Farming Hematopoietic Stem Cells


Modern civilization is the result of our ability to master agriculture. As populations grew, a continual food supply cultivated from seeds was a necessity that allowed communities to expand and other endeavors to be pursued. Arguably, agriculture may be our greatest achievement.

In many ways, hematology is in the early stages of its own agricultural revolution with current efforts to grow red blood cells, platelets, cancer-killing T-cells, and myriad other cell and tissue types. Much like feeding a growing population, the goal of these farming efforts is to have a reliable source of life-saving cells to treat every patient who comes through the door. For diseases that can be treated with bone marrow transplantation, the aim is to cultivate and grow enough hematopoietic stem cells (HSCs). Current efforts in HSC expansion have shown some promise, but healthy stem cells to “seed” this farming effort are required. For instance, HSCs from a matched donor cord blood unit can be cultivated and grown to sufficient numbers to allow for successful engraftment in a patient. However, this seed source is still somewhat limited and the allogeneic nature of these expansion efforts is not ideal for many diseases. In some cases, a patient’s own cells could be used to seed the culture, but the underlying genetic cause of the disease or subsequent genetic hits may tant those stem cells as a starting material for farming efforts.

In 2006, Dr. Shinya Yamanaka reintroduced four transcription factors (OCT4, Sox2, KLF4, and MYC) into adult mouse fibroblasts that could revert the cells to an “induced pluripotent state” (iPS) capable of re-differentiating into multiple cell types. This discovery concretized the ability to generate patient-specific stem cells. Since then, several groups have tried to use this new seed source, iPS cells or embryonic stem (ES) cells, to generate HSCs for transplantation.2

Inducing iPS or ES cells to differentiate toward a hematopoietic fate requires the cells to engage a specific epigenetic landscape, and the factors involved are not completely elucidated. Prior attempts using human or mouse pluripotent cells as a starting material could only produce progenitors with limited engraftment, short lifespan, or little T-cell differentiation potential.1,4 Two reports published at the same time by the groups of Drs. George Daley and Shahin Rafii outline new farming approaches to produce bona fide HSCs (Figure).1

In the July/August issue’s President’s column, Dr. Kenneth Anderson highlighted the need to facilitate the sharing of research-grade data for ASH members and the hematology community. To that end, ASH has committed to developing its own data registry. We are excited to share with you ASH’s vision for a registry.

Medicine is generating an unprecedented amount of information that could transform clinical care and yield new insights into the mechanisms of disease. In recent years, we have witnessed the development and growth of professional society-driven registries designed around the needs of their specialty and their membership. While existing registries tend to focus on a specific disease or set of diseases, to date there has not been a centralized effort that addresses the landscape of malignant and nonmalignant hematologic diseases.

Rare diseases present unique needs, and research-focused registries offer a solution for sharing knowledge through collaboration. A single point of access for relevant information will serve as a vehicle for building a comprehensive knowledge base for rare hematologic diseases. Employing this valuable asset will enable researchers to more quickly and accurately answer critical questions, including disease prevalence, affected populations, and key sociodemographic data.

ASH has the ability to play a vital role in facilitating the exchange of information on hematologic diseases. As a trusted convener, ASH stands apart as the neutral party most suited to supporting collaboration and coordination of efforts. As a trusted professional society, ASH is best positioned to serve as the honest broker of knowledge supporting new discoveries, treatment breakthroughs, and novel approaches to treating patients with blood disorders worldwide. Accordingly, we are pleased to announce ASH’s commitment to develop the ASH Registry.

ASH’s registry is envisioned as a mission-driven, ground-breaking initiative that will harness the power of big data to conquer blood diseases worldwide. Through the registry, ASH will initiate a shared information resource to advance collaborative hematologic research around the globe. This approach ensures the ability to meet research needs as a primary capability, leading to opportunities to repurpose registry data to meet a variety of future needs. The data generated by the ASH Registry is anticipated to be of enormous interest to ASH members, particularly investigators looking to test and validate research hypotheses. As the registry expands and matures over time, we see additional opportunities to benefit additional audiences.

The registry will initially focus on sickle cell disease and multiple myeloma. These two diseases were selected based on existing scientific priorities as well as ongoing activities related to ASH’s scientific research agenda. For sickle cell disease, a current gap in longitudinal research resources exists, creating the need to track patients from birth through adulthood. Further, there is a great potential for new therapies supported by longitudinal study. For multiple myeloma, there are several approved agents and therapeutics under development that would benefit from longitudinal study. Though initially focused on these two diseases, the registry will expand over time to include new areas of focus.

The registry is currently engaged in early development activities and is focused on building the core structure necessary to support a research tool of this magnitude. One of ASH’s unique resources is its one-of-a-kind global community of members who bring content expertise to the study and management of hematologic diseases. The ASH Registry will harness this extraordinary resource by engaging ASH membership at every step along the development and implementation process.

An initial registry oversight group has been developed to provide overall strategic guidance to the registry. Under the guidance of this group, processes and procedures related to governance, data use, regulatory concerns, analyses, publications, and other considerations have been or are being developed. The registry data collection infrastructure is being constructed, and initial participants for the first two diseases are being solicited.

As we progress, we are eager to hear from ASH members and others who are interested in registry activities and who would like to volunteer their expertise to assist with ongoing efforts. We are looking for individuals with expertise in key areas, including data science and health information technology. If you are interested in finding out more about volunteer opportunities for the registry, please contact us at registry@hematology.org.

ASH Announces Its Vision for Hematologic Big Data

**MELISSA FRANCISCO, MBA, AND WILLIAM A. WOOD, MD, MPH**

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2. Associate Professor of Medicine, Division of Hematology/Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC.

In the July/August issue’s President’s column, Dr. Kenneth Anderson highlighted the need to facilitate the sharing of research-grade data for ASH members and the hematology community. To that end, ASH has committed to developing its own data registry. We are excited to share with you ASH’s vision for a registry.

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Farming Hematopoietic Stem Cells

Dr. Ryohichi Sugimura and colleagues combined two previous methodologies. First, they used morphogens to direct differentiation of human pluripotent stem cells (both ES and iPS cells) into an embryonic tissue called hemogenic endothelium. This tissue eventually gives rise to blood stem cells in vivo, though the transition to HSCs in vitro had never been achieved previously. Next, they screened 26 candidate hematopoiesis-specific transcription factors to further promote reprogramming of the iPSC-derived hemogenic endothelium into a blood–stem-cell state. They recovered seven key transcription factors (ERG, HOXA5, HOXA9, HOXA10, LCR, RUNX1, and SPI1) that are necessary and sufficient to convert hemogenic endothelium into functional hematopoietic stem and progenitor cells. Cells transduced with these factors could successfully produce multiple lineages of blood cells in the bone marrow and peripheral blood circulation when implanted into immunodeficient mice. Some mice were able to mount a human immune response after vaccination. Human cells that engrafted in these mice could also be transplanted in secondary recipients. Overall, the combined approach of chemically driven differentiation followed by transcription factor–mediated cell fate conversion produced functional hematopoietic stem and progenitor cells from human pluripotent stem cells.

Dr. Raphael Lis and colleagues took a different approach to generate HSCs. Since HSCs share a common ancestor with endothelial cells in the embryo (the hemogenic endothelium), the authors hypothesized that it might be possible to switch the fate of endothelial cells into HSCs directly—a transdifferentiation approach. To achieve this, they used a combination of a co-culture system and ectopic expression of transcription factors. Endothelial cells purified from adult mice were co-cultured with a supportive cell line, which the authors had previously shown could expand HSCs in vitro, consisting of human endothelial cells in which the Ait pathway is constitutively activated. The murine endothelial cells were transduced with four transcription factors (FGF1, GFI1, RUNX1, and SPI1) under the control of a doxycycline-inducible promoter. Administration of dox in culture allowed the cells to transdifferentiate and expand, then dox was removed and the cells were transplanted in mice. The result was multi-lineage engraftment, including functional T-cell compartments, and bona fide HSCs as evidenced by secondary transplantation.

For the moment, these results are mostly a proof of the feasibility of HSC generation from this alternative seed source, but they are a tantalizing breakthrough. Starting from induced pluripotent cells (Sugimura et al) or endothelial cells (Lis et al), two groups could generate hematopoietic cells with multilineage reconstitution potential in vivo, including particular functional T-cell progeny, which had eluded previous efforts. This lays a framework to study the ontogeny of HSCs in a controlled environment and identify novel regulators. Many approaches remain to be improved: The HSCs generated by Dr. Sugimura and colleagues did not engraft as well as normal adult human HSCs, and the work of Dr. Lis and colleagues was entirely done in mouse cells. Regardless clinical applications, the absolute number of HSCs generated in these experiments is several orders of magnitude lower than what is required to transplant in a human. Additionally, both approaches relied on lentiviruses to introduce extra copies of transcription factors into the genome of the cells. Some of these genes are also linked to leukemia, and thus, the risk of malignant transformation associated with this approach should be carefully assessed. A reprogramming approach entirely induced by small molecules would be more desirable in that regard. With the expansion of diseases that can be treated by bone marrow transplantation, coupled with the increased in potential patients, a continual supply of high-quality HSCs will be needed. A stem cell agricultural revolution may ultimately meet this demand.

59th ASH Annual Meeting & Exposition

Save the date for the 59th ASH Annual Meeting and Exposition taking place December 9-12, 2017, in Atlanta. The meeting will provide an invaluable educational experience and the opportunity to review thousands of scientific abstracts highlighting updates on the hottest topics in hematology. Attendees will also be able to network with the top minds in the field and a global community of more than 25,000 hematology professionals. Important dates to keep in mind include:

- August 9 – Advance registration and housing opens for non-members
- September 27 – Collaboration room request site opens
- October 20-30 – Call for Late-Breaking Abstract submissions
- November 1 – Abstracts become available online & advance registration deadline
- November 15 – Housing reservation deadline

For more information about attending the 2017 ASH Annual Meeting, the premier event in malignant and nonmalignant hematology, visit www.hematology.org/annual-meeting.

