In Anticipation of the Wave

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When I was a kid, my father would tell us stories about his dad, a general practitioner in rural Indiana. During the late 1940s, the years of the polio epidemic, Grandpa didn’t let anybody near the car. None of the kids were allowed in the garage. Each night, arriving home after making rounds, he climbed out of the car, stripped and stood in his underwear in the garage to wash himself with a solution of bleach and water, so that he wouldn’t carry the virus to his family.

I’m writing this during the third week of March 2020. The coronavirus pandemic has hit our nation’s coasts, but the surge is still in the future for those of us in Wisconsin. I’m (nearly) beyond the stage of obsessively checking the news. For my sanity’s sake I’ve signed off Twitter and am largely relying on the links curated by the ASH website (www.hematology.org/COVID-19) for relevant medical information. The whole experience feels a little like standing shin deep in the ocean, facing out, but wearing a blindfold. At first you feel safe, with the sun warm on your face. But then, the temperature of the water changes a bit; it gets a little cooler. There is a pull that starts at your ankles, the sand scurries in new directions around your feet, the water level drops. The wave is coming, but you have no understanding of how large it will be.

Rational fear may be a relatively new emotion for many of us. This is different from anxiety. (Did I double check the creatinine before I signed that order? Will this trial accrue? Is she mad at me?) But rational fear has been a companion to physicians, nurses, and health care workers throughout history. Physicians have waded in to treat patients during plagues and war. They have worked in refugee camps and leprosy colonies. They have opened the car door and let fear sit in the passenger seat as they drove through snowstorms to deliver babies, to attend to the dying, to minister to those who suffer.

And it has occurred to me that the work of hematology might give us some unique expertise in the midst of all this Sturm und Drang. For example, one of the things that feels most recognizable, as I sit in teleconferences about workforce management or supply-chain questions, is the experience of making decisions with incomplete data. Our profession, whether we are choosing induction for a newly diagnosed leukemia patient, pulling the trigger on thrombolytics in a patient with acute pulmonary embolism, or making any of a thousand other decisions, constantly requires that we act before we have certainty, making choices based on what is statistically likely to happen, even if things seem fine at the time. And that’s what disaster planning seems to be about, from what I can see. It requires the resolve to act early; better to be overprepared and underutilized than underprepared and overwhelmed.

As hematologists we are also very good at imagining the worst possible scenario. I’ve been mocked many times by my family for this, but the habit has served me well. Our training instills in us a seemingly endless list of complications that we anticipate and then work to prevent or circumvent. Why else do we prescribe so many prophylactic medications or line up potential third-line clinical trial options for a patient who has not yet failed second-line...
In Anticipation of the Wave

(Cont. from page 1)

treatment? And then we have the other set of worries: What if they are p53 mutated? What if they get sepsis? What if they are HLA-sensitized? When should I transplant? Many of the decisions we are now making in the COVID-19 era currently require that same brand of pessimistic imagination. What if all our doctors or advanced practice providers get exposed? What if we don’t have an adequate blood supply? What if we run out of gowns? ASH President Dr. Stephanie Lee, in a call earlier this week told me that the experts say in situations, preparations seem alarmist until the disaster hits, then they seem inadequate.

Finally, I think training for hematology teaches you how to simultaneously hold in balance both large-scale statistics and the personal aspects of your decision-making. Today, I sat with a patient—a 57-year-old woman with favorable-risk acute leukemia in first remission. I am well aware of her statistical chances of cure. I am also aware that the likelihood of death, should she contract COVID-19, is sixfold higher than someone her age without cancer. And I know that my recommendation about the timing of consolidation preparations seem alarmist until the disaster hits, then they seem inadequate.

Looking ahead, I am hopeful that the rest of 2020 improves and that we can hold our annual meeting in December. ASH continues to monitor the situation and will prioritize the health of our volunteers, staff, and meeting attendees, recognizing that health care providers have a special responsibility to keep themselves healthy in order to provide care to others and avoid becoming vectors for transmission.

As events have unfolded, I’ve been feeling uncomfortably reactive. Probably like most of you, when changes and restrictions are announced, I’ve found myself saying, “I should have thought of that!” I believe that the next few weeks are critical to making sure we’re as prepared as possible. In my role as ASH President, I am committed to the Society doing whatever it can to help our field be proactive and prepared in the face of one of the more frightening challenges in modern times.

ASH has developed a mechanism to help share useful information about the novel coronavirus with hematologists. This is not the forum to review all that our medical teams have done to prepare for and battle this illness, but it is a way to crowdsource materials and tips on caring for our patients and for one another. It’s a start, and it can be expanded to address members’ needs; so let us know what is helpful. If you’ve seen something really useful, please pass it along to us via a form on ASH’s COVID-19 webpage (www.hematology.org/covid-19) for possible dissemination.

Stay healthy and safe, and let’s unite to help each other get through this. 

Stephanie J. Lee, MD, MPH
COVID-19 Resource Webpage for Hematologists

ASH has developed and is maintaining a webpage (www.hematology.org/COVID-19) that contains a series of resources, as a medium to exchange information and assist hematologists in navigating the COVID-19 public health crisis. The page is being updated with new links and information on a consistent basis, and users can sign up for email alerts to stay abreast of the latest tools.

In addition to providing general resources, guides from subspecialty societies, journal articles, and links to data repositories, the resources page provides a series of frequently asked clinical questions (www.hematology.org/covid-19/faq). This series covers a variety of malignant, nonmalignant, and practice-related topics and is expertly curated by a team of ASH members.

If there is a hematology-related COVID-19 resource that has been helpful to you that is not listed on the webpage, or if you encounter a specific issue or question that ASH can help address, please fill out and submit the feedback form located at the bottom of the page.

COVID-19 and Career Development Awards

While ASH is continuing to support hematologists through a variety of awards, we understand that the entire medical community is currently focused on addressing the current public health emergency. If these circumstances are preventing you from participating in or applying for one of our programs, we encourage you to contact awards@hematology.org.

COVID-19 Funding Opportunities From NHLBI

The National Heart, Lung, and Blood Institute (NHLBI) is offering a new award opportunity to support research investigating the host response; associated heart, lung, and blood disease; impact on transfusion safety; and short- and long-term clinical outcomes of individuals with COVID-19 and SARS-CoV-2. Of particular interest are studies that use human research or unique model systems to study the consequences of SARS-CoV-2 infection. Visit grants.nih.gov/grants/guide/notice-files/NOT-HL-20-757.html to learn more and apply online.

ASH Research Collaborative COVID-19 Surveillance Registry for Malignant Hematology

On April 1, 2020, the ASH Research Collaborative (ASH RC) Data Hub launched a new COVID-19 Surveillance Registry focused on capturing high-level data on patients worldwide who are both COVID-19 positive and diagnosed with a past or present hematologic malignancy. The registry’s goal is to provide open-access, near-real-time observational data to hematologists and their patients. The registry is designed for investigators with a focus on the hematologic aspects of COVID-19 and SARS-CoV-2 infection. Registration is available online at www.ashresearchcollaborative.org/covid-19-registry.

Consult-a-Colleague

Consult-a-Colleague is a service for ASH members that helps facilitate the exchange of information between hematologists and their peers. Members with inquiries that are directly related to COVID-19 should refer to www.hematology.org/COVID-19 for more general information, prior to submitting a question. Additionally, if you or a colleague at your institution have identified problems and/or solutions related to COVID-19 that may be of interest to the broader hematology community, please submit them using the form on the ASH COVID-19 resources page.

ASH Meetings Update

ASH is closely monitoring the impact of COVID-19 as the health and safety of our members and their patients is our top priority. We encourage you to monitor our meeting webpages to stay aware of the latest updates. Below are updates on several of our meetings:

- **Highlights of ASH in Latin America.** ASH and the Associacao Brasileira de Hematologia, Hemoterapia, e Terapia Celular have postponed this meeting to 2021. Exact dates and locations will be announced soon.

