Convalescent Plasma for COVID-19: An Old Therapy for a Novel Pathogen

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The concept of passive immunization, including use of convalescent plasma (CP) to treat an infectious disease, originated more than 100 years ago. In 1890, physiologists from Germany treated patients with diphtheria, initially, with sera from immunized animals, and subsequently, with sera or whole blood from recovered patients. Until the development of antimicrobials in the 1940s, the use of passive immunization became one of the mainstays of therapy for infectious disease. Numerous reports during the Spanish flu pandemic of 1918 to 1920 demonstrated efficacy of CP in cases of that highly lethal viral infection. A meta-analysis of 1,703 patients with Spanish Flu treated with CP in eight different studies, suggested markedly reduced mortality. Since then, CP has been used for dozens of infectious diseases, including varicella, measles, and Ebola, with largely anecdotal studies suggesting some benefit.

Recently, multiple outbreaks of different coronaviruses with high mortality rates, including SARS-CoV-1 in 2003, MERS in 2012, and SARS-CoV-2 in the present day, have renewed interest in passive immunization with CP. Use of CP was trialed in MERS and more recently, with sera or whole blood from infected humans, and subsequently, with sera or whole blood from recovered patients. This nonrandomized series of cases found that patients treated before day 14 were more likely to be discharged from the hospital compared to those treated after day 14.

Back in February, when the first cases of COVID-19 were detected in China and we were worried that Chinese New Year celebrations might fuel the spread of this dreaded disease in our community, there were persistent questions around what would be in store for our service. There were scarce publications, but through our hematology lens, we saw that COVID-19 was associated with lymphopenia and mild thrombocytopenia, and disseminated intravascular coagulation occurred in end-stage disease in some patients. None of these signals seemed unusual with severe viral pneumonia, which can result in severe acute respiratory distress syndrome in some patients and trigger an overwhelming inflammatory response and cytokine storm. We’ve seen all that before in some hematologic diseases. So, we asked our intensive care unit (ICU) colleagues not to measure ferritin because it could generate unnecessary concerns for hemophagocytic lymphohistiocytosis. We thought our work was done.

Then, as the wave of infection spread to Europe, North America, and most of the world, medical literature started trickling out from China that suggested a different story. Retrospective studies highlighted that many patients had very high levels of D-dimer and fibrinogen. However, these appeared to occur with only moderate thrombocytopenia and near-normal prothrombin time, partial thromboplastin time, fibrinogen levels, and D-dimer levels. We anxiously awaited more data while the death toll climbed in Italy and other parts of Europe.

As the pandemic grew, reports of hypercoagulopathy emerged. Colleagues from China observed an alarming association between high D-dimer levels and disease severity, need for critical care support, and all-cause mortality. One study showed that in 191 patients, D-dimer greater than 1.0 μg/mL on admission was associated with in-hospital death (odds ratio, 18.4; 95% CI 2.6-128.6). Another found that among 311 patients who had a D-dimer level greater than 3.0 μg/mL (sixfold higher than the upper limit of normal), better survival was observed in those selected to receive anticoagulant prophylaxis (mainly with low-molecular-weight heparin). These studies did not report the incidence of thrombotic events, and routine thromboprophylaxis is not standard in China because of the baseline relatively low risk of venous thromboembolism (VTE). They also did not account for any differences in clinical characteristics, underlying comorbidities, or treatments that could have influenced the risk of death. It was this realization that D-dimer elevation is nonspecific for thrombosis, and very high levels are commonly found in other disease states (e.g., sepsis, cancer) and even healthy physiological conditions (e.g., second and third trimester of pregnancy). Conversely, elevated D-dimer has been associated with an increased risk of thrombosis and poor overall survival in cancer patients. Moreover, hypercoagulability resulting in an 18-fold risk of VTE has been previously described in critically ill patients with H1N1 acute respiratory distress syndrome. Is critical illness driving the risk for thrombosis, or is thrombosis causing the multisystem organ failure seen in COVID-19? We anxiously awaited more data while the death toll climbed in Italy and other parts of Europe. We wondered if high rates of thrombosis would be observed with routine thromboprophylaxis. The first publications from the Netherlands, France, and Italy all reported a high incidence of venous and possibly arterial thrombosis, despite standard thromboprophylaxis. These largely retrospective analyses estimated incidence rates ranging from 16.7 to 27.6 percent in critically care patients, and approximately 6.5 percent in medical ward patients. Unfortunately, all of these studies had very short-term follow-up, some used screening ultrasonography, and some included suspected....
President’s Column