Beat AML Update

The Leukemia & Lymphoma Society (LLS) has announced the expansion of the Beat AML Master Trial, which was originally launched in October 2016. ASH recently partnered with LLS to help spread the word about this pivotal trial, which looks to test new, innovative therapies for acute myeloid leukemia (AML) – the cause of more than 10,000 deaths every year. The past four decades have seen little change in the standard of treatment for AML (usually a combination of toxic chemotherapies).

To date, more than 70 patients have enrolled in the trial, and six leading cancer centers across the United States including the Ohio State University Comprehensive Cancer Center, Memorial Sloan-Kettering Cancer Center, Oregon Health & Science University, Knight Cancer Institute, the University of Colorado Cancer Center, and the University of Chicago Comprehensive Cancer Center are participating, with four more expected to join by the end of this summer. Additionally, four major biopharmaceutical companies are providing investigational targeted therapies, with three more expected to join soon. The number of active treatment arms is now five.

The Beat AML Master Trial should continue for at least two years, eventually including 500 patients between 15 and 20 clinical sites. ASH will continue to monitor this trial in collaboration with LLS, and update its members accordingly. For more information, visit www.lls.org/beat-aml.

The Hematologist Welcomes Editor-in-Chief Designee, Dr. Laura Michaelis

The Hematologist: ASH News and Reports is happy to announce its new Editor-in-Chief, Laura Michaelis, MD, for the upcoming term of 2018-2020. Dr. Michaelis is associate professor of medicine and associate vice chair of the Department of Medicine at the Medical College of Wisconsin/Froedtert Hospital. Dr. Jason Gotlib, our current Editor-in-Chief, congratulates Dr. Michaelis and expresses his excitement for the future of the publication saying, “Laura is a wonderful choice to take on the editorial reigns of The Hematologist. With her journalism background and editorial leadership of ASH News Daily in 2015, Laura brings substantial experience to the position. I’m sure that her passion for hematology and creative instincts will resonate with hematologists who look to The Hematologist to digest the latest breakthroughs in our field, as well as the education, clinical, and research initiatives of the Society.”

Two Remaining Dates to Attend the AML Matters Program

AML Matters is an education program designed to improve the diagnosis and treatment of acute myeloid leukemia (AML); it is hosted by ASH, the American Society for Clinical Pathology, National Marrow Donor Program, Oncology Nursing Society, and The France Foundation. Participants will actively engage in multidisciplinary, interactive small-group activities, including discussion of a case-based tumor board, diagnosing AML, treatment decision-making, minimum residual disease/first complete remission and the role of transplants, and relapsed/refractory disease. The program will next take place on October 20, in Durham, North Carolina, and on October 27 in Philadelphia. For more information, visit www.hematology.org/meetings/17277.aspx.

Blood Review Series on Precision Medicine

A new review series from Blood features six articles that highlight research and clinical opportunities in precision medicine:

- Diagnosis and classification of hematologic malignancies on the basis of genetics
- Genetic predisposition to hematologic malignancies: management and surveillance
- The relative utilities of genome-wide, gene panel, and individual gene sequencing in clinical practice
- High-throughput sequencing for noninvasive disease detection in hematologic malignancies
- The National Cancer Institute genomic data commons as an engine for precision medicine
- Ethical considerations in genomic testing for hematologic disorders

This series provides an overview of the sequence-based panels available to hematologists to assist with diagnosis, prognosis, and treatment of hematologic malignancies. Additionally, it addresses practical concerns regarding the use of genomic profiling in clinical practice. Visit bloodjournal.org/collection/review-series for more information.

Register to Participate in the 2017 ASH Foundation Run/Walk

The fifth annual ASH Foundation Run/Walk will take place Sunday, December 10, 2017, during the 59th ASH Annual Meeting in Atlanta. Proceeds from all individual and group registration fees as well as additional donations will benefit the ASH Sickle Cell Disease Initiative Fund. Registration is now open and will end on Saturday, December 9, at 6:00 p.m. Please note that there will be no race-day registration available. When you register, you will have the opportunity to invite friends and family to make a donation in support of the ASH Foundation. ASH will recognize those teams that generate the largest amount of donations on the ASH website and in ASH News Daily. For more information and to donate, visit www.hematology.org/foundation/run-walk/17277.aspx.
Ask the Hematologist

PAUL MOSS, MD
Professor of Haematology, University of Birmingham, Birmingham, United Kingdom

The Case
A 14-year-old girl was diagnosed with acute lymphoblastic leukemia (ALL) and underwent therapy with a standard ALL regimen. Unfortunately, the disease relapsed within 10 months following completion of treatment and an autologous stem cell transplant was performed from a sibling donor. Relapse of ALL occurred again after seven months and at this stage the patient was considered for therapy in a clinical trial of CD19-specific chimeric antigen receptor (CAR-T) T cell therapy.

The Question
What are the practical issues that hematologists need to know about during the introduction of CAR-T cell therapy?

The Response
CAR-T cell therapy promises to rewrite the lexicon of cancer treatment. Current therapies have made remarkable advances in first-line management of conditions such as ALL, and diffuse large B-cell lymphoma (DLBCL). Survival curves have improved almost inexcusably, particularly for younger patients, but huge challenges remain. A substantial proportion of patients fail to respond to first-line therapy, treatment is prolonged and intensive, and in the setting of disease relapse, the options become depressingly limited. Is it too much to believe that CAR-T cells will address all of these challenges?

B-cell ALL will see the first widespread application of CAR-T cells. Indeed on July 12, 2017, Novartis announced that the 10 members of the Oncologic Drugs Advisory Committee of the U.S. Food and Drug Administration (FDA) had voted unanimously to recommend approval of tisagenlecleucel (CTLA019) for the treatment of relapsed or refractory pediatric and young adult patients with ALL. This positive assessment was based largely on the ELIANA study (NCT02433849), which was the first pediatric global CAR-T cell therapy registration trial and which took place at 25 centers in the United States, Canada, European Union, Australia, and Japan.

CAR-T cell therapy has been developed from relatively small clinical studies within academic centers, and very few hematologists have experienced the practical challenges of managing a CAR-T cell protocol. This profile will now change at a considerable pace, and cellular therapy is likely to become a “standard option” for patients across many countries.

The selection of patients for CAR-T cell therapy will be limited by future license, cost, and access to clinical studies. The approach is likely to become a standard option for patients with relapsed/refractory ALL.1 Responses in patients with relapsed DLBCL are so encouraging that this indication is likely to follow in short order. Response rates in chronic lymphocytic leukemia are less certain, but even in this common condition of options, patients are badly needed for patients who relapse from current oral therapies. Indeed, CD19 is present on most B cell malignancies, and as such, mantle cell lymphoma, marginal zone lymphoma, follicular lymphoma, and Waldenström macroglobulinemia are also in play.

Methodology
Collection and transduction of autologous T cells is achieved by leukapheresis, from which cells such as monocytes and B cells are removed before the T cells are activated with mitogens such as anti-CD3/CD28 antibody-coated beads. Lentinial or retroviral vectors carrying the CAR construct are then used to transduce activated T cells over one to two days before they are expanded in the laboratory and cryopreserved. Currently this complex process is restricted to a few specialized manufacturing sites. As the applications of CAR-T cells expand, it seems reasonable to consider that this may be extended to include additional sites, perhaps even to local units that undertake processing of stem cell collections. Transduced cells can then be shipped to the clinical site following release testing.

A key factor in the success of CAR-T cell therapy is the ability of the infused T cells to proliferate and expand. Indeed, in the CTL019 trials, the time to peak T cell expansion was 10 days in patients who obtained a complete remission, compared with 20 days in those with no response. The degree of CAR-T cell expansion and the duration of transgene detection (102 vs. 28 days) were also markedly higher in patients who responded to therapy (Table). In order to encourage T cell engraftment, most patients are given a lymphodepleting conditioning therapy, which must be completed between two and 16 days prior to T cell infusion. This treatment creates “space” within the peripheral lymphoid pool, and T cells then undergo rapid expansion through the process of homoclotic proliferation. Typical regimens include fludarabine and cyclophosphamide, but there is interest in the development of experimental approaches that might omit this stage of the protocol.

The number of T cells that is infused has been a key variable in different studies. The pivotal registration trial for CTL019 used a single infusion of 0.2 to 5 million transduced viable T cells/kg for patients below 50 kg and a dose of 0.1 to 250 million T cells for those greater than this weight. As such, a typical cell dose of 100 million T cells is equivalent to the number of lymphocytes present in only 100 mL of blood. Interestingly, no association has been seen between the dose of T cells in the CTL019 trials and the degree of T cell expansion, which suggests that the optimal number of cells for infusion is currently unclear. The approach of using defined ratios of transduced CD4+ and CD8+ T cells has been associated with both robust T cell expansion and clinical response,2 and it is clear that optimization of graft engineering will play a key role in the evolution of CAR-T cell therapy.

Toxicity
Adverse effects following CAR-T cell therapy remain a significant concern. The major problem remains cytokine release syndrome (CRS), which is seen in up to 80 percent of patients and may reach grade 3/4 in half of these cases. Higher levels of disease burden and a rapid onset of symptoms are predictive of more severe effects and CRS normally lasts for around eight days. Tumour lysis syndrome is much less of a concern and is well-managed using standard approaches. Treatment algorithms for CRS can include administration of anti-interleukin (IL)-6 cytokine-directed therapy with agents such as tocilizumab and siltuximab, which are needed in around one third of cases. Support with vasopressors or ventilatory support is required for only a minority of patients.