- **ASH Meeting on Lymphoma Biology.** This meeting has been cancelled. ASH encourages those who had planned on submitting abstracts for this meeting to instead submit them for consideration to the 2020 ASH Annual Meeting. The abstract submission site will open on June 4, 2020.

- **ASH Meeting on Hematologic Malignancies.** Join us September 10-11, at the Hilton Chicago. The meeting features top experts in the field presenting the latest clinical research. Attendees will have the opportunity to interact with colleagues in an intimate, small group setting with no competing sessions. Registration opens May 6.

The Hematologist Launches New Podcast Series Covering COVID-19

The Hematologist has launched a special podcast series on COVID-19 to help hematologists stay abreast of the latest resources for researchers and clinicians, as well as to provide on-the-ground perspectives from around the community. In the first installment, “How ASH Supports the Hematology Community During COVID-19,” Editor-in-Chief Dr. Laura Michaelis speaks with ASH President Dr. Stephanie Lee about the latter’s experience in Seattle and how ASH leadership and members are coming together to use their combined knowledge and resources to keep hematologists informed and empowered. In the second episode, Dr. Lee speaks with Dr. Martin Tallman of Memorial Sloan Kettering Cancer Center about how his practice treating patients with leukemia and other blood cancers has shifted during the COVID-19 public health emergency. Visit www.soundcloud.com/ash_hematology to hear the latest and to subscribe.
How to Use a Geriatric Assessment in an Older Patient With Acute Myeloid Leukemia

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THE CASE

A 75-year-old woman presents to the emergency department with pancytopenia and a two-week history of fatigue. Her medical history includes hypertension, hyperlipidemia, diabetes, and osteoarthritis. Her Eastern Cooperative Oncology Group (ECOG) performance status was 1. Laboratory findings were white blood cell count, 2.0 × 10^9/L with 25 percent blasts; absolute neutrophil count, 1.2 × 10^9/L; hemoglobin, 10.4 g/dL; and platelets, 112 × 10^9/L. Renal and liver function, prothrombin time/ partial thromboplastin time, fibrinogen, uric acid, and phosphorus were normal. Lactate dehydrogenase was elevated (250 U/L). A bone marrow biopsy was performed, which showed acute myeloid leukemia (AML) with no myelodysplastic changes and blast count of 39 percent. Flow cytometry was positive for CD13, CD33, CD34, CD117, and human leukocyte antigen-DR. Cytogenetics were normal. Fluorescence in situ hybridization did not show a RUNXTERUXIN, MLL, PML-RARA, or CBFB-specific rearrangement. Mutation panel was negative for FLT3, NPM1, CEBPA, or IDH1/2 mutations.

THE QUESTION

What is the evidence for performing geriatric or fitness assessments?

OUR RESPONSE

A geriatric assessment is a multidimensional assessment used to evaluate the health of an older adult. It uses validated measures to assess geriatric domains including physical function, comorbidities, cognitive function, psychological health, nutritional status, medications, and social support. It can sometimes be referred to as a “fitness” or “frailty” assessment since a geriatric assessment can help determine fitness, but these terms are not synonymous. A geriatric assessment uncovers vulnerabilities that are not detected in routine clinical practice and predicts morbidity and mortality, which may help with treatment decision-making. A geriatric assessment can also guide supportive care interventions and improve patient-oncologist communication as well as patient and caregiver satisfaction.

In a prospective study of older adults with largely good performance status (78% ECOG ≤1) who were scheduled to receive intensive therapy for AML, geriatric assessment detected a high prevalence of impairments: 41 percent basic activities of daily living (ADL), 50 percent instrumental ADL (IADL), 52 percent objectively measured physical performance (Short Physical Performance Battery [SPPB] <9), 28 percent cognitive function, 40 to 59 percent psychological distress, and 42 percent Hematoepoietic Stem Cell Transplantation Comorbidity Index (HCT-CI) score greater than 4. Both impaired cognition and objective physical performance were associated with worse overall survival. Several other studies in older patients with AML and myelodysplastic syndromes (MDS) also found that impaired AML, impaired IADL symptoms (fatigue, pain), and higher comorbidity burden were predictive of worse survival.

Concordant evidence supporting the value of geriatric assessment has been documented in hematologic malignancies including lymphoma, multiple myeloma, MDS, and in the pretransplantation setting. The predictive value extends beyond survival and includes treatment-related outcomes and health care utilization. For example, among older adults with MDS receiving azacitidine, those with impairments in IADL, cognition, and mobility were more likely to discontinue therapy, and those with physical impairment and higher comorbidity burden had worse survival.

Among specific domains assessed in a geriatric assessment, measures of physical function and cognition seem to be high yield for predicting increased risk of morbidity or mortality in the context of AML therapy and among those with hematologic malignancies more broadly. Self-reported basic ADLs and instrumental ADLs can identify functional vulnerability associated with worse outcomes among AML patients receiving less intensive therapy. Impairment has also been associated with higher health care utilization and worse survival among adults 75 years and older with varied hematologic malignancies. Objective testing of physical function is more sensitive than self-report and adds value to assessment of vulnerability. As mentioned, the SPPB (a composite test including gait speed, balance, and standing balance) was predictive of survival among older adults treated intensively for AML. Gait speed alone may be an efficient screening test. Gait speed has been a consistent predictor of health outcomes in older populations. Among adults 75 years or older with varied hematologic malignancies, decrease in gait speed was associated with higher mortality, greater odds of unplanned hospitalization, and higher hospitalization costs. Similarly, in the same population, a simple five-word recall measure of working memory identified prevalent cognitive impairment, which was associated with worse survival.

Finally, there is evidence to support repeating geriatric assessment measures during treatment to assess the impact of therapy on physical, cognitive, and emotional health. Geriatric detected vulnerabilities are not static but can be influenced positively and negatively by treatment and AML complications. For example, among older adults with AML receiving intensive therapy, clinically meaningful declines in physical function and changes in emotional well-being can be measured at the time of remission, which may influence tolerance to subsequent therapies and quality of life. Information from the geriatric assessment can help direct ongoing personalized supportive care and decision-making.

How are geriatric or fitness assessments performed in the clinic or inpatient setting, and how much time do they take?

A cancer-specific geriatric assessment generally takes approximately 15 to 30 minutes, keeping in mind that most of the assessments are self-reported and can be administered without assistance from a health-care professional. Objective assessments (i.e., gait speed and cognition testing) are administered by staff and typically take approximately five minutes, including instructions if performed routinely.

Geriatric assessment has been successfully implemented in AML trials conducted in the cooperative group setting. The length of time depends on the number of assessments included. In general, it is recommended that each of the geriatric domains be assessed, but some of the domains may be obtained from the electronic medical record (e.g., comorbidities, medications, and weight).

Practices that use geriatric assessment often have patients complete the self-reported portion of the assessment prior to clinic visits in the outpatient setting. These are mailed out or sent electronically in advance to patients for completion at home, or they are administered as part of a check-in process prior to the clinic visits. In the inpatient setting, paper surveys or electronic surveys via a tablet can be administered. A physical/hospitalist/primary care professional (e.g., patient care technician, nurse, advanced practice professional) can be trained to perform the objective assessments.

If time and resources prohibit the incorporation of a full geriatric assessment, and there are no geriatrics or geriatric oncology services available, certain geriatric domains or assessment programs may be considered. Physical function, cognition, and comorbidities have been shown to be of highest yield. These assessments may include the following: 1) physical function (self-reported questions such as ADL and IADL or objective testing such as an SPPB, Timed Up and Go, or gait speed), 2) comorbidity burden (HCT-CI or Cumulative Illness Rating Scale [CIRS] or CIRS-Geriatric), or 3) cognition (Mini-Mental State Examination or Blessed Orientation-Memory-Concentration or 5-word recall).

How do geriatric or fitness assessments guide interventions?