The New Normal

Patients treated for cancer often talk about the “new normal,” or how life changes after a life-altering diagnosis. As I write this, it’s been two and a half months since the COVID-19 experience started in the United States and four and a half months for China. I’ve passed through disbelief, hyperalertness, and anxiety, and am now in a state of resignation about the “new normal.” I thought now might be a good time to consider some of my hopes and fears about a post–COVID-19 new normal for the hematology field. Fears first...

Trainees and academic junior faculty in 2020 face severe headwinds. For these groups, COVID-19 came at the worst possible time. Trainees have lost clinical training opportunities and their laboratory time has been severely curtailed. Graduating trainees face hiring freezes. For junior faculty, many institutions have automatically added a year onto promotion calendars, which is good for the extra time, but bad because it reflects how universal the loss of productivity and momentum has been. ASH remains committed to providing the same or greater support for career development and urges institutions, foundations, and government to do the same.

Non–COVID-19 research funding will suffer. As attention and resources have shifted so dramatically to COVID-19, research not related to the disease may be neglected for the next few years. Yes, the novel coronavirus must be controlled, but the burden of all the other human diseases remains, and setbacks to research momentum and funding for those other diseases is collateral damage that will have long-lasting repercussions. Philanthropic foundations that fund a significant percentage of hematology research and training may no longer have the resources to do so as the economic catastrophe decreases charitable contributions. Many such not-for-profits focus on research of rare diseases like those faced by our patients.

Public and clinical trial standards for COVID-19 research must improve. Many have noticed lower acceptance thresholds for any paper or project with the “coronavirus” or “COVID-19” key words. I believe this was justifiable early in the pandemic, but I trust that we will be returning to stricter standards for COVID-19 research reporting. Clinicaltrials.gov lists more than 1,800 clinical studies in the pipeline, many involving single centers, small numbers of participants, and duplicative questions. These studies represent great effort, possibly channeled from non–COVID-19 research, and I fear that many will not yield the desired information.

Here are my hopes for the new normal:

Clinical research should improve based on what we’ve learned. We now know it is possible for protocol development, institutional review board approval, contracting, and study startup to be lightning quick when necessary. We also have shown that most items on trials’ schedules of events aren’t really needed for patient safety, and that telemedicine can substitute for some of this information. We have shown that much of our reliance on face-to-face meetings can be transferred to clinical research more generally? It took decades to arrive at our current bloated and defensive documentation. How did we get to rigidity without rationale and how can we keep from going back?

Telemedicine is here to stay, and it’s a great option in many circumstances. It’s convenient for both patients and providers, and much can be accomplished despite the lack of vital signs and physical exams. Used appropriately, telemedicine could make our health care system much more efficient and equitable. Videoconferencing can replace some in-person meetings. Many of us traveled far too often pre–COVID-19 and have enjoyed the reprieve afforded by the travel ban. Videoconferencing works pretty well when everyone is virtual but may not be as pleasant when some participants are in-person. Also, I miss those side conversations and hanging out with my colleagues between meeting responsibilities. In the new normal, I’ll probably travel less, reserving it for times when being there in person is really important.

COVID-19 helped me understand how my patients feel. My specialty is allogeneic hematopoietic cell transplantation, so my patients are used to worrying about environmental cleanliness, catching a life-threatening infection from someone else, and any signs of infection. COVID-19 has helped me understand a little better what they live with every day.

The COVID-19 crisis has caused so many deaths and disrupted every aspect of life, but it has also revealed many ways that things can be done better, including in hematology. As we rebuild, I hope we can preserve the best innovations that were implemented, so at least some good can emerge from this tragedy.

Stephanie J. Lee, MD, MPH

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Dr. Michaelis has no relevant conflicts of interest to disclose.