Neurological toxicity is a perplexing and common feature of CAR-T cell therapy and includes features such as seizure, confusion, and encephalopathy. Similar features have been seen with antibodies that engage T cells, such as BI72– (bispecific T-cell engagers; Amgen Inc.) therapy, and it is unknown if this results from cytokine release or direct T cell toxicity. These features usually resolve within the first 30 days. The long-term effects of CAR-T cells are currently uncertain. Gene therapy trials using retroviral vectors have been previously associated with secondary leukemia due to insertional mutagenesis, but the CTL019 vector incorporates a self-inactivating lentiviral vector and no such cases have been previously associated with secondary leukemia due to insertional mutagenesis, but the CTL019 vector incorporates a self-inactivating lentiviral vector and no such cases have been previously reported in CAR-T cell studies. Persistence of CAR-T cells will also suppress normal T cell function, and prophylactic immunoglobulin infusions may often be required.

Table. Comparison of peripheral blood transcriptase cellular kinetic parameters in responders vs. non-responders – pooled data from Studies B2202 and B2205J

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistics</th>
<th>Responder</th>
<th>Non-responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0–24h (copies/µg DNA × days)</td>
<td>n = 61</td>
<td>51,000 (17.8)</td>
<td>156,000 (99.4)</td>
</tr>
<tr>
<td>Cmax</td>
<td>n = 61</td>
<td>55,700 (155.4)</td>
<td>20,000 (71.6)</td>
</tr>
<tr>
<td>Tlast</td>
<td>n = 62</td>
<td>102 (17.8, 380)</td>
<td>27.8 (20.9, 83.9)</td>
</tr>
</tbody>
</table>

Abbreviations: definitions: AUC0–24h, exposure or levels of transgene attained during the initial 28 days following infusion of tisagenlecleucel; Cmax, maximum (peak) expansion of transgene post-tisagenlecleucel infusion; CV, coefficient of variation; Responder, patient with CR or CRi; Tlast, time of last observed quantifiable transgene.


The Hematologist: ASH NEWS AND REPORTS
Clinical Activity
The clinical responses to therapy have been highly encouraging. Remission rates of 70 to 95 percent are typical for patients with relapsed or refractory ALL, and up to 75 percent of patients remain in remission at six months. Although the median time of follow-up remains quite short, early evidence suggests that remissions are robust, and typically around 80 percent of patients remain alive after one year of follow-up. Minimal residual disease negativity within the bone marrow, typically defined as being less than 0.01 percent, is commonly achieved. The elimination of CAR-T cells is remarkably swift, and in patients who respond to CAR-T cell therapy, transgene levels in the bone marrow are typically at the highest level at day 28, followed by a subsequent drop, and were measurable up to six months.

The BiTE antibody blinatumomab has a defined role in the management of relapsed ALL, and the potential role of CAR-T cells must be assessed in relation to its proven utility. Currently no analysis of the two agents in a “head-to-head” clinical study has been reported, and until that time, it is impossible to assess their relative merits. However, the selection for loss of CD19 expression is a concern, and as such, it may not prove feasible to use the two approaches in a sequential manner.

Future Directions
Although CD19+ lymphoid diseases have served as the focus of CAR-T cell therapy, the approach is rapidly being applied in other disease settings. Within multiple myeloma, the field is moving rapidly, with considerable encouragement from the targeting of B-cell maturation antigen, CD138, and IL-6R chain. The identification of tumor-selective targets has proven difficult in the development of CAR-T cell therapy for myeloid diseases, but proteins such as CD33 and CD123 may offer hope.

The introduction of a single transgene to encode the CAR antibody (typically anti-CD19) is only the start of our journey (Figure). A range of additional genetic modifications is being explored to drive the constitutive or inducible expression of cytokines or ligands that can extend cell survival, improve tissue localization, and even offer the opportunity to delete transplanted cells if problems arise. These so-called “armedored CARs” offer a glimpse into the opportunities that will arise in the next few years.

Future opportunities for CAR therapy are impressive. CTL019 has received Breakthrough Therapy designation from the FDA, which will now consider the Biologics License Application. It is now timely to suggest that all substantial hematologic departments should consider the establishment of a specialist immunotherapy clinic. On our highways, the rise of autonomous cars is such that many physicians can start at least to abandon their self-driven vehicles. At a therapeutic level, the introduction of CAR-T cell therapeutics is to be so rapid that all hematologists will soon need to learn to drive again.

Return to the Case
A leukapheresis was performed, and T cells were transfected with a lentiviral vector containing the extracellular domain of a CD19-specific antibody fused to the intracellular domain of the CD3ζ chain. On day 0, 100 million cells were infused without complication. After 48 hours, the patient became pyrexic (40.2°C), hypotensive, and drowsy, and these symptoms of cytokine release syndrome were matched by continuing detection of the CD19-transgene revealed that transduced T cells were detectable for weeks after infusion, but subsequently became undetectable. The patient was discharged from hospital within four days but was troubled by grade 3 neutropenia; immunoglobulin infusions were also administered due to continuing febrile episodes. The efficacy of CAR-T cells is remarkably swift, and in patients who respond to CAR-T cell therapy, transgene levels in the bone marrow are typically at the highest level at day 28, followed by a subsequent drop, and were measurable up to six months.

The BiTE antibody blinatumomab has a defined role in the management of relapsed ALL, and the potential role of CAR-T cells must be assessed in relation to its proven utility. Currently no analysis of the two agents in a “head-to-head” clinical study has been reported, and until that time, it is impossible to assess their relative merits. However, the selection for loss of CD19 expression is a concern, and as such, it may not prove feasible to use the two approaches in a sequential manner.
A few weeks after our conversation, a 48-year-old woman (N.S.) was transferred to the Stanford inpatient hematology service under the care of my colleague Dr. Caroline Berube. She presented with withering fatigue, diarrhea, liver function abnormalities, severe thrombocytopenia, hepatosplenomegaly with liver dysfunction, and hypoplasminogenemia and weight loss. She was diagnosed with AITD816V-positive mast cell leukemia with an associated unclassified myelodysplastic/myelo proliferative neoplasm (MCL-MDS/MPNU). Knowing this patient was at death’s door, I corded with the hope that he could provide pre-clinical data to substantiate treatment of this patient with midostaurin. In fact, Dr. Joe Growney in his lab had transformed Ba/F3 cells with AITD816V and showed that the 50 percent inhibitory concentration (IC50) of midostaurin was 30 to 40 nM (concentrations achievable in vivo).2,3 In contrast, imatinib’s IC50 was 1 μM, confirming the mutation’s resistance to the drug.4,5 We conveyed these data to Pam, who, with the U.S. Food and Drug Administration (FDA), signed off on my petition for a single-patient, compassionate-use protocol using midostaurin.

On June 20, 2003, N.S. became the first SM patient in the world to receive midostaurin. She achieved a partial response, with resolution of her liver dysfunction and portal vein thrombosis, disappearance of circulating mast cells, and a marked reduction of serum histamine levels. She was discharged home with a striking improvement in quality of life, taking joy in the mundane daily tasks. After three months, her SM was well controlled but her MDS/MPN transition to secondary AML, betraying her prior history of transformation and taking her life in 2006. However, we learned many lessons from N.S., which laid the foundation for further development of midostaurin in advanced SM. When she left this world, she hitched a ride on the tail of Manni’s comet at a time when it was gaining inevitable momentum.

In 2005, we initiated our investigator-initiated trial (IIT) of midostaurin with DRC’s Dan DelAngelo, and Dr. Timothy Graubert, then at Washington University’s Siteman Cancer Center. Hematopathologist Dr. Tracy George, with whom I collaborated closely at Stanford, served as the central pathologist. Ultimately, we treated five years to accrue 26 patients from this rare disease population. In 2008, Tracy and I headed to Budapest to present our interim results at the annual meeting of the International Society for the Study of Mastocytosis (ECSM). This organization, led by Professor Peter Valent, represents the most authoritative group of lab-based and clinical mast cell disease researchers in the world. After Tracy and I presented our preliminary data, we were peppered with enthusiastic questions. A palpable excitement spread throughout the conference. We knew this was a turning point.

Representatives from Novartis attended the Budapest meeting to finalize ongoing plans for a global trial of midostaurin in advanced SM. Along the banks of the Danube, European, North American, and Australian investigators came together to commit to the international trial, eventually numbering 29 sites. The year before, Tracy had traveled to Cabo San Lucas, in the heart of the Cabo, to meet with Professor Hans-Peter Horny, the father of modern mast cell pathology. He had been recruited to a central pathologist for the global study. At the microscope, Dr. Horny quizzed Tracy about her knowledge of mast cell disease diagnosis and pathology. She passed his interrogation and thereafter was recruited to evaluate samples from patients recruited at U.S. and Canadian sites, while Dr. Horny managed the review of European and Australian patients. Along with Honny and George, a Study Steering Committee (SSC) was convened, with myself as Chair, consisting of Professors Andreas Reiter, Hanneke Kuin-Nelemans, Cem Akin, Karim Hartmann, and Peter Valent. All was now in place to proceed. The trial accrued 116 patients from 2003 to 2013, and our SSC met on average every six months from 2008 to 2015 to adjudicate patient eligibility, histopathology, efficacy, and safety. The yearly ECNM conferences and lively discussions arising from our SSC meetings provided an incomparable education in mast cell disease and forged indelible relationships among us colleagues.

Shirley Baxter6 came to Stanford from Plymouth, Minnesota, with a diagnosis of SM with chronic eosinophilic leukemia (SM-CEL). When she arrived on our doorstep in 2011, interventional therapy had failed to retard the ravaging effects of her disease. She was crippled by nausea, diarrhea, and severe malaise, as well as organ damage consisting of hypoalbuminemia with a 60-pound weight loss, hepatosplenomegaly, edema, anemia, severe eosinophilia, and extensive cutaneous mastocytosis. Just before commencing the global trial in August of that year, she flew from England to New York ICIC12 to be admitted to the Ahwahnee Hotel, ostensibly as a final sojourn to find peace and solitude in one of our country’s most glorious nature sanctuaries. Shirley Baxter would defy the odds. In 2015, she celebrated her 50th wedding anniversary, and in 2016, she made a triumphant return to Yosemite and the Ahwahnee (renamed the Majestic Yosemite). She was one of the 60 percent of patients on the study who responded, with resolution of nearly all signs and symptoms of disease while maintaining good tolerance of midostaurin. Based on the results of our IIT and the global study, midostaurin was approved by the FDA in April 2017.7 This past July, Shirley returned for her last visit to Stanford to transition to commercial drug supply, just short of six years on the trial. During a prior visit, Shirley and Bill traveled to the nearby Pigeon Point Lighthouse (see Figure 2, online only), which was built in 1871 to help ships safely navigate the California coastline. We stood on the point (landmark above), I imagine that the heavenly light piercing the temperamental sky is the pending breach of Manni’s comet, returning to Earth in a gravity-defying orbit, everlastingly perching itself in the lantern room of the lighthouse. Tethered to his comet’s tail is N.S., our first SM patient treated with midostaurin, as well as L.R., who remain on study for 11 years, only to succumb to acute leukemia just three months before FDA approval.