There is increasing interest in using geriatric assessments to allocate treatment for older adults. At this time, the evidence supporting an optimal assessment strategy to allocate treatment in AML is insufficient given the complex interplay of fitness and disease biology. Randomized trials that include geriatric assessment measures are lacking. Instead, a geriatric assessment provides information to consider during an informed discussion about treatment and can guide supportive care interventions. If vulnerabilities are identified earlier in the disease course, interventions can be instituted to reverse impairments, with the potential to improve treatment tolerance and outcomes. For example, physical therapy or an exercise program could be recommended to address functional impairment. For cognitive impairment, strategies to prevent delirium should be considered, as well as engaging family, caregivers, and nurse navigators during hospitalization. Management can be instituted for polypharmacy to reduce drug interactions, and depressive symptoms can be addressed with counseling and/or pharmacologic therapy.

CASE CONCLUSION...

The patient underwent a geriatric assessment. She was independent in her ADLs and most IADLs, except shopping. She reported one fall in the previous six months. Her HCT-CI was 1 (diabetes mellitus; recent falls). Medications were amlopidine, lisinopril, atorvastatin, acetaminophen, metformin, aspirin, omeprazole, and vitamin D. She had not lost weight. She is married with two daughters. She lives at home with her husband but both daughters live within 10 miles. She scored 26 out of 30 on the Mini-Mental State Examination and 2 out of 15 on the Geriatric Depression Scale (negative screen for both). She scored 7 out of 12 on the SPPB (<9 indicates physical vulnerability).

The patient’s geriatric assessment revealed several vulnerabilities, including impairment in IADL and SPPB, polypharmacy, and a fall. These impairments indicate potential higher risk for complications and possibly shorter survival compared to an adult with none of these vulnerabilities. After informed discussion, she was enrolled onto a clinical trial evaluating the combination of azacitidine and venetoclax with a novel therapeutic agent. Several supportive care interventions were recommended based on her geriatric assessment. She was referred to physical therapy and started an exercise program. A gait evaluation was performed, and a cane was recommended. Home safety evaluation was performed, and the patient received a medical alert bracelet due to risk of falls.
Her daughter was asked to check in with the patient daily. After medication review with the oncologist and pharmacist, omeprozole was discontinued.

As demonstrated in this case, geriatric assessment can inform management of older adults with AML. Routine collection of geriatric assessment measures in clinical trials will further inform treatment selection and personalized care.


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T-cell Lymphoblastic Leukemia: What Are the Prospects for Novel Immunotherapy?

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The Case
A 22-year-old woman presented to an academic medical center with a four-week history of night sweats and tender proptosis. Right eye examination showed a congested conjunctiva with central necrosis. A soft tissue density (2.8 cm) in the anterior mediastinum was compressing the superior vena cava. A CT scan of the chest, abdomen, and pelvis revealed no enlarged lymph nodes and a normal-sized spleen. The complete blood count revealed a white blood cell count of 7.7 × 10^9/L; hemoglobin, 10.4 g/dL; hematocrit, 29 percent; platelets, 88 × 10^9/L; and absolute neutrophil count, 3.5 × 10^9/L. There were 20 percent blasts in the white cell differential count.

A cell suspension from a marrow aspirate was examined by flow cytometry, and the blast population expressed CD7, CD34, CD56, cyttoplasmic CD3, human leukocyte antigen–DR, and partial CD15. The blast population was negative for CD1a, CD2, CD4, CD8, CD5 (dim), CD10, CD20, CD22, CD117, CD64, CD14, CD79a, and TdT. Chromosome analysis revealed a near triploid composite karyotype with 77 × 81 chromosome cells. The molecular study revealed no mutations in NOTCH1, FLT3, or IDH2. The spinal fluid did not contain leukemia cells. The lactate dehydrogenase was 327 U/L (normal range, 118-225 U/L). Her diagnosis was early T-cell precursor acute lymphoblastic leukemia (ETP-ALL). She was started on a standard four-drug induction regimen that included vincristine, dexamethasone, daunorubicin, and pegaspargase, including central nervous system prophylaxis.

Minimal residual disease (MRD) assessment was performed by multiparameter flow cytometry on day 29 of induction therapy and revealed a value of less than 0.1 percent. The patient continued on a pediatric consolidation regimen of augmented Berlin-Frankfurt-Munster (aBFM) protocols with the addition of nelarabine. Following completion of the consolidation course, MRD assessment was repeated and showed detectable disease (≥0.1%). Given the high risk of relapse based on the end-of-consolidation MRD assessment, the patient was referred for allogeneic hematopoietic cell transplantation (HSCT). As the patient was preparing for allogeneic HSCT, a marrow biopsy was performed as part of the pretransplant evaluation, and she was found to have 35 percent blasts in the aspirate specimen, consistent with relapsed T-cell ALL.

Current State of T-ALL Treatment/Challenges in Diagnosis and Management
T-lineage ALL (T-ALL) is curable for most children and adolescents and young adults (AYAs), defined as those aged 15-39 years, with contemporary frontline chemotherapy regimens. For children and AYAs, the pediatric-inspired, modified aBFM backbone including cytarabine, daunorubicin, and dexamethasone, the regimen from the trial of the University of Rochester, Rochester, NY

Table. Selected Immunotherapy Trials for T-lineage Acute Lymphoblastic Leukemia

<table>
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<tr>
<th>T-cell Antigen</th>
<th>Immunotherapy</th>
<th>Trial Phase</th>
<th>Clinical Trial</th>
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<tr>
<td>CD5</td>
<td>CD5 CAR T</td>
<td>Phase I</td>
<td>NCT03081910/Baylor College of Medicine</td>
</tr>
<tr>
<td>CD7</td>
<td>CD7 CAR T</td>
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<td>NCT03690011/Baylor College of Medicine</td>
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<td>UCART7</td>
<td>Phase I</td>
<td>Not yet recruiting/Washington University</td>
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<td>TRBC1 CAR T</td>
<td>Phase I</td>
<td>NCT03580574/United Kingdom</td>
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<td>Daratumumab</td>
<td>Phase I/II</td>
<td>NCT03384654/Multiple international sites</td>
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<td>Isatuximab</td>
<td>Phase II</td>
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Further, there was low CD38 expression on normal lymphoid and myeloid cells and nonhematopoietic organs, suggesting minimal “off target” toxicity. The lab expanded research on the surface of lymphocytes, including T and B lymphocytes, plasma cells, and natural killer cells. Its functions include regulation of intracellular calcium and signal transduction of immune cells. The laboratory of Dr. David Teachey and colleagues have designed CAR-T constructs targeting CD5 and CD7 to eliminate normal T-cell subsets and cause T-cell aplasia. Only time or potentially curative HSCT can result in CAR-T fratricide during manufacturing and therefore limit ex vivo expansion and therapeutic potency of the autologous cell product. Once fratricide is resolved, there remains the issue of prolonged T-cell aplasia. CAR-T cytotoxicity against normal lymphocytes and their precursors will suppress overall T-cell function and induce temporary or prolonged immunodeficiency, clinically similar to that observed following HSCT. There is no easy, clinically useful treatment to help with prolonged T-cell aplasia. Only time or potentially curative HSCT (as allogeneic HSCT terminates the activity of CAR-Ts) restores normal hematopoiesis and ultimately replenishes T-cell populations. In contrast, the prolonged B-cell aplasia, from targeting CD19 in B-cell malignancies, can be treated with intravenous immunoglobulin. Lastly, there is a risk of genetically modifying circulating malignant T-lymphoblasts, which could facilitate a treatment-resistant tumor clone.