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ASH Releases the COVID-19 Research Agenda in Hematology

Many new clinical questions are emerging daily from the COVID-19 pandemic. As the infections continue, the development of novel severe hematopoietic complications has changed the perception of COVID-19 as a pulmonary disease, into a blood disease as well. In response to these health issues, the “COVID-19 Research Agenda in Hematology” was developed. This document explores the key underlying research questions that, to date, lack scientific evidence to inform clinical practice and treatment efforts. The Society believes that answers to these research questions are of utmost importance to better comprehend the underlying biology of COVID-19, to recognize the interaction of the virus with underlying hematologic conditions, and to inform clinical options to save lives. With the emergence of a deeper understanding of COVID-19 and the hematologic implications of this infection, new questions will arise. We welcome feedback and additional suggestions. View the COVID-19 Research Agenda at www.hematology.org/research/agenda/ash-covid-19-research-agenda-for-hematology.

Access Recording of Webinar on Use of Convalescent Plasma During COVID-19

The use of convalescent plasma (CP) collected from previously infected individuals to protect or treat humans dates back almost 100 years. Today, CP could provide short- to medium-term humoral immunity against COVID-19; however, the use of CP is an interim approach while vaccines and effective drug therapies are being developed. Learn about the collection of, regulation of, and treatment with CP in this webinar (https://buff.ly/2IWWTDDU), which was moderated by Chair of ASH’s Committee on Practice, Dr. Chancellor Donald and featured Drs. Peter Marks (U.S. Food and Drug Administration), Beth Shaz (AABB), and Evan Bloch (Johns Hopkins).

Submit Your Abstract to the 2020 ASH Annual Meeting

Abstract submission for the 2020 ASH Annual Meeting is now open. Abstracts accepted for or presented as part of any meeting regardless of size (in-person or virtual) since January 1, 2020, are eligible for submission, provided they meet the eligibility criteria (visit www.hematology.org/meetings/annual-meeting/2020-call-for-abstracts for more details). All abstract submissions must be made electronically through ASH’s online abstract submission system. The deadline to submit an abstract is Tuesday, August 4, 2020, 11:59 p.m. (PDT).

Mark your calendar for other key dates: Members-only registration and housing begins July 21, 11:00 a.m. Eastern time. Learn more at www.hematology.org/meetings/annual-meeting.

Get Ready for the 2020 ASH Meeting on Hematologic Malignancies: A Virtual Experience

During this global pandemic, ASH is focused on the wellbeing of the hematology community while providing important education to hematologists around the world. Accordingly, the Society has decided to transition the ASH Meeting on Hematologic Malignancies to a virtual experience. The program, combining both live and on-demand sessions, provides an opportunity for attendees to be part of a unique ASH experience featuring leading experts, comprehensive clinical content, and opportunities for engagement. Features of the ASH Meeting on Hematologic Malignancies: A Virtual Experience include:

• On-demand sessions released between August 27 and September 10 (visit the website for schedule updates)
• Live sessions discussing the impact of COVID-19 on hematologic malignancies
• The “How I Treat” presentation format — a vital, ongoing part of the meeting
• Viewable content available to registered participants, even after the meeting concludes.

Similar to previous years, the Society will also offer the ASH Consultative Hematology Course in conjunction with the ASH Meeting on Hematologic Malignancies (special combination registration pricing will be available) as a virtual experience.

Registration is now open. Visit www.hematology.org/meetings/hematologic-malignancies for more information and to sign up for email updates.

Weekly COVID-19 Podcast Series From The Hematologist

Twelve podcasts in the special The Hematologist COVID-19 podcast series are available via SoundCloud and iTunes. The series explores the intersection between hematology and COVID-19 through conversations with health care professionals currently on the front lines of this public health crisis and has covered an extensive series of topics. Guests discuss the use of social media for information dissemination; post-traumatic stress disorder in health care professionals treating patients with COVID-19; convalescent serum studies; hematologists working outside their field of expertise and using their hematologic knowledge to treat patents with the novel coronavirus; unique issues facing patients with sickle cell disease during the pandemic; managing the blood supply; the ASH Research Collaborative’s COVID-19 Registry for Hematology; controversies surrounding anticoagulation in patients with COVID-19; challenges experienced by clinical trialists dealing with COVID-19; and promoting wellness for physicians who have experienced a complete change in how they practice. More podcasts are planned. Visit www.soundcloud.com/ash_hematology/sets/covid-19-updates to listen.
MINI REVIEW