To the Editor:

In Dr. Andrew Roberts’ review of the article by Dr. Amy Hughes and colleagues8 in the May/June issue of The Hematologist—In the Long Term for Deep Molecular Response: The As the Immune System Steps Up, The Hematologist. 2017;14[3]-[9], he writes, “Patients who achieve a deep molecular response to imatinib (and other TKIs tyrosine kinase inhibitors) have a normal survival expectancy as a result of their response that can be maintained without ongoing TKI therapy. But whether re-establishment of immunity is central to the ability to stop imatinib successfully is unknown.”

Quite right. However, the title offers a rather different implication: A step up in the immune system is how CML therapy-free remission is achieved. The study by Dr. Hughes and others also implies this: “Immunotherapies control CML in patients with deep molecular response to midostaurin or imatinib...” When you get rid of a lot of CML cells, the remaining cells are immunologically very different. Why didn’t they say that this was not mean is this why CML does not recur after stopping TKI therapy? To address the question of whether immune surveillance is important in controlling CML, we used several strategies. We found evidence in CML incidence in persons with hemispheric, congenital, or organ-specific deficiencies. We also found only 25 excess cases of CML amongst 441,232 recipients of solid organ transplants receiving immune suppression with 2 million person-years at-risk observation.

These data and others suggest immune surveillance is a rather unlikely explanation of why some patients stopping TKI therapy do not relapse. More generally, the immune system is often invoked to explain seemingly mysterious events in medicine and biology. However, several other explanations such as measurement error and chance (concepts anathema to most scientists and physicians) are in equal or more likely explanation of therapy-free remission in CML. Let’s give immune surveillance a break; it’s tired.

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Gerhard Opelz, MD
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Re: the critique of Drs. Gale and Opelz is welcome, and their data highlight that immune suppression per se does not appear to have reversed immune effects and decreased PD-1 and immune suppressors. Blood. 2017;130:1144-1156.

Dr. Gale and Dr. Opelz are serving as editors of the Global CML steering committee of the Global CML registry. They have contributed to the CML registry in multiple capacities, including coordinating the registry’s Advisory Board and receiving honoraria from Novartis.

The critique of Drs. Gale and Opelz is welcome, and their data highlight that immune suppression per se does not appear to have reversed immune effects and decreased PD-1 and immune suppressors. Blood. 2017;130:1144-1156.

Congress Returns from Summer District Work Period to Continue Work on FY 2018 Budget

After adjourning for much of August, Congress resumed work in early September on passing the 12 needed spending bills before the fiscal year (FY) ends on September 30. However, despite appropriators making significant progress on many of the annual spending bills, it is unlikely that the House and Senate will vote and reach a final agreement prior to the start of FY 2018 on October 1.

In mid-August, the House Appropriations Committee passed its version of the Labor, Health and Human Services, Education and Related Agencies (Labor-HHS-ED) spending bill along a party line vote, clearing the way for the bill to be considered by the full House of Representatives. The bill recommends a total increase of $1.1 billion (3.3 %) for the National Institutes of Health (NIH). Specifically, the measure provides $34.7 billion in base funding for NIH, a $943.4 million (2.8 %) increase over the comparable FY 2017 funding level. The bill also fully utilizes the $496 million designated for specific NIH initiatives in the Innovation Account established in the 21st Century Cures Act, bringing the bill’s total NIH funding level to $35.2 billion in FY 2018.

However, because of budget caps that are in place from the Budget Control Act of 2011, increases for important programs such as NIH may come at a very high cost to other NIH programs. Overall spending in the House version of the FY 2018 Labor-HHS bill is $5 billion (3 %) less than current levels, resulting in substantial cuts to numerous public health programs including the Centers for Disease Control and Prevention (CDC) and the Health Resources Services Administration (HRSA). While the Senate has not yet determined funding levels for specific programs such as NIH, the overall allocation provided to the Senate Labor-HHS-ED Appropriations Subcommittee for all federal health, education, and labor agencies is flat, ensuring that an increase in funding to one will mean a cut to another. ASH recently joined the advocacy community in sending a letter to congressional leaders urging them to consider spending caps for FY 2018 and beyond to allow congressional leaders to provide needed funding to NIH without further cuts to other important public health programs.

At this time it is unclear when the bill will be considered in the full House or when the Senate may begin consideration of its version of the FY 2018 Labor-HHS bill. If Congress cannot reach a decision about spending bills by October 1, it has two options: 1) Pass a temporary continuing resolution that extends federal agency and program funding unchanged from the current year or 2) shut down the government until it can come to an agreement on spending.

Grassroots support is critical as the FY 2017 budget process continues. In late September, ASH will convene its seventh annual Advocacy Leadership Institute (ALI) to educate members on how to become effective advocates for hematologic research and practice; following advocacy training, ALI participants will meet with congressional offices to discuss the importance of biomedical research. The Society is also a sponsor and supporter of the fifth annual Rally for Medical Research Bill Day taking place September 14, 2017, in Washington, DC, during which thousands of participants from more than 300 partnering organizations will be meeting with House and Senate offices to call on our nation’s policymakers to make funding NIH a priority and raise awareness about the importance of continued investment in scientific research. Congressional meetings are an important component of ASH’s advocacy efforts and provide an opportunity for members of Congress and their staffs to gain insight on issues of concern to hematologists and their patients. However, the Society needs the help of all of its members in bringing these important issues to the attention of the U.S. Congress and other governmental agencies. Visit the ASH Advocacy Center at www.hematology.org/Advocacy for information on how you can join the Society’s efforts and become an advocate for hematologic research.

*Reminder to Respond to Survey on ASH Advocacy*

ASH is conducting a survey of all members in the U.S. to learn about what advocacy topics matter most to them and the ways in which they would like to engage with their elected officials. This is an opportunity to help shape the future of ASH’s advocacy and policy efforts in Washington. All U.S. members were sent an email with a link to the survey in early August; please take time to fill out this important survey to help drive the issues that matter most to hematologic research.

ASH Observes National Sickle Cell Awareness Month

As National Sickle Cell Awareness Month approaches in September, ASH celebrates the progress that has been made in one year since the Society and partner organizations announced the formation of the Sickle Cell Disease Coalition (SCDC), launched a Call to Action on Sickle Cell Disease (SCD), and issued the State of Sickle Cell Disease: 2016 Report. The SCDC membership now comprises close to 50 national and global groups, and recent enhancements have been made to the SCDC website to highlight the Coalition’s important work.

Additionally, ASH continues to work with federal agencies and the U.S. Congress to help enhance and expand government activities in SCD research, training, and services. In August, Dr. Alexis Thompson, ASH President-Elect, presented an update about ASH’s multifaceted initiative on SCD at the National Heart, Lung, and Blood Institute’s Annual SCD Clinical Research Meeting and underscored how the Society plans to work with federal agencies on the various components of the initiative.

ASH also continues to encourage congressional champions to introduce legislation to strengthen current federal SCD programs and increase funding for federal SCD programs. As this issue goes to press, the Society remains hopeful that the Senate will introduce the SCD legislation in September. ASH also continues to encourage the Centers for Medicare & Medicaid Services to test innovative payment models for SCD care delivered by health care professionals, as well as take other important steps to improve reimbursement for SCD care and treatment, including the following activities: In July, ASH submitted a letter encouraging the Virginia Medicaid Program to reconsider its denial of bone marrow transplantation authorization requests for individuals with SCD participating in the Blood and Marrow Transplant Clinical Trials Network; and on September 5, ASH plans to host a webinar on appropriate SCD coding.

To learn more about ASH’s multifaceted SCD initiative, visit www.hematology.org/Advocacy/4329.aspx.

ACA Repeal Effort Defeated in Senate

After spending months crafting legislation to repeal and replace the Affordable Care Act (ACA), in late July, the U.S. Senate had its chance to vote on and pass repeal legislation. However, the legislating body could not garner enough support to pass any of the bills presented. These included a piece of legislation from 2015 that would repeal but not replace the ACA; the Better Care Reconciliation Act, a bill the Senate had been working on for two months; and finally, what was being called the “skinny repeal,” which would have rolled back several key provisions of the ACA. Three Republican Senators, Susan Collins, Lisa Murkowski, and John McCain, joined Democrats to vote against this final measure.

ASH had expressed concern with the various Senate proposals and the ACA repeal bill that passed the House in early May, noting that the proposals would reduce overall access to coverage and treatment and would negatively affect patients with hematologic diseases and disorders. ASH was also concerned about the bills’ proposed elimination of the Public Health and Prevention Fund which has supported many critical projects at the CDC, including investments in immunizations and health-care associated infections. Currently the Fund comprises approximately 12 percent of the CDC’s budget and should be preserved.

It is unclear what will happen next, but we are likely to see hearings and bipartisan discussions about legislation to stabilize the individual market in the coming weeks and months. ASH will continue to monitor this process and will send updates as necessary.
Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening complication of heparin therapy—a common anticoagulant treatment that induces prothrombotic complications. The prothrombotic mechanism arises from the binding of platelet-activating IgG-specific antibodies to the heparin-platelet factor 4 (PF4) complex. This complex of heparin-PF4 and IgG-specific antibodies binds to the platelet Fc receptor causing activation and release of granules from the platelet. The platelet count will decrease as the platelets are activated and the patient is at risk for developing thrombotic complications. The pretest probability of HIT versus other causes of thrombocytopenia is initially evaluated by assessing the clinical picture and the timing and degree of platelet count decrease, embodied in the 4Ts score. The widely used laboratory assessment for HIT antibodies is an enzyme-linked immunosorbent assay (ELISA) that detects antibodies against H-PF4. These assays are highly sensitive; however, they have only moderate specificity. The lower specificity is due to the nonpathogenic antibodies being indistinguishable from the true HIT-causing antibodies. IgG, IgA, and IgM antibodies against the H-PF4 complex can be detected, but only the IgG antibody class can bind to the Fc receptor and cause subsequent platelet activation, thrombocytopenia, and the clinical prothrombotic state.

Initially, the available commercial and laboratory-developed tests (LDT) for HIT antibodies detected all three classes of antibodies. Now, IgG-specific commercial tests and LDTs have been developed in an attempt to increase the diagnostic specificity for HIT. Both IgG-specific and polyspecific antibodies ELISA assays are available. However, there is considerable confusion and contradictory information about which test type is better for the diagnosis of clinically significant HIT. With this controversy, the International Society of Thrombosis and Hemostasis stated a preference for the IgG-specific ELISA assay, as it most closely parallels the pathogenic mechanism of HIT that is needed for binding to the Fc receptor on the platelet to cause activation. After this recommendation, a meta-analysis of essentially all the studies on HIT ELISA assays (comparing both IgG-specific and polyspecific assays) demonstrated no difference in sensitivity and specificity between IgG-specific assays and polyspecific assays. This meta-analysis was too broad in its comparison of studies since it used different populations and reference standards. A second, more closely comparable meta-analysis was performed by Dr. Helleh Husseinzadeh and colleagues with the caveat of using only studies with direct comparability of the IgG-specific and the polyspecific ELISAs.

In the more rigorous meta-analysis assessment of HIT ELISA studies, the authors pooled the data from nine published studies where both IgG-specific and polyspecific ELISA methods directly compared the sensitivity of the two HIT methods were essentially identical (0.97; 95% CI, 0.95-0.99), but the IgG-specific method was significantly better for specificity compared to the polyspecific method (0.87; 95% CI, 0.85-0.89 vs. 0.82; 95% CI, 0.80-0.84). The negative predictive values (NPV) for IgG-specific and polyspecific methods were both high and similar (0.99 [CI 0.99-1.00]). Conversely, the positive predictive value (PPV) was significantly better for the IgG-specific method compared to the polyspecific method (0.56; 95% CI, 0.52-0.61 vs. 0.32; 95% CI, 0.28-0.35). In seven of the nine studies, the results were compared with the functional conformational assay, the serotonin release assay (SRA). The IgG-specific method and the polyspecific method still had similar sensitivity when compared to the SRA, but the specificity was still better for the IgG-specific method when compared to the SRA reference standard. Of note, many clinicians assume that all SRA results are similar, but significant variation in SRA methodology was found between these reported studies.

Based on this selective meta-analysis of H-PF4 ELISA methods, the sensitivity and NPV were similar for both the IgG-specific method and the polyspecific method, but the difference is in the specificity and the PPV results in which the IgG-specific ELISA method is clearly superior to the polyspecific method. This was true for both studies using the SRA reference method and those that did not. Therefore, the IgG-specific ELISA method has better diagnostic accuracy compared with the polyspecific ELISA method at standard methodological use. For laboratories investigating the establishment of a HIT antibody–specific assay or laboratories contemplating a change of methodology, these studies support the use of the IgG-specific antibody ELISA method because of its superior specificity and PPV.


**Better Accuracy for the Laboratory Detection of HIT Antibodies Using IgG-specific ELISA Assays**

**Primary Central Nervous System and Testicular Lymphoma: From Genes to Action in One Year**

Advances in genomic technology have allowed for the more rapid identification of recurrent genetic alterations in tumors, many of which are targetable with existing therapies. As such, the time from discovery of pathologic events to delivering potential therapeutic strategies, all of which can be targeted with existing drugs.


By June 2017, and based on these results, Dr. Lakshmi Nayak and colleagues had treated five patients with either multiply recurrent PCNSL (n=4) or with a CNS relapse of PTL following a thopteba-based autologous stem cell transplant (n=1) with the anti-PD1 antibody nivolumab. They observed an incredible 100 percent response rate in these five heavily chemotherapy refractory patients, with four of five complete responses. Responses were observed within a median of three treatments, and responses have been durable, ranging from 13 to 17+ months. CNS lymphomas were ongoing in four of five patients (although one had relapsed outside of the CNS during therapy), with one patient relapsing at 17 months after having received only two doses of nivolumab. Based on these results, nivolumab is being investigated as a therapy for relapsed/refractory PCNSL and PTL (CheckMate 647, clinicaltrials.gov identifier NCT02857426). This is a remarkable example of the power of our current technologies to identify recurrent and actionable genetic alterations associated with a specific malignancy and to translate these findings into effective clinical strategies with direct patient benefit in an unprecedented timeframe.

**Advances in Genomic Technology Have Allowed for the More Rapid Identification of Recurrent Genetic Alterations in Tumors, Many of Which Are Targetable with Existing Therapies.**

**Caron A. Jacobsen, MD**

Dr. Jacobsen indicated no relevant conflicts of interest.

**Primary Central Nervous System and Testicular Lymphoma: From Genes to Action in One Year**


Among the candidate driver genes identified to be associated with these chromosomal gains and losses are NFkB1 on chromosome 3q12.3 and CDKN2A on chromosome 9p21.3. Amplification of 9p24.1, containing the genes for PDL1 and PDL2, was also identified as a recurrent alteration in PTL as well as in the extension cohort of Epstein Barr Virus (EBV)–negative PCNSL. EBV-positive PCNSL was associated with increased expression of PDL1 and/or PDL2 in the absence of any copy number alterations. Inhibition of PDL1, then, may be a promising therapy in these patients. Additionally, unique chromosomal rearrangements involving PDL2 were identified in several of these tumors, as well as recurrent rearrangements involving activation of BCL6 and inactivation of ETV6. In both the discovery cohorts and extension cohorts of PCNSL and PTL, mutations in Toll-like receptor (TLR) signaling component genes MYD88 and CD79B occurred at high frequency (>80%), with all CD79B mutations occurring in the context of a coincident MYD88 mutation. Similarly, a vast majority of EBV-negative PCNSL and PTL tumors had an activating mutation in MYD88, and/or copy number gain of chromosome 3q12.3 with amplification of NFkB1, whose product IκB is downstream of TLR activation. This near-uniform activation of TLR signaling suggests that therapies that inhibit IRAK1/4, IRF4, and/or BTK may be active in these diseases. Finally, very few of these tumors harbor mutations in TP53, but instead exhibit copy number loss of CDKN2A on chromosome 9p21.3, which lies upstream in the p53 pathway, thus making these tumors potential candidates for therapy with drugs that inhibit MDM2/4.

Thus, out of this comprehensive genetic investigation of these two diseases emerged three potential therapeutic strategies, all of which can be targeted with existing drugs.
Tranexamic Acid: Another Tool for Treatment of Postpartum Hemorrhage


Postpartum hemorrhage is the most common cause of maternal death internationally. Tranexamic acid, an agent that inhibits fibrinogen and plasmin breakdown by plasmin, has been shown to reduce bleeding following surgery and major trauma. Clinical investigators therefore turned to tranexamic acid as a potential candidate to reduce the severity and consequences of postpartum hemorrhage.

The WOMAN study was a double-blind, placebo-controlled trial conducted in 21 countries. Women (age ≥ 16 years) with a clinical diagnosis of postpartum hemorrhage (estimated blood loss ≥ 500 mL after vaginal delivery, ≥ 1,000 mL after caesarean section, or any blood loss causing hemodynamic instability) were randomly assigned to receive 1 g of tranexamic acid intravenously or placebo, in addition to usual care.

At the start of the trial, the primary outcome was a composite of all-cause death or hysterectomy within 42 days of randomization. However, it was later changed to death due to bleeding (and the sample size was increased) based on two findings that emerged while the study was underway. First, it became clear that patients were being enrolled in the study and undergoing hysterectomy at the same time instead of waiting to see if the study drug stopped the bleeding in trial subjects. Second, the results of a large clinical trial evaluating tranexamic acid in trauma patients reported a reduction in mortality due to bleeding. Secondary outcome measures included thromboembolic events, surgical interventions, complications, and other adverse events, and quality of life.

The majority of the 20,060 women in the trial underwent in-hospital vaginal deliveries, and approximately half were enrolled within one hour of delivery. There were 483 maternal deaths, of which 72 percent were attributed to bleeding. The risk ratio for death due to bleeding with tranexamic acid was 0.78 (95% CI, 0.62-0.98; p=0.03) after adjustment for baseline risk factors. If tranexamic acid was given within three hours of delivery, the risk ratio for death due to bleeding was 0.89 (95% CI, 0.52-0.91; p=0.008). No benefit was seen if tranexamic acid was given longer than three hours after delivery. The incidence of thrombosis and other complications did not differ between groups.

The results of the WOMAN study show that tranexamic acid reduced maternal mortality due to postpartum hemorrhage by approximately 30 percent if given within three hours of delivery. Reduction in mortality is arguably always clinically significant; however, the effect size for this trial seems small, and the upper limit of the confidence interval lies close to no effect. Given that treatment of postpartum hemorrhage often consists of multiple interventions at once (e.g., manual compression, surgical intervention, use of uterotonics, transfusion of coagulation factors), it is difficult to tease out the role tranexamic acid played in controlling bleeding. Furthermore, only 30 percent of subjects had an estimated loss of greater than 1,500 mL of blood and/or a systolic blood pressure less than 90 mmHg. These clinical features suggest that the baseline risk of death due to bleeding in the study population was generally low. However, an important caveat to this conclusion is that small bleeds can rapidly, and unpredictably, become life-threatening bleeds if not treated.

Perhaps the most noteworthy finding of this large study is the low frequency of thrombosis. This patient population is known to have a high baseline thrombotic risk; therefore, the absence of an increased risk with tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring. While the benefit of tranexamic acid in a study of this size is reassuring.
Clinical and histopathologic distinction between inherited versus acquired bone marrow failure is challenging. Both are characterized by peripheral cytopenias and marrow hypocellularity; the distinction is important, as risks of and responses to various therapies differ between the two, as do their natural histories. This is particularly relevant in the context of hematopoietic stem cell transplantation (HSCT) because the recognition of an underlying inherited disorder informs the timing and indication for HSCT, transplant approaches (i.e., many inherited disorders are associated with excessive transplant regimen-related toxicities and may require specialized reduced-intensity conditioning regimens), and appropriate donor selection. Both the importance of accurately recognizing inherited from acquired marrow failure and its therapeutic relevance are highlighted in recent work by Dr. Aaron Seo and colleagues. These investigators identified and characterized germline biallelic-loss-of-function mutations in thrombopoietin (THPO) as a cause of bone marrow failure unresponsive to HSCT, and responsive to thrombopoietin-mimetic therapy in an informative family.

Thrombopoietin is a glycoprotein class 1 hematopoietic cytokine produced primarily in the liver. THPO signaling, via its receptor MPL, is essential for both megakaryopoiesis and hematopoietic stem cell maintenance. In mice, knockout studies of Thpo or Mpl result in reduced numbers of hematopoietic cell progenitors and thrombocytopenia. In humans, autosomal recessive loss-of-function mutations in MPL result in congenital amegakaryocytic thrombocytopenia, with affected children presenting initially with isolated thrombocytopenia and subsequently developing progressive pancytopenia due to a reduction in bone marrow hematopoietic stem cells.

Dr. Seo and colleagues report on five children from three consanguineous families presenting with early-onset thrombocytopenia and subsequent bone marrow failure. Four of the children underwent HSCTs from various related and unrelated donor sources for progressive marrow failure using both aplastic anemia and myelodysplastic preparatory regimens. This resulted in engraftment failure or persistent bone marrow failure despite donor cell engraftment, consistent with the cause of the marrow failure being extrinsic to the hematopoietic cell. Three of the four children treated with HSCT died posttransplant. Notably, serum thrombopoietin levels were measured in two of the five patients studied and were found to be undetectable. Thrombopoietin levels are typically high in bone marrow failure syndromes such as aplastic anemia, where levels are inversely proportional to megakaryocytic mass as opposed to peripheral platelet counts. These two individuals (one of whom failed HSCT) were treated with the thrombopoietin receptor agonist romiplostim (final dose 5 μg/kg subcutaneously weekly) and responded with improved trilineage hematopoiesis, including normal count recovery in one individual.

Whole exome or targeted sequencing of known inherited marrow failure genes in the patients identified heterogeneous mutations in THPO in affected family members, which segregated with the phenotype in an autosomal recessive fashion and are predicted to be damaging by in silico analyses (THPO: c.295C>T; R99W and c.469C>T; R157X: NM_000460.3). To determine whether the R99W and R157X function, R99W and wild-type control THPO were generated and used to assay MPL-dependent cell survival and proliferation in vitro. Both wild-type and mutant THPO supported MPL-dependent cell survival and proliferation. The authors noted that the R157W allele introduces a stop codon in the middle of the protein that results in the loss of a critical protein domain known to be required for normal THPO secretion. They concluded that both mutations likely affect THPO serum levels without affecting THPO function, consistent with their functional analysis of the R99W mutant and the undetectable thrombopoietin levels measured in the patients.

A previous study reported germline loss-of-function mutation in the THPO gene which segregated with aplastic anemia and mild thrombocytopenia in the homzygous and heterozygous state, respectively. The current study, the first to report that patients with germline THPO mutations resulting in marrow failure did not have evidence of myelodysplasia or full donor engraftment) but respond to thrombopoietin mimetic therapy. An undetectable THPO level was an important diagnostic clue to the underlying genetic etiology. This work also nicely highlights how gene discovery in small family kindreds permits us to discover new genes and pathways contributing to inherited marrow failure, and informs the pathways regulating hematopoiesis more broadly. How best to incorporate THPO level testing and broad genetic screening for an underlying genetic cause in patients presenting with marrow failure deserves further study.


Dr. Robert I. Lien and colleagues took an innovative approach when interrogating a pre-existing data set to test the hypothesis that the presence of SCT is associated with changes in fitness and risk for hypertension, diabetes, and metabolic syndrome. The team evaluated the Coronary Artery Risk Development in Young Adults (CARDIA) study, a cohort with 25 years of follow-up of patients including 1,995 African Americans. SCT was present in 6.8 percent of the African-American population (136 of 1,995), and in the course of 25 years, 46 percent (738 of 1,590), 18 percent (288 of 1,631), and 40 percent (645 of 1,611) of all participants developed hypertension, diabetes, and metabolic syndrome, respectively. However, the presence of SCT compared to those without SCT was not associated with any of the assessed morbidities, including exercise duration (p=0.62), estimated metabolic equivalent of tasks (p=0.80), maximum heart rate (p=0.41), and heart rate at two minutes recovery (p=0.28). Using multivariate analysis, the research team did not find any evidence that SCT was associated with an increased hazard ratio of hypertension (hazard ratio, 1.22; 95% CI, 0.91-1.60; p=0.19), diabetes (hazard ratio, 1.48; 95% CI, 0.72-2.27; p=0.30), or metabolic syndrome (hazard ratio, 1.26; 95% CI, 0.92-1.74; p=0.15).

For young adults with SCT, the absence of significant medical morbidities such as chronic cardiovascular disease, diabetes, or metabolic syndrome should not be misinterpreted to mean that a diagnosis of SCT is irrelevant to affected individuals. In fact, knowledge of the presence of SCT should initiate a series of formal preconception genetic counseling sessions about the risk of the affected individual bearing children with sickle cell disease (SCD). These discussions should be documented in electronic medical records for future reference, for family planning, and for the assessment of rare medical complications associated with SCT such as traumatic hyphema, renal medullary carcinoma of the kidney, and splenic infarction. In the two African American cohort studies with 47,644 soldiers and 1,980 young adults is the lack of mention as to whether detection of SCT leads to formal preconception genetic counseling for those affected: Despite noteworthiness in the care of individuals with SCD, including hematopoietic stem cell transplantation, and now gene therapy, the unanswered public health challenge (both in the United States and internationally) is how to effectively educate individuals with SCT about their risk of having children with SCD. One hundred years after discovery of SCT in modern medicine, we still await evidence-based strategies for informing individuals about SCT in a way that is culturally sensitive and informative about the risks of having a child with SCD.
Early T-cell precursor (ETP) acute lymphoblastic leukaemia (ALL) is a clinically and biologically unique sub-entity of typical ALL (T-ALL) arising from early thymic progenitor cells and comprising 12 to 16 percent of T-ALL in children.1-4 While historically ETP ALL was associated with a poor prognosis, several pediatric studies have demonstrated that outcomes are now not inferior with response-based contemporary TALL therapy.1-4 Comparative data in adults have been lacking, prompting a comprehensive analysis of adult patients with ETP ALL treated with pediatric-approach therapy on the Group for Research on Adult Acute Lymphoblastic Leukaemia (GRAALL)-2003 and -2005 studies. Dr. Jonathan Bond and colleagues analyzed 213 patients with newly diagnosed T-ALL who were treated on the GRAALL-2003 phase II (n=49) and GRAALL-2005 (n=164) trials and met the inclusion criteria of having available diagnostic material for categorization as ETP-TLL. ETP-ALL was defined immunophenotypically using criteria of Coustan-Smith as reduced or absent expression of CD1a, CD5, and CD8, with expression of stem cell or myeloid markers.2 Forty-seven patients (22.1%) met criteria for ETP-ALL. Forty-one patients with T-ALL were profiled by RNA-sequencing (8 ETP-ALL, 35 non-ETP-ALL), and there were found to have distinctive patterns of gene expression that mirrored those observed in pediatric patients with ETP-ALL. The adult ETP-TALL cohort also had distinct clinical differences that included a proportion of male patients, older age, and lower presenting white blood cell counts when compared with the non-ETP-ALL cohort. Patients with ETP-ALL were also more likely to have incomplete rearrangement of T-cell receptor genes and markedly elevated rates of absence of blastic deletion of the TCR locus, which was not unexpected given the immature phenotype.

The authors also performed targeted next-generation sequencing in 172 patient samples (37 ETP, 135 non-ETP) using a panel comprising genes known to be mutated in pediatric ETP-ALL.2 Mutations were observed in 82.9 percent of the ETP patients versus 63.7 percent in the non-ETP cohort. Adult ETP-TALL and pediatric ETP-ALL are defined by a genotype very similar to that of pediatric ETP-ALL, with alterations in cytokine receptor and RAS signaling; hematopoiesis; and histone modifications. The only exception was that significantly more mutations in ETP-ALL were identified in adult compared to pediatric ETP-ALL and not pediatric cases. Similar to pediatric ETP-ALL, alterations in the JAK-STAT pathway were common, occurring in approximately one-third of ETP-ALL cases.

Outcomes of ETP-ALL patients were also assessed. Despite similar remission rates of 87 percent in adults and 92.3 percent in non-ETP, the ETP patients showed significantly higher rates of end-induction minimal residual disease (MRD) positivity (a 101), a response pattern also observed in children. Despite early chemotherapy resistance, however, five-year event-free survival (EFS) and overall survival (OS) rates for ETP patients were not inferior to those in the non-ETP cohort (5-year EFS, 51.1% vs. 58.1%, and 5-year OS, 59.6% vs. 66.5%, for the ETP and non-ETP cohorts, respectively). However, a significantly greater proportion of patients with ETP-ALL met protocol-specific criteria for transplantation in first complete remission (CR1) due largely to poor induction treatment responses (48.9% vs. 28.9%). The authors separately analyzed the impact of allogeneic stem cell transplantation (allo-SCT) on outcomes in ETP-ALL. Among the 124 patients who met criteria for allo-SCT in CR1, there was a trend for better OS in the ETP group who underwent transplantation (hazard ratio, 0.36; p=0.07) but not in the non-ETP group, suggesting that intensification with allo-SCT ablated the negative prognostic impact of early chemotherapy resistance in the ETP subgroup.

This is the largest report of uniformly diagnosed and treated adults with ETP-ALL, a phenotypically defined subset with unique genomic features. This report demonstrated that adult ETP-ALL is very similar to its pediatric counterpart both clinically and biologically. One main genetic distinction is a higher frequency of in-frame mutations in genes involved in DNA methylation among adults, perhaps suggesting greater similarities to myeloid disease. This study demonstrated that while patients with ETP-ALL are more likely to have a higher rate of end-induction tumor burden, this is effectively overcome by intensified, response-based therapy in both children and adults. In children, this has been largely achieved by intensified chemotherapy, with transplantation in CR1 generally reserved for persistent MRD at the end of consolidation (or day 78) or for frank induction failures. The indications for transplantation in CR1 were broader in both this study and were based on early patterns of treatment resistance during induction rather than the later time point of MRD assessment, and therefore, a greater proportion of patients were allocated to transplantation. Regardless of the approach, response-based therapy in both children and adults with ETP-ALL has been shown to be effective in improving CR1 and CR2 rates, and therefore further assessing the role of transplantation in CR1 when using MRD-based stratification, therapeutic targeting of the JAK-STAT pathway may be another approach to investigate in this unique disease subset.

References

ChIP and Coronary Heart Disease: Clonal Hematopoiesis Increases Atherosclerosis


The term CHIMP (clonal hematopoiesis of indeterminate potential)1 entered the hematology lexicon after seminal research from several groups in 2014 revealed that upwards of 10 percent of people older than 70 years with normal blood counts have readily detectable mutations in genes associated with acute myeloid leukemia and myelodysplasia.2,3 These people had a 10-fold higher risk of developing hematologic cancer, and an excess mortality seemed logical given accepted models of leukeogenesis. Surprisingly, however, much of the higher risk of death in one study was due to coronary heart disease,2 and this observation required confirmation and further explanation. Dr. Siddhartha Jaiswal and colleagues have now reported a follow-up study that addresses these issues. Whole-exome sequencing of 74 myeloid cancer associated genes was used to identify CHIMP carriers in subjects from multiple large cohort studies established to examine other questions. The association between CHIMP and coronary heart disease (CHD) was confirmed using a nested case-control study of subjects enrolled in two prospective cohort studies. An increased risk of experiencing a myocardial infarction or undergoing coronary revascularization was found in each study for CHIMP carriers, and meta-analysis calculated that risk to be 1.9 times that of non-CHIMP carriers.3 Significant differences were observed between CHIMP carriers and non-CHIMP carriers when comparing cardiovascular disease events and total mortality.1,4 Comparative data in adults have been lacking, prompting a comprehensive analysis of adult patients with ETP ALL treated with pediatric-approach therapy on the Group for Research on Adult Acute Lymphoblastic Leukaemia (GRAALL)-2003 and -2005 studies.
In October 2016, a panel of experts including genetic hematologist-oncologists, endocrinologists, radiologists, genetic counselors, and other experts in the field gathered to share and discuss follow-up recommendations on the approach to diagnosis and management of children with a genetic predisposition for malignancies. This workshop was dedicated to pediatric cancer predisposition conditions.

This workshop produced 17 publications on a variety of topics related to genetic cancer predisposition. Follow-up recommendations include:

1. Recommendations for cancer surveillance screening include early tumor surveillance and psychosocial issues. Recommendations for cancer surveillance screening include early tumor surveillance and psychosocial issues.
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17. Recommendations for cancer surveillance screening include early tumor surveillance and psychosocial issues.

Presentation

Clinical suspicion for CPS (Table) is a prerequisite step to establishing a diagnosis. Heightened suspicion is necessary in certain scenarios including: 1) strong, relevant family history and referral for genetic counseling and testing among oncology practices; 2) a broad differential diagnosis of a variety of central and peripheral nervous system tumors, which includes gliomas and choroid plexus carcinomas. The list of specific cancer diagnoses associated with CPS is varied, but no previously identified familial mutation, a broader examination may be required. Exome/whole genome sequencing (WES/WGS), and single nucleotide polymorphism microarrays. Each method has its own unique advantages and may be used alone or in combination, depending on the clinical scenario.

Technological advancements including development of large-scale biologic databases, techniques for examining tissue samples, and the rapid and inexpensive incorporation of precision medicine into all aspects of cancer care. Although often overlooked, disease prevention through early tumor surveillance is one of the most important steps in the prevention of cancer. Early detection of cancer predisposition syndromes (CPS) can significantly improve outcomes for affected children.

Follow-up recommendations include:

1. Early detection of cancer predisposition syndromes (CPS) can significantly improve outcomes for affected children.
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In conclusion, the workshop highlighted the importance of multidisciplinary collaboration between pediatric cancer susceptibility disorders and their relevance to hematologists as highlighted in the recent AACR workshop. For a comprehensive review of this topic we encourage readers to follow the publication reference included in the AACR workshop.

References

<table>
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<tr>
<th>Primary Associations</th>
<th>Syndrome</th>
<th>Associated Hematopoietic Malignancy</th>
<th>Other Associated Malignancy</th>
<th>Mutation(s)</th>
<th>Clinical Features</th>
<th>Screening Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFS</td>
<td>AML, ALL</td>
<td>Soft tissue sarcoma, osteosarcoma, breast, choroid plexus carcinoma, medulloblastoma, congenital neuroblastoma, gastric, colorectal</td>
<td></td>
<td>TP53</td>
<td>N/A</td>
<td>Children: (Birth to 18 y/o) Leukemia: CBC annually ACC: Adipose US q 3-4 mo, if US insufficient</td>
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<td>CMMRD</td>
<td>NHL, T-ALL, B-ALL, AML</td>
<td>GI, endometrial, brain</td>
<td></td>
<td>MLH1, MSH2, USH2, PMS2, EPCAM</td>
<td>Caffe au lait macules, hyper- and hypopigmented skin changes, venous anomalies, corpus callosum agenesis, mild immunodeficiency, early onset cancer</td>
<td>Leukemia: CBC q 6 mo starting at 1 y/o, consider BM evaluation Lymphoma: Abdom US q 6 mo starting at 1 y/o Brain: MRI brain at diagnosis q 6 mo</td>
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<td>RAS activating syndromes</td>
<td>JMLL, AML, AMI, TAM</td>
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<td>NF1, PTPN11, KRAS, CBL</td>
<td>Short stature, phototropism, recumbent posture, nail dystrophy, lymphedema, pulmonary fibrosis, hepatic fibrosis</td>
<td>Leukemia: CBC annually, consider BM evaluation Head and neck SCC: ENT screening annually starting at 16 y/o</td>
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<td>Fanconi anemia</td>
<td>AML, MDS</td>
<td>Head and neck SCC, anogenital</td>
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<td>FA VINCA-E, RAD51D, BRCA4</td>
<td>Short stature, microcephaly, hypoplastic aplastic thumb, small or absent radius, hypopigmented skin macules, bone marrow failure</td>
<td>Leukemia: CBCs q 4 mo, BM evaluations annually Head and neck SCC: ENT screening annually starting 15 y/o</td>
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<td>DCK1, TERT, TER, others</td>
<td>Nail dystrophy, lazy skin pigmentation, oral leukoplaikia, pulmonary fibrosis, hepatic fibrosis</td>
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<tr>
<td>Bloom</td>
<td>NHL, AML, MDS, ALL</td>
<td>Sarcoma, GI, breast, GI carcinoma, WT, medulloblastoma, retinoblastoma</td>
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<td>BLM</td>
<td>Short stature, photosensitivity, gastrointestinal reflux, decreased fertility, insulin resistance, immunodeficiency</td>
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<td>NHL</td>
<td>Medulloblastoma, glioma, RMS, breast, prostate</td>
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<td>Ovarian, breast, prostate, gastric, pancreatic, melanoma, leiomyoma, sarcoma</td>
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<td>ATM</td>
<td>Cerebellar ataxia, conjunctival telangiectasia, ocular motor aprasia, chordeothesis, immunodeficiency</td>
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<tr>
<td>Down syndrome</td>
<td>ALL, TAM, AML</td>
<td>N/A</td>
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<td>Trisomy 21</td>
<td>Short stature, developmental delay, congenital heart defect, muscular hypotonia, single transverse palmar crease, characteristic facial appearance (hypertelorism, broad nose, epicanthal folds, upslanting palpebral fissures, protruding tongue)</td>
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<td>Monosomy 7</td>
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<td>GATA2</td>
<td>Immunodeficiency, lymphedema, deafness, hypertelorism, hydrocele, other congenital anomalies</td>
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<td>B-ALL</td>
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<td>PAX5</td>
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<td>AML</td>
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<td>CEBPA</td>
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<td>Solid tumors, GI</td>
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<td>ETV6</td>
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<td>RUNX1,1</td>
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<td>AML, MDS</td>
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<td>SAMD9</td>
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<td></td>
<td>SAMD9L</td>
<td>Axatia</td>
<td>Annual CBCs/BM evaluations</td>
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</table>

LFS, Li-Fraumeni syndrome; AML, acute myeloid leukemia; ALL, acute lymphoid leukemia; ACC, adenocortical carcinoma; CBC, complete blood count; Abd, abdomen; US, ultrasound; DHEAS, dehydroepiandrosterone sulfate; MRI, magnetic resonance imaging; WBMR, whole-body MRI; GI, gastrointestinal; CMMRD, constitutional mismatch repair deficiency; NHL, non-Hodgkin lymphoma; BM, bone marrow; GLI, germinatory; Gyn, gynecologic; JMLL, juvenile myelomonocytic leukemia; MPNST, malignant peripheral nerve sheath tumor; RMS, rhabdomyosarcoma; JXG, juvenile xanthogranuloma; MDS, myelodysplastic syndrome; SCC, squamous-cell carcinoma; ENT, ear-nose-throat; WT, Wilms tumor; LDH, lactate dehydrogenase; HL, Hodgkin lymphoma; TAM; transient abnormal myelopoiesis; PFD/AMM, familial platelet disorder with predisposition to acute myelogenous malignancy.
The Potential Utility of Immunotherapy for AML

STUDY TITLE: A Phase IIb Study Evaluating the Safety and Pharmacology of Atezolizumab (Anti-PD-L1 Antibody) Administered in Combination With Immunomodulatory Agents in Participants With Acute Myeloid Leukemia (AML)

CLINICALTRIALS.GOV IDENTIFIER: NCT02892318

SPONSOR: Hoffmann-La Roche

PARTICIPATING CENTERS: Multicenter national trial with 18 open sites across the U.S.

STUDY DESIGN: This study is a phase Ib, nonrandomized, open-label trial of the safety of combining the anti-PD-L1 antibody atezolizumab with the novel hypomethylating agent guadecitabine in older adults with acute myeloid leukemia (AML), who are not eligible for standard induction therapy. There are two safety cohorts in this trial consisting of treatment-naïve patients who are deemed unfit for induction chemotherapy by the following standards: age either > 70 or 65 to 69 with ECOG score of 2, intermediate- or adverse-risk cytogenetics, or otherwise deemed unfit for chemotherapy, and a second cohort for relapsed or refractory AML of any age or fitness. Both of these safety cohorts have planned expansion cohorts, and the trial is actually intended to have an umbrella design where other immunomodulatory agents can be combined with atezolizumab in the future.

RATIONALE: Harnessing the immune system to target cancer is an idea that has been around for decades but that recently came to the forefront of cancer research with the success of so-called “checkpoint blockers” — antibodies that block inhibitory signals on T-cells allowing for release of the “brakes” on anticancer cytotoxic T-cells. The most widely successful target for this new immunotherapy is the PD-1/PD-L1 axis. Programmed cell death 1 (PD-1) is a cell surface receptor on T-cells that negatively regulates T-cells after binding its ligands (primarily PD-L1, but also PD-L2), which are upregulated by inflammatory T-cells after binding its ligands (primarily PD-L1, but still 5.7 months. Preclinical investigations conducted in solid tumors has suggested that blocking the ligand PD-L1 can be more effective than blocking the PD-1 receptor. Besides the trial highlighted here with atezolizumab, there is also ongoing investigation of another PD-L1 inhibitor, durvalumab, in combination with HMA.

Other exciting developments in immunotherapy for AML include a trial of the PD-1/PD-L1 blockers with the next generation of checkpoint inhibitors such as TIM-3 antibodies (NCT03066648). TIM-3 is another T-cell surface receptor that contributes to T-cell exhaustion upon binding its ligand, phosphatidylserine. Other combinations could be considered, such as an immunotherapeutic signal antagonist with a stimulatory signal agonist such as 4-1BB. These stimulatory T-cell signals are the same as those utilized for current CAR-T cell construction and cause growth and survival promoting autoregulatory effects on the T-cells. Thinking beyond T-cells, other killer cells of the immune system, such as natural killer (NK) cells or macrophages could be exploited. Lirudinum is an antibody against KIR inhibitory receptors on NK cells that failed to show significant activity over placebo in a Phase II trial in AML this year, but appears to boost the efficacy of PD-1 blockade in head and neck squamous-cell carcinoma. Another approach is to help macrophages and dendritic cells overcome suppression by tumors that express CD-47, a ligand for the SIRP-α receptor that facilitates phagocytosis, also called the “don’t eat me” signal. The safety and efficacy of this is currently being tested in a Phase I study (NCT02414002). Although the results of these clinical trials are still quite nascent, the experience with immunotherapeutics for many forms of cancer to date, combined with the heterogeneity of AML, suggest that success with any of these agents may be found only in particular subgroups of AML patients. Therefore, a critical step in future development of these drugs will be identifying the patients in whom immunotherapy will be most useful and when to use it.


Dr. Taylor and Dr. Abdel-Wahab indicated no relevant conflicts of interest.
JUNE 29, 2017


Dr. Mark Levis presents a timely Spotlight review of the FLT3 inhibitor midostaurin, the first new agent approved for the treatment of acute myeloid leukemia in more than 15 years.

JULY 6, 2017


In this plenary paper, Dr. Haochen Xu and colleagues describe a new function for the metalloprotease ADAMTS13 in blood vessel formation after brain ischemia. Using multiple approaches, they demonstrate an impressive role of ADAMTS13 in neovascularization and vascular repair in mice after ischemic stroke.

JULY 13, 2017


Donated platelets show functional variability that is consistent within individual donors. This has raised the question whether donated platelets from those with more activated platelets are cleared more rapidly and are therefore less effective. Dr. Anne M. Kelly and colleagues demonstrate equivalent platelet increments with transfusion from high and low responder donors, obviating the necessity of screening for platelet function in platelet donors.


Dr. Bradley M. Haverkos and colleagues examine the outcomes for patients with relapsed lymphoma following allogeneic hematopoietic cell transplantation treated with nivolumab or pembrolizumab. They report an excellent response rate, but an alarmingly high rate of severe and refractory graft-versus-host disease.

JULY 20, 2017


This seminal paper brings direct proof for a major role of hepcidin in innate immunity, represents a great step forward in our understanding of the role of hepcidin in protection against certain infections, and provides tempting potential therapeutic applications for hepcidin analogues.


Dr. Samuel A. Merrill and colleagues report in a well-defined series of adult patients with atypical hemolytic syndrome in remission after therapy with eculizumab, the monoclonal antibody directed against complement factor D, that treatment can be safely discontinued in most of the patients without subsequent recurrence.

JUNE 1, 2017


In this week’s plenary paper, Dr. Angela Stoddart and colleagues use genetic mouse models to demonstrate that WNT signaling from niche cells contributes to myelodysplastic syndromes (MDS), suggesting that WNT downregulation may offer a novel pathway for MDS therapy.


Dr. Renato D. Lopes and colleagues examine intracranial hemorrhage in the ARISTOTLE trial, which compared the efficacies of apixaban with warfarin for treatment of atrial fibrillation. They report that this devastating complication occurs increasingly with age and concomitant aspirin and that it is less common with apixaban than with warfarin.

JUNE 8, 2017


This intriguing clinical paper reports PD-1 blockade in four patients with relapsing or primary refractory central nervous system (CNS) lymphoma and one patient with testicular lymphoma relapsed in the CNS. All patients responded and four achieved long-lasting complete remissions.


Dr. Rebecca A. Gardner and colleagues report encouraging results of a phase 1 trial with 45 children and young adults with relapsed or refractory B-lineage acute lymphoblastic leukemia. Their study found a remarkably high minimal residual disease-negative complete remission rate after treatment with a uniquely formulated chimeric antigen receptor (CAR)-T cell product of defined CD4/CD8 composition genetically modified with a CD19-specific 4-1BB-ζ CAR lentiviral vector.


Dr. Kohta Miyawaki and colleagues identify a primitive unique progenitor cell population that generates megakaryocytes and platelets in adult humans. They show that it is expanded in myeloproliferative neoplasms, including essential thrombocythemia.

JUNE 22, 2017


Donated platelets show functional variability that is consistent within individual donors. This has raised the question whether donated platelets from those with more activated platelets are cleared more rapidly and are therefore less effective. Dr. Anne M. Kelly and colleagues demonstrate equivalent platelet increments with transfusion from high and low responder donors, obviating the necessity of screening for platelet function in platelet donors.


Dr. Bradley M. Haverkos and colleagues examine the outcomes for patients with relapsed lymphoma following allogeneic hematopoietic cell transplantation treated with nivolumab or pembrolizumab. They report an excellent response rate, but an alarmingly high rate of severe and refractory graft-versus-host disease.

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This seminal paper brings direct proof for a major role of hepcidin in innate immunity, represents a great step forward in our understanding of the role of hepcidin in protection against certain infections, and provides tempting potential therapeutic applications for hepcidin analogues.


Dr. Samuel A. Merrill and colleagues report in a well-defined series of adult patients with atypical hemolytic syndrome in remission after therapy with eculizumab, the monoclonal antibody directed against complement factor D, that treatment can be safely discontinued in most of the patients without subsequent recurrence.
A Woman With Hypergammaglobulinemia and Diffuse Lymphadenopathy

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A 73-year-old woman with a history of autoimmune hepatitis presented with abdominal pain and fever. On further examination, the patient was noted to have hypergammaglobulinemia, elevated lactate dehydrogenase (LDH), and diffuse lymphadenopathy on imaging. An excisional biopsy of a superficial lymph node was performed.

The images below are of a hematoxylin & eosin stain depicting architectural effacement by this proliferation of medium sized mononuclear cells (Figures A and B) containing numerous wisps of follicular dendritic cell meshworks (Figure C) and few scattered Epstein-Barr virus (EBV)+ cells (Figure D).

What is the most likely diagnosis?
A. Histiocytic sarcoma
B. Angioimmunoblastic T-cell lymphoma
C. Chronic myelomonocytic leukemia
D. EBV+ large B-cell lymphoma
E. Follicular dendritic cell tumor

For the solution to the quiz, visit The Hematologist online, www.hematology.org/Thehematologist/Images.

Dr. Parilla and Dr. Venkataraman indicated no potential conflicts of interest.

Put your fellow readers to the test, and send us your Image Challenge submissions! Email case descriptions and image files to the Managing Editor at jlllorens@hematology.org.