Despite the technical and clinical challenges, several laboratories have developed CAR-T constructs, using strategies that address each of the technical and clinical hurdles described above, and early-phase clinical trials are underway (Table). Investigators at Baylor University have designed CAR-T constructs targeting CD5 and CD7 that eliminate fratricide, but these common T-lineage antigens will eliminate normal T-cell subsets and cause profound immunosuppression, so current trials are designed as a “bridge to transplant.” In the United Kingdom, scientists have used TRBC1 as a target, which

(Cont. on page 12)
Transplantation in Sickle Cell Disease: Who, When, and How

In 2020, one of the hottest debates in sickle cell disease (SCD) asks the question, “What are the indications for BMT?” It is clearly a data-free zone. SCD is a serious public health problem around the world, killing nearly 100,000 people a year globally. In 2010 there were more than 300,000 newborns with SCD. In the United States, SCD is the most common inherited blood disease affecting nearly 100,000 children and adults. Therefore, there are many more patients with SCD than with acute myeloid leukemia, a disease for which precise indications for transplantation do exist. The annual cost for medical care for patients with SCD in the United States exceeds $1 billion. For adults with SCD, the average annual cost of medical care exceeds $35,000 USD per year.9 While survival of patients with SCD has improved in developed countries owing to improved supportive care, use of blood transfusions, prophylactic antibiotics, and drug therapy with hydroxyurea, none of these interventions are curative. Despite these advancements, most adults and many children develop a chronic debilitating condition, leaving more than 30 percent of adults on disability and more than 50 percent of patients unemployed.10 Median survival is shortened by more than two decades, and quality of life is severely impacted due to complications such as chronic pain, narcotic dependence, stroke, renal failure, thrombosis, pulmonary hypertension, blindness, priapism, and infection.

Allogeneic bone marrow transplantation (ABMT) can cure SCD. In 1984, Dr. F Leonard Johnson and colleagues reported a successful ABMT of a child with leukemia and SCD who was cured of both disorders.4 As of 2013, there were 1,238 BMTs for SCD reported to the Center for International Blood and Marrow Transplant Research and the European Society for Blood and Marrow Transplantation-ECord.5 This was followed by a series of nonrandomized of myeloablative ABMT from matched sibling donors for children with SCD.6,7 These data firmly established that SCD is a potentially curable disease following myeloablative ABMT from a healthy human leukocyte antigen (HLA)–matched sibling donor. However, BMT is seldom used for these patients owing to perceived toxicity and lack of suitable donors. The medical problems described above make some of these patients unsuitable for therapy such as transplantation. Moreover, BMT is only available in developed countries; however, these countries also have obstacles that limit the availability of BMT to only half of the patients with SCD, such as availability, transplant related morbidity and mortality, and engraftment difficulty in patients with SCD.8,9 The past decade has witnessed dramatic improvements in increasing safety and expanding the donor pool for patients in need of BMT. However, despite the fact that BMT is more available than before, particularly given the availability of nonmyeloablative conditioning,10 there is no consensus among hematologists as to the indications for BMT in patients with SCD.

It is important to remember that patients with SCD are interested in BMT, so we must present them with a rational, evidence-based set of indications for the procedure. Drs. Suparno Chakrabarti and David Bareford surveyed 30 adult patients with SCD about their feelings toward receiving a reduced-intensity BMT for the management of their disease.11 Fifty-two percent were willing to accept a 10 percent transplant-related mortality, and a third of patients, could accept even a 30 percent transplant-related mortality rate. Most patients (62%) were willing to accept a 10 percent risk of graft failure, 50 percent were willing to accept infertiltiy, but only 20 percent considered chronic graft-versus-host disease acceptable. In fact, 60 percent of those surveyed would consider joining a clinical trial of reduced intensity BMT. If patients are willing to try this intervention despite symptomatic children with SCD should be transplanted as soon as possible if they have a fully matched HLA-sibling donor; however, this is not universally accepted given variable clinical trajectories. In adults, patients common indications have included cerebrovascular disease, recurrent vaso-occlusive crisis despite hydroxyurea, osteonecrosis, red cell alloimmunization, and recurrent ACS.8,10 While pulmonary hypertension is a known cause for morbidity and mortality in these patients, there is no agreement as to whether or not patients with this condition should proceed to transplantation, and at least in one study, such individuals were excluded.10 Some degree of renal dysfunction should not be seen as a reason to avoid transplantation (given the use of nephrotoxic drugs such as calcineurin inhibitors or BUDARABINE); however, data on patients receiving transplants for this indication on renal replacement therapy are limited.12 The indications for BMT in children and adults with SCD will continue to evolve as the availability of alternative donors, engraftment rates, and safety of BMT increases.

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) currently has open studies evaluating the role of ABMT in patients with SCD. Given the relevance of the BMT CTN, it is important to look into their eligibility for such studies. BMT CTN 1507 is a study of reduced intensity conditioning using haploidentical donors. BMT CTN 1503 compares BMT to standard non-BMT care for adolescents and young adults with SCD. Both studies have similar enrollment criteria. Regarding SCD-specific manifestations in children, they are looking for children with a neurological event (stroke or abnormal MRI) or abnormal transcranial Doppler ultrasonography. For adults, beyond the neurological event, it is required that they have two or more episodes of ACS in the prior two years, history of three or more episodes of pain crises per year in the preceding two years, transfusion dependence, or a tricuspid valve regurgitant jet velocity of 2.7 m/s or greater. Patients also need to be eligible for BMT by standard criteria (e.g., good cardiac, pulmonary, and renal functions). These indications are similar but not identical to others used on previous studies.

ASH has developed clinical practice guidelines on SCD. A panel on transplantation is working on clarifying some of the issues related to indications. I suspect that now that BMT is becoming more prevalent due to the use of alternative donors, consensus will develop so that we will all be able to tell our patients who, when, and how.

MULTIPLE MYELOMA (MM) IS AN INCURABLE CLONAL PLASMA CELL MALIGNANCY AND THE SECOND MOST COMMON ADULT HEMATOLOGIC MALIGNANCY, WITH AN INCIDENCE OF 31,000 CASES PER YEAR.1 Although immunomodulatory agents, proteasome inhibitors, and monoclonal antibodies significantly improved outcomes in MM, patients still experience disease relapse and resistance to therapy. This raises the need to develop new drugs that can control and eradicate tumor cells more efficiently and durably.

Immunotherapy is now a growing and promising approach in MM, especially adoptive T-cell therapy (such as chimeric antigen receptor T-cell [CAR-T] therapy) and bispecific antibodies, which are showing promising results in relapsed or refractory patients. Earlier CAR-T trials in MM indeed showed impressive response rates. However, these responses lacked durability2 and thus opened the door for improved designs that could induce a sustainable antymyeloma effect.

The potency of antibodies in MM has been demonstrated with monoclonal antibodies (mAbs) targeting different MM-specific antigens (CD38, SLAMF7, and BCMA). Bispecific antibodies are engineered to recognize two distinct molecular targets: one specific to the cancer cell of interest and the other on T cells (mainly CD3). This T-cell engagement will direct them to elicit a cytotoxic response toward the cancer cells. This approach has proven to be clinically effective for the bispecific antibody blinatumomab, which targets CD3 and the protein CD19 in B-cell acute lymphoblastic leukemia.3 Moreover, clinical trials of bispecific antibodies targeting CD38 and BCMA in MM have shown promising interim results.

In a recent article in Nature Cancer by Dr. Lan Wu and colleagues, the authors developed a trispecific antibody with three antigen-binding sites targeting CD3 and CD28 on T cells plus CD38 on myeloma cells. CD28 belongs to a class of proteins called costimulatory receptors, which is a critical mediator of T-cell signaling following T-cell receptor activation and drives its proliferation and survival.

The authors showed that the CD28-binding domain augmented the trispecific antibody’s activity by creating three versions of the antibody in which different combinations of the three binding domains were mutated. They tested these versions in three MM cell lines and a humanized NOD/SCID/γ-null (NSG) mouse model, which had human primary CD8+ T cells, inoculated with the NCI-H929 human myeloma cell line. The results of both in vitro and in vivo experiments proved that a functional CD28-targeting domain boosted the T-cell activity above that observed using antibodies lacking it.

The authors also reported that the trispecific antibody stimulates Tp31 function and CD8 memory T cells, which are known to enhance antitumor immunity. They also argued that CD28 expression on myeloma cells could improve antibody affinity and T cell recognition and lysis. Previous studies reported that CD28 is detected on primary myeloma cells in approximately one-third of newly diagnosed patients and increases in frequency during myeloma progression and extramedullary disease.4 Indeed, the sensitivity of the CD28 knockout cells to T-cell cytolyis was reduced tenfold to 100-fold.

One of the questions yet to be answered is about the risk of cytokine release syndrome with this trispecific antibody in clinical trials. Cytokine release syndrome could occur after excessive stimulation of T cells and can lead to multorgan failure. In 2006, six healthy volunteers who received a single dose of a CD28 superagonist mAb became critically ill with immune-related toxicities.5 Dr. Wu and colleagues argue that they included a special scFv fragment in the antibody structure, which targets CD38 and BCMA, and made it a trispecific antibody with three antigen-binding sites targeting CD3 and CD28 on T cells and CD38 on myeloma cells. CD28 belongs to a class of proteins called costimulatory receptors, which is a critical mediator of T-cell signaling following T-cell receptor activation and drives its proliferation and survival.

In conclusion, this study provides preclinical data for this trispecific antibody and warrants further clinical investigation to assess its safety and efficacy. It would be interesting to see whether the use of this antibody would induce a deep and durable response in relapsed or refractory patients as well as those refractory to anti-CD38 mAbs. The trispecific antibody platform is flexible and promising for designing more precise therapies for different targets and signaling molecules in various cancers.

Are We Capable of Curing Follicular Lymphoma, But Just Afraid to Say It?


When I see patients with newly diagnosed follicular lymphoma (FL) in clinic, I usually tell them their disease is not curable but very treatable, and can be successfully managed over a long period. I tell them...
Lower Risk for Fractures Is Another Win for Direct Oral Anticoagulants


For patients requiring long-term anticoagulation for thromboembolism prevention, possible adverse effects outside of the risks for bleeding and recurrent thromboembolism include osteoporosis, a common consequence. Osteoporosis is more frequent in women, and this risk increases with age. Bone loss in patients receiving anticoagulants is important to consider since it increases the risk of osteoporosis and fractures.1 In a previous systematic review and meta-analysis, direct oral anticoagulants (DOACs) and VKAs had similar fracture rates.2 Two recent studies shed new light on the comparative risk of fractures in oral anticoagulant users.

The first study by Casper Binding and colleagues examined patients in Danish national registries with nonvalvular atrial fibrillation (AF) who were new users of oral anticoagulation and had been treated for at least 180 days. Outcomes included an individual analysis and a composite outcome of hip fractures, major osteoporotic fractures, any fracture, and initiation of osteoporotic medications. After excluding 23,749 patients, 25,182 DOAC-treated patients and 12,168 VKA-treated patients were compared in a multivariate Cox proportional hazard model adjusted for baseline differences in comorbidities and other medications. Patients treated with DOACs were less likely to have a major osteoporotic fracture (HR, 0.85; 95% CI, 0.72-0.99), any fracture (HR, 0.85; 95% CI, 0.74-0.97), and initiation of osteoporosis medication (HR, 0.83; 95% CI, 0.71-0.95), but not specifically hip fractures (HR, 0.91; 95% CI, 0.74-1.13). The standardized two-year risk of any fracture was 3.77 percent (95% CI, 3.37-4.19%) in VKA-treated patients and 3.09 percent (95% CI, 2.85-3.39%) in DOAC-treated patients. The frequency of the various DOACs included was not provided, and the results were not further stratified into outcomes for specific DOACs.

In the second study, Dr. Pamela Lutsey and colleagues performed a study using data from administrative claims databases in patients with nonvalvular AF from 2010 through 2015. A total of 162,275 new users of oral anticoagulation were included; they had a mean age of 68.9 years and were predominately male (62%). Outcomes defined by International Statistical Classification of Diseases and Related Health Problems-9 (ICD-9) codes were hip fractures (inpatient), fractures requiring hospitalization, and all fractures (inpatient and outpatient). Warfarin was the most common anticoagulant (n=82,625) followed by rivaroxaban (n=35,252), dabigatran (n=31,647), and apixaban (n=17,751). DOACs as a group when compared to VKAs had a lower risk of all fractures (HR, 0.93; 95% CI, 0.88-0.98) and fractures requiring hospitalization (HR, 0.93; 95% CI, 0.87-0.98), but not hip fractures requiring hospitalization (HR, 0.91; 95% CI, 0.78-1.07). When each DOAC was compared to warfarin individually, rivaroxaban and apixaban both had a lower risk for fractures requiring hospitalization and all fractures. Apixaban compared to warfarin was the only DOAC to show a statistically significant reduction for all outcomes including hip fractures requiring hospitalization (HR, 0.87; 95% CI, 0.84-0.90). Dabigatran did not show a statistically significant reduction in risk compared to warfarin; however, there was a trend toward lower risk for fractures requiring hospitalization (HR, 0.88; 95% CI, 0.79-0.98). In a subgroup analysis for dabigatran, there were differences based on patient characteristics. Patients treated with dabigatran did have a significantly decreased risk for hospitalized fractures if they had osteoporosis (HR, 0.74; 95% CI, 0.68-0.90), were women (HR, 0.78; 95% CI, 0.60-0.92), or were younger than 75 years (HR, 0.75; 95% CI, 0.59-0.96). A matched analysis was then performed comparing apixaban to rivaroxaban and apixaban to dabigatran and found no significant differences for any of the fracture outcomes.

These studies with different methodologies using data from different sources both demonstrate a modest reduction in fracture risk with DOACs compared to VKAs for patients with nonvalvular AF. Rather than a positive effect on bone density for DOACs, these data are better interpreted as data demonstrating real clinical implications for VKAs’ interference with bone metabolism. With the additional data from these two large and well controlled studies, clinicians can have more detailed conversations about outcomes other than recurrent thromboembolism and bleeding with patients who may need to remain on oral anticoagulation for decades. For patients who would otherwise be a candidate for a DOAC but remain on VKAs, this information may provide a rationale for them to switch, especially those patients with risk factors or those who already have osteoporosis.


Gut Microbiome Diversity Influences Transplant Risk (Cont. from page 1)

Furthermore, the group then examined pretransplant fecal microbiome diversity in cohort 1 and showed similar results, with better survival outcomes seen in patients with higher microbiome diversity. Compared to healthy controls, the pretransplant microbiome diversity is significantly reduced in both cohorts. This reflects the patient preparation regimen referred for transplantation, as many patients with malignant disorders may have already incurred microbiota damage due to prior chemotherapy or oral intake, mucositis, and significant prior broad-spectrum antibiotic exposure. Lower microbiota diversity was associated with an abundance of pathogenic genera including Enterococcus, Klebsiella, Enterobacter, Staphylococcus, and Streptococcus. This highlights a strong link between lower microbiome diversity, antibiotic exposure, and antibiotic-resistant organism colonization.

Interestingly, the link between GVHD-related mortality and poor microbial diversity was only seen in recipients of T-cell–replete grafts (compared with CD34-selected stem-cell-only grafts, where no donor T cells are infused). This supports the hypothesis that there is an interplay between the gut microbiome and early T-cell–driven alloreactivity (Figure). Previous studies have shown that microbiome diversity may mitigate intestinal inflammation.3

This study raises numerous questions. For example, can microbiome diversity be enhanced either prior to or during transplantation? So far, probiotic-based therapies have failed to improve microbiome diversity,4 and while fecal transplantation has been explored as a treatment for the eradication of multidrug resistance bacteria and recurrent Clostridium difficile colitis, including in immunocompromised patients,5 it is only in its infancy as a pertransplant therapy. Alternatively, a more pragmatic solution may lie in judicious antibiotic selection. Pseudoclostridium/bacteroidum- or metronidazol-based antibiotic regimens seem to have the most profound effect on microbial diversity, and it may be that avoidance of highly selective regimens may relatively preserve microbiome diversity. Altogether, these data provide provocative evidence that low patient microbiome diversity may represent a modifiable risk factor that can be targeted to improve AHSTC outcomes.6


Figure

Higher Microbiome Diversity

Lower Microbiome Diversity


Drs. Grabek and Lane indicated no relevant conflicts of interest.
Using Artificial Intelligence to Enhance Diagnosis: Is Resistance Futile?

Dr. Mohlman and colleagues therefore created a CNN that can identify morphologic features down to the pixel level. To create the CNN, diagnostic hematoxylin and eosin–stained slides of 34 cases of BL and 36 cases of DLBCL were digitally scanned at 200x magnification. Each digitized side was then broken down into multiple JPEG files that were 1,712 × 1,112 pixels in size. This created a training set of 1,033 images of BL and 4,800 images of DLBCL. Parts B and C of the Figure illustrate the CNN input material, individual subcropped images (indicated by the inset black boxes) from larger tissue profiles of BL and DLBCL. While various subcrop sizes and layers of the network were explored, the optimal CNN used 672 × 672 pixels subcrops scaled down to 224 × 224 pixels and had a depth of 82 network layers. In total, 258,327 attributes were used to classify each individual image as either BL or DLBCL (including multiple different morphologic variants) in the training set.

To assess the accuracy of their CNNs, the researchers tested the CNN against a new cohort of nine cases of BL (1,637 total images) and 10 cases of DLBCL (730 total images). Their best-performing algorithm had an accuracy of 87.6 percent for all images and correctly diagnosed 17 of 19 unknown cases overall. Of the 17 correct cases, 10 had 100 percent of images classified correctly, five cases had 76 to 99 percent classified correctly. Complicating factors affected the success of the CNN included varying proportions of non-neoplastic tissue (including parenchymal tissue, fat infiltration, and non-neoplastic infiltrating lymphocytes), crush artifact, and dispersion/noncohesion of the neoplastic cells (such as fixation artifact; Figure part D). These types of samples were underrepresented in the training set, and more replete training might improve the diagnostic precision of AI.

These exciting findings highlight the diagnostic prowess of AI and raise the controversial question of whether it will eventually replace human microscopists. However, this hematologist audience should not worry about the potential loss of their friendly neighborhood pathology consultant. For all pathology AI development, a pathologist’s involvement in the development and testing phases is critical. As the understanding of pathobiology expands, pathologists develop and apply new classification systems that are often more nuanced than their predecessors. This leads to an increased need for expert interpretation and consultation. The role of AI is to augment, not replace, human expertise. While AI can assist pathologists in their daily practice, it cannot replace the critical thinking and clinical judgment that only humans can provide.

Dr. Mohlman and colleagues have illustrated the use of CNNs in the occasionally challenging, but clinically important, distinction between Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL) not otherwise specified.

Two autologous CD19-directed chimeric antigen receptor (CAR) T-cell therapies are now available as a standard of care for lymphoid malignancies in several other countries.

These therapies use the patient’s own polytropic T cells transduced with a CAR, reprogramming them against surface CD19 on malignant B cells. Despite impressive response rates, autologous T-cell therapies have drawbacks including severe toxicities, treatment delays due to capacity limits and an approximately three-week production time, high cost of manufacturing and delivery logistics for each bespoke product, and negative effects of exhausted T cells, typical in cancer patients.

The development of allogeneic CARs is an area of widespread and intense effort as they could potentially overcome some of these limitations. Time to treatment could be shortened by obtaining an off-the-shelf product manufactured in advance. Costs could be reduced by simplified logistics and streamlined manufacturing. Finally, the negative impact of T-cell exhaustion could be bypassed by using immune cells from healthy individuals. To realise this potential, however, it is not relevant with autologous CARs must be overcome. When allogeneic effector cells are adoptively transferred, they may harm the patient by causing graft versus host disease (GVHD), or they may be rejected. One approach to avoid the use of conventional allogeneic T cells is to transduce the CAR along with gene editing machinery to remove the native T-cell receptor that is a primary mediator of GVHD and reduce alloreactivity. An alternative approach, as recently reported by Dr. Eni Lu and colleagues relies on T cells transduced into allogeneic natural killer (NK) cells, which do not contain a T-cell receptor, rather than autologous T cells.

This phase I/II cell dose escalation study tested allogeneic CAR-NK NK cells, derived from previously frozen cord blood, for patients with relapsed or refractory B-cell malignancies. CAR NK cells were administered at a planned dose of 1 x 10^6, 1 x 10^7, or 1 x 10^8 cells per kg of body weight. The CAR construct contained a CD28 and CD3ζ signaling domain, as well as IL-15 expression known to promote NK cell activity, and a rimiducid inducible caspase-9 in case the cancer patients. Despite impressive response rates, despite impressive response rates, five of nine patients received a CAR-NK product that was partially human leukocyte antigen (HLA) matched at four of six HLA loci, while two were HLA mismatched. Six of 11 CAR-NK products were selected due to the presence of a killer immunoglobulin-like receptor (KIR) ligand mismatch, which might potentiate activity of the CAR due to the biology of NK cells’ ability to recognize self.

The treatment was well tolerated without any cases of cytokine release syndrome or neurotoxicity. There were no cases of tumor lysis syndrome and no hematologic grade 3 or 4 toxicities. Remission was not used to activate the caspase-9 safety switch in any patients. At a median follow-up of 13.8 months (range, 2.8-20 months), an objective response was seen in eight (73%) of 11 patients, and a complete response was seen in seven (64%) of 11 patients. Responses were confirmed by day 50 in all responders. Five of eight responders underwent some form of posttransplantation therapy. Expansion of CAR NK cells was seen as soon as three days after infusion, and patients achieving a remission had a higher degree of expansion of their CAR NK cells compared to responders, a phenomenon described in other CAR-T cell trials. The CAR construct was detectable in the blood of patients as long as one year after therapy; however, persistence did not correlate with on-going response or relapse. In stark contrast to autologous CAR T-cell therapy, inflammatory cytokines such as IL-6 were not elevated in the serum following CAR-NK cell therapy compared to baseline. Similarly, IL-15 levels in the serum were not elevated. Tests for anti-HLA antibodies against the mismatched alleles were not found, though testing for cellular mediated rejection was not conducted.

What have we learned from this trial? Despite a small number of treated patients, allogeneic CD19-directed CAR NK cells, derived from cord blood, can induce remissions with relatively few toxicities in relapsed/refractory B-cell malignancies. Although the safety profile seems highly favorable, it remains unclear if allogeneic CAR NK-cell therapy could overcome limitations of existing autologous CAR T-cell therapies. First, the trial did not demonstrate true off-the-shelf capabilities: Manufacturing was done for each product immediately before infusion, and the authors note that NK cells are difficult to cryopreserve. Second, lower cost for the therapy is uncertain given the one to one patient to product manufacturing, and the logistics of both procuring cord blood and shipping fresh product. Finally, although the ability of these cells to induce durable remissions is unknown; only one of eight patients with relapse or refractory T-ALL with current therapy.

Conclusion
In summary, immunotherapy is a much-needed option for patients with resistant or relapsed T-ALL. The patient in the case report had few treatment options, especially given the initial use of nelarabine. She received mitoxantrone and cytarabine as salvage chemotherapy and did achieve a second remission. She is now more than 100 days post-HCT and remains in remission. Her case is atypical, however, as most patients do not respond to salvage chemotherapy. The adult cooperative cancer groups, together with the Children’s Oncology Group, are working currently on the next series of clinical trials for T-ALL, some of which plan to incorporate daratumumab. CAR-T trials in progress may provide further progress toward an effective treatment for the significant fraction of children and adults who have relapsed or refractory T-ALL with current therapy.


Dr. O'Dwyer indicated no relevant conflicts of interest.
FEBRUARY 27, 2020

In a study reported in this Plenary Paper, Dr. Olli Duva and colleagues used functional drug and CRISPR screens to uncover new biology about modulation of responses to chimeric antigen receptor (CAR) T-cell therapy. Their findings suggest that anti-CD19 CAR T-cell therapy can be enhanced through use of small molecules that target death receptor signaling.