The Challenge We Face: Sickle Cell Disease and the COVID-19 Pandemic

Ahmar U. Zaidi, MD, and Caterina P. Minniti, MD

The American writer, James Baldwin, wrote, “not everything that is faced can be changed, but nothing can be changed until it is faced.” This idea particularly reverberates for patients and physicians who stand at the intersection of COVID-19 and sickle cell disease (SCD). As a community burdened by the impact of COVID-19, the reorganization of patients with SCD who may become infected was challenging to forecast. SCD is a hereditary hematologic condition punctuated by episodes of acute exacerbation, progressive vasculopathy, end organ damage, and shortened life span. It has often led to stigmatization of these patients in the United States as well as difficulty accessing quality care.1

In light of this, numerous questions emerge: How would the current pandemic further challenge the biopsychosocial battle that each COVID-19–infected patient would inevitably face? How would an already fractured medical system, barely able to provide quality and equality in the care these patients, respond? How would the presence of SCD exacerbate patients’ social support system and medical care team. COVID-19 has an unquestionable ability to devastate this fragile balance by disrupting the social support and overwhelming medical care. Social distancing amidst a pandemic has resulted in the crumbling of social support systems that require proximity to loved ones. This lack of social support has driven deep divides into the landscape of these patients’ well-being. Moreover, the re-deploying of nurses, social workers, and physicians, both by hospital administrators and infection have incapacitated the health delivery system. The already meager resources available to them. SCD centers across the country, already stretched dangerously thin, are experiencing new challenges in their ability to care for individuals with medically complex SCD.

Necessity drove innovation in the SCD provider community, and hordes of dedicated and committed individuals proactively sprung into action. As the wave of COVID-19 hit the SCD population, the commendable, combined efforts of ASH (www.hematology.org/covid-19/covid-19-and-sickle-cell-disease), the Sickle Cell Disease Association of America (SCDAA), and many others around the globe, ensured that the SCD provider community was well-equipped to manage the pandemic and well-positioned to study its effects despite limited resources. The Medical and Research Advisory Committee of the SCDAA, led by Drs. Breen Andemariam and Lewis Hsu, collated opinions on the management of COVID-19 from SCD experts around the world (www.sicklecelldisease.org), and Dr. Julie Panepeinto created Secure-SCD, an SCD–COVID-19 registry (www.sickledisease.org) with an urgency worthy of the devastating pandemic at hand. Physicians began to engage in immediate exchanges of information and discussion of challenging SCD and COVID-19 cases through an email forum created days before the first wave of sick patients hit our shores.2,3

Thanks to these efforts, people with SCD, especially those already connected to the health care system, have been able to receive lifesaving information and education about COVID-19, participate in webinars that address the medical and social impact of COVID-19 and the resultant isolation, and get help navigating the complex and often discordant recommendations that we are bombarded with by the media and different health care organizations. An early adoption of telehealth by many institutions, including ours, has led to the management of complications at home and a substantial decrease in emergency department visits and hospital admissions. Furthermore, existing research infrastructure has been repurposed to support clinical care and education, both in the United States and abroad. A query of Secure-SCD, as of April 25, 2020, indicates a 10 percent mortality rate among 105 patients with SCD and COVID-19. Some of these deaths occurred in individuals who previously had a mild disease course. Thankfully, the much-anticipated shortage of blood has not occurred yet, and we have been able to continue providing evidence-based care to our patients.

Despite the massive scale of infection and mortality impact of COVID-19, the pathophysiology of organ damage remains elusive and a double-edged sword — the risk of thrombosis must be based on laboratory parameters and their local

but unconfirmed pulmonary embolism (imaging not feasible due to isolation). It is also challenging to interpret the data when centers have different criteria for hospital and ICU admission, when to perform imaging, thromboprophylaxis strategies, and other therapies (eg, hydroxychloroquine, anti-IL-6 medications, anti-complement therapies, and antivirals). Patients across studies may not have comparable comorbidities and severity of illness (and hence overall risk for thrombosis). Some clinicians at hospitals that have faced a tsunami of COVID-19 admissions have escalated thromboprophylaxis up to full therapeutic intensity based on laboratory parameters and their local experience. Excessