methodologies and to provide further understanding of the effect of Ph-like status and IO on MRD response. Recently, this study has cleared the initial tolerability phase and is accruing to the randomized phase III portion. This trial represents a promising approach to improving outcomes for AYAs, as well as an unparalleled opportunity for scientists to better define ALL disease biology, which will hopefully lead to further treatment advances.


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A 73-year-old woman with a long-standing history of anemia for which she received intravenous iron infusions, and a history of clinically significant antibody (anti-E), was transfused one unit of matched pRBC in the emergency department for dizziness and anemia with borderline microcytosis (hemoglobin, 6.9 g/dL; mean corpuscular volume, 80.7 fL). The patient also had a history of heart failure and chronic kidney disease. She was admitted approximately one week later with chest pain and was found to have an elevated pro-B-type natriuretic peptide and high-sensitivity troponin. Her hemoglobin subsequently dropped from 8.5 g/dL to 6.9 g/dL, lactate dehydrogenase was elevated (1,209 U/L), and haptoglobin was undetectable (<20 mg/dL). A transfusion reaction evaluation was ordered. No new clinically significant antibodies were detected, direct antiglobulin test (DAT) was negative, and (out of an abundance of caution) an eluate was performed that was negative as well. The patient received ongoing transfusion support and had worsening renal failure and decompensated heart failure.

Peripheral blood showed abnormal red cell findings (Figure 1) with erythroblastosis (not shown). Aspirate showed trilineage hemopoiesis with erythroid predominance (Figure 2). Core biopsy showed hypercellular marrow (Figures 3 and 4) with focal areas of marrow damage (Figure 5). Hemoglobin high-performance liquid chromatography (HPLC) was performed (Figure 6).

**What is the diagnosis?**

A. Pure erythroid leukemia  
B. Hemoglobin SS disease  
C. Hemoglobin SC disease  
D. Delayed hemolytic transfusion reaction

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**F Concentration = 1.5%**  
**A2 Concentration = 3.4%**

*Values outside of expected ranges

**Analysis comments:**

For the solution to the quiz, visit The Hematologist online, www.hematology.org/TheHematologist/Image-Challenge.