MARCH 12, 2020

In this Plenary Paper, Dr. Courtney DiNardo and colleagues describe the molecular correlates of acute myeloid leukemia (AML) response and resistance to venetoclax in combination with hypomethylating agents or low-dose cytosine arabinoside. They identify specific response-modifier driver mutations that may be clinically applied to stratify patients in future trials or to inform selection of regimens in current practice.


Dr. Pengpeng Liu and colleagues report exciting preliminary clinical data on the potentially curative role of immune checkpoint inhibition for the treatment of Epstein-Barr virus–associated hematopoietic lymphohistiocytosis.

MARCH 19, 2020

Chronic granulomatous disease (CGD), caused by inactivating mutations in the NADPH oxidase (NADPH) oxidase complex, is characterized by poor antimicrobial control and hyperinflammation. In a study reported in this Plenary Paper, Dr. Zhimin Song and colleagues elucidate the pathophysiology of aberrant inflammation in CGD, demonstrating that loss of oxidative activity leads to excessive neutrophil activation through upregulation of the inflammatory protein leukotriene B4.
Bringing Immunotherapy to the Front Line in Childhood Leukemia

Editor’s Note: Normally in Clinical Trials Corner, Contributing Editors are asked to summarize a single study. Here, Drs. Teachey and Si have reviewed three large studies that are moving immunotherapy into the treatment of children with acute lymphoblastic leukemia (ALL). While childhood ALL is often called out as the poster child for multiagent chemotherapy, there is still significant room for improvement in outcomes, and each of these trials has design elements that capitalize on what has been learned about prognostic markers at time of diagnosis and during the course of treatment.

STUDY TITLE: A Study to Investigate Blinatumomab in Combination With Chemotherapy in Patients With Newly Diagnosed B-Lymphoblastic Leukemia (AALL1731)

PARTICIPATING CENTERS: Children’s Oncology Group (COG) Institutions (anticipated to open at more than 220 centers in the United States, Canada, Australia, and New Zealand)

ACCRUAL GOAL: 6,720 patients

STUDY DESIGN: Currently, COG stratifies patients with B-cell acute lymphoblastic leukemia (B-ALL) into risk groups based on anticipated event-free survival (EFS); (Table 1). These risk groups are derived from parameters including age, white blood cell (WBC) count at diagnosis, presence or absence of extramedullary disease, disease response, and leukemic blast biology. AALL1731 is a phase III clinical trial that investigates the use of blinatumomab in combination with chemotherapy in patients with newly diagnosed standard risk (SR) or Down syndrome (DS) B-cell ALL. Blinatumomab is a bispecific single-chain antibody that targets CD19. Although the five-year overall survival (OS) rate for most patients with National Cancer Institute (NCI) SR B-ALL is greater than 90 percent, based on the relative number of these patients, they still account for approximately half of the overall relapsed population in childhood B-ALL. Patients with SR-average and SR-high disease (see Table 1 for definitions) will be randomized to standard chemotherapy or standard chemotherapy plus two cycles of blinatumomab. The rationale for use of blinatumomab in the SR population is based on the excellent outcomes seen in relapsed/refractory (r/r) B-ALL and the low toxicity profile. Data presented at the 2019 ASH Annual Meeting demonstrated that a subset of children with first relapse B-ALL treated on the AALL1331 trial exhibited superiority and tolerability of blinatumomab compared to intensive chemotherapy prior to stem cell transplantation (SCT). The most common severe toxicities seen with blinatumomab are cytokine release syndrome (CRS) and neurotoxicity. Risk of CRS and neurotoxicity correlate with disease burden, and blinatumomab is only given to patients with low disease burden on AALL1731. The inclusion of patients with DS is based on inferior survival compared to non-DS patients from both increased treatment-related mortality and higher rate of relapse. Patients with DS and without consolidation failure, defined as end of consolidation (EOC) minimal residual disease (MRD) less than 1 percent, will receive three blocks of blinatumomab to replace selected cytotoxic chemotherapy to preserve antileukemia efficacy while reducing toxicity. Finally, AALL1731 will confirm if all patients can be treated with a uniform duration of therapy regardless of sex. This is the standard practice in many cooperative groups, whereas the COG has historically treated male patients with an extra year of therapy.

STUDY TITLE: Inotuzumab Ozogamicin and Post-Induction Chemotherapy in Treating Patients With High-Risk B-ALL, Mixed Phenotype Acute Leukemia, and B-LLy (AALL1732)

PARTICIPATING CENTERS: COG Institutions (anticipated to open at more than 220 centers in the United States, Canada, Australia, and New Zealand)

ACCRUAL GOAL: 3,689 patients

STUDY DESIGN: CD22 is highly expressed in most cases of childhood B-ALL, making it an attractive target for therapeutic strategies. AALL1732 is a phase III randomized trial of inotuzumab ozogamicin (InO) for newly diagnosed patients with high-risk (HR) B-ALL. This trial will stratify NCI HR B-ALL patients into two risk groups (Table 1). Patients with NCI HR B-ALL who do not meet the HR-favorable definition and who have EOC MRD less than 0.01 percent will be randomized to receive or not receive two cycles of InO, an antibody drug conjugate composed of a humanized IgG monoclonal CD22-targeted antibody linked to calicheamicin. The trial’s primary endpoint is to determine if adding InO improves five-year disease-free survival (DFS). Patients with Ph-like ALL can remain on study or they may pursue alternative therapy but then would need to be removed from protocol therapy. Rationale for the use of InO in frontline therapy in patients with HR B-ALL is based on several adult clinical trials that have demonstrated impressive results in r/r B-ALL. AALL1621 is an ongoing phase II trial that prospectively evaluates InO’s toxicity profile and efficacy as a single-agent therapy in pediatric patients with r/r B-ALL. Data presented at the 2019 ASH Annual Meeting demonstrated complete remission (CR)/CR with incomplete hematologic recovery (CRI) rate of 58 percent, and 65.4 percent of responders achieved MRD less than 0.01 percent. More severe toxicities, including hepatotoxicity and sinusoidal obstructive syndrome (SOS), are seen with InO as compared with blinatumomab, which is part of the rationale to use this novel immunotherapy in a higher risk population with inferior EFS. AALL1732 will include nonrandomized interventions to investigate survival in B-ALL and mixed-phenotype acute leukemia when treated with standard therapy. Finally, AALL1732 will also confirm if all patients can be treated with a uniform duration of therapy regardless of sex.

STUDY TITLE: Study of Efficacy and Safety of Tisagenlecleucel in HR B-ALL EOC MRD Positive Patients (AALL1712, CASSIOPEIA)

PARTICIPATING CENTERS: Anticipated to open in more than 50 centers in North America and Europe

ACCRUAL GOAL: 140 patients

STUDY DESIGN: CASSIOPEIA is a phase II, single-arm, open-label, multicenter trial whose purpose is to evaluate the efficacy and safety of tisagenlecleucel in pediatric and young adult patients (aged 1-25 years) with de novo HR B-ALL in first CR (Cri) who have EOC MRD 0.01 percent or higher. Tisagenlecleucel is a second-generation chimeric antigen receptor modified T cell, where autologous peripheral blood T cells have been genetically modified ex vivo to target CD19 on the surface of B-cells. The U.S. Food and Drug Administration (FDA) approval of tisagenlecleucel was based on results from the ELLIANA trial that demonstrated OS of 96 percent at six months, and 79 percent at 12 months in children and young adults with r/r B-ALL. Investigators in the AALL1712 trial hypothesize that use of tisagenlecleucel not only offers the possibility of eliminating residual disease, but also could serve as definitive therapy without the need for consolidation with allogeneic SCT (aSCT). Patients who are not in remission are not eligible. Thus, tisagenlecleucel could also offer a better safety profile than seen in other trials similar to blinatumomab high-tumor burden is associated with higher risk of severe CRS and neurotoxicity. Patients will be offered a second infusion of tisagenlecleucel if they have evidence of B-cell recovery less than six months after initial infusion or have re-emergence of MRD positivity without

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<th>Table. AALL1731 and AALL1732 Postinduction Risk Groups</th>
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<td><strong>Risk Group</strong></td>
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<td>5-yr EFS</td>
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Adapted from a table provided by Rachel Rau, MD. Abbreviations: DT, double trisomies of 4 and 10; EOC, end of consolidation; EOI, end of induction; HR, high risk; HR-Fav, high risk favorable; MRD, minimal residual disease; PB, peripheral blood; SR, standard risk; SR-Avg, standard risk average; SR-Fav, standard risk favorable; VHR, very high risk.
malignancy, and multiagent chemotherapy has led to dramatic improvements in OS, many patients continue to relapse and have poor survival.6 Many of the improvements in survival within the past 50 years have been through intensification of cytotoxic chemotherapy regimens; however, we have reached a point where further intensification of conventional chemotherapies has proven too toxic, and any improvement in disease control is mitigated by treatment-related mortality. An attractive alternative mechanism to attempt to improve cures is the incorporation of immunotherapies. Multiple immunotherapies have demonstrated impressive efficacy in heavily pretreated populations and may offer the benefit of higher cure rates without excessive toxicity. The encouraging results in patients with r/r B-ALL serve as the basis for the investigation of three different immunotherapies in de novo patients with B-ALL. Future trials may take this approach further by eliminating more cytotoxic agents and combining immunotherapies in order to target multiple surface antigens and avoid relapse from antigen loss. There is still work to be done, as the development of effective immunotherapies that can be moved into the front line for T-cell ALL, infant ALL, and acute leukemia of ambiguous lineage are needed. Early-phase trials that include these populations are ongoing, and hopefully in the next few years we will see the paradigm shift for patients with these forms of leukemia.

Adjusting How We Diagnose Deep Vein Thrombosis

**STUDY TITLE**: Age-adjusted D-dimer Cutoff Levels to Rule Out Deep Vein Thrombosis: A Prospective Outcome Study (ADJUST-DVT)

**CLINICALTRIALS.GOV IDENTIFIER**: NCT02384135

**SPONSOR**: University Hospital, Geneva

**ACCRUAL GOAL**: 3,900 participants

**PARTICIPATING CENTERS**: Multiple sites in Canada, France, and Switzerland

**STUDY DESIGN**: This is a prospective cohort management study examining the utility of an age-adjusted D-dimer cutoff in combination with clinical pretest probability for the diagnosis of deep vein thrombosis (DVT). The age-adjusted cutoff is defined as “negative” as follows: if patient’s age is less than 50 years, D-dimer is less than 500 µg/L; if patient’s age is greater than 50 years old, D-dimer less than 500 µg/L divided by patient’s age multiplied by 10. This contrasts with prior DVT diagnostic studies that used a fixed cutoff of 500 µg/L. This study compares the five-year DFS after tisagenlecleucel infusion in de novo patients with B-ALL. Hopefully in the next few years we will see the paradigm shift for patients with these forms of leukemia.

**COMMENT**: Given the established relationship (and often coexistence) between DVT and PE along with the expected age-related increase in baseline D-dimer, this study is a natural next step from the aforementioned ADJUST-PE study.

**RATIONAL**: D-dimer results have previously been extensively validated for the exclusion of DVT, particularly in combination with clinical prediction rules. The cutoff value for categorizing D-dimer results as negative has generally been set at a fixed, low level of 500 µg/L to achieve higher sensitivity and negative predictive value. However, D-dimer results are not specific to VTE and are known to increase with age, which may limit their specificity in older patients. In this study, the authors have implemented a management algorithm that is expected to validate the specificity and safety of using an age-adjusted D-dimer cutoff in combination with the dichotomized Wells DVT score. A similar management algorithm was validated in the ADJUST-PE study for the diagnosis of PE using age-adjusted D-dimer and two-level clinical probability (Wells or revised Geneva score) and was found to increase the proportion of patients with suspected PE who could safely be excluded on the basis of negative chest imaging (64.2-29.7%). Furthermore, a recent individual patient-data meta-analysis suggested that approaches using graduated D-dimer cutoffs adjusted to age or differing clinical pretest probability for DVT, instead of a fixed cutoff for all non-high-probability patients, demonstrated good specificity and negative predictive value.3

HR and VHR cutoff levels to rule out pulmonary embolism: The ADJUST-PE study. JAMA. 2014;311(17):1736-1745.

**OUTCOMES**: As part of the study, the authors evaluated the age-adjusted D-dimer cutoff levels associated with the diagnosis of deep vein thrombosis (DVT) and pulmonary embolism (PE). The study included 3,900 patients from multiple sites in Canada, France, and Switzerland. The primary outcome was the five-year DFS after tisagenlecleucel infusion in de novo patients with B-ALL.

**METHODS**: This is a prospective cohort management study examining the utility of an age-adjusted D-dimer cutoff in combination with clinical pretest probability for the diagnosis of deep vein thrombosis (DVT). The age-adjusted cutoff is defined as “negative” as follows: if patient’s age is less than 50 years, D-dimer is less than 500 µg/L; if patient’s age is greater than 50 years old, D-dimer less than 500 µg/L divided by patient’s age multiplied by 10. This study compares the five-year DFS after tisagenlecleucel infusion in de novo patients with B-ALL. Hopefully in the next few years we will see the paradigm shift for patients with these forms of leukemia.

**RESULTS**: This study is a natural next step from the aforementioned ADJUST-PE study. The study included 3,900 patients from multiple sites in Canada, France, and Switzerland. The primary outcome was the five-year DFS after tisagenlecleucel infusion in de novo patients with B-ALL. Hopefully in the next few years we will see the paradigm shift for patients with these forms of leukemia.

**DISCUSSION**: As part of the study, the authors evaluated the age-adjusted D-dimer cutoff levels associated with the diagnosis of deep vein thrombosis (DVT) and pulmonary embolism (PE). The study included 3,900 patients from multiple sites in Canada, France, and Switzerland. The primary outcome was the five-year DFS after tisagenlecleucel infusion in de novo patients with B-ALL. Hopefully in the next few years we will see the paradigm shift for patients with these forms of leukemia.

**CONCLUSION**: As part of the study, the authors evaluated the age-adjusted D-dimer cutoff levels associated with the diagnosis of deep vein thrombosis (DVT) and pulmonary embolism (PE). The study included 3,900 patients from multiple sites in Canada, France, and Switzerland. The primary outcome was the five-year DFS after tisagenlecleucel infusion in de novo patients with B-ALL. Hopefully in the next few years we will see the paradigm shift for patients with these forms of leukemia.

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Intramedullary Hemolysis in Myelodysplastic Syndromes

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A 68-year-old man with Gilbert’s syndrome was referred for evaluation of fatigue and pancytopenia. Examination revealed scleral icterus. Automated blood counts reported a white blood cell count of 1.8 × 10^9/L; hemoglobin, 10.4 g/dL; mean cell volume, 99 fL; platelet count, 59 × 10^9/L; nucleated red blood cells (NRBCs), 11 percent; reticulocytes, 10 percent; and absolute reticulocyte count, 342 × 10^9/L (by flow cytometry; Sysmex XN hematology analyzer). Additional laboratory results showed total bilirubin at 7 mg/dL; direct bilirubin, 0.39 mg/dL; and haptoglobin undetectable, with a negative direct antiglobulin test for IgG (including low affinity IgG), C3, IgM, and IgA. No iron, vitamin B12, copper, paroxysmal nocturnal hemoglobinuria clone or G6PD deficiency was detected. Peripheral blood (PB) smear is shown in the Figure (part A; 40×). Bone marrow evaluation demonstrated 95 percent cellularity, erythroid hyperplasia, trilineage dysplasia, and no increase in blasts or abnormal karyotype. A myeloid somatic mutation next-generation sequencing panel showed no mutations.

What is the most likely cause of the patient’s macrocytic anemia?

A. Direct antiglobulin (Coombs) test–negative autoimmune hemolytic anemia  
B. Hypersplenism due to Gilbert’s syndrome  
C. Intramedullary hemolysis from myelodysplastic syndrome  
D. Microangiopathic hemolytic anemia

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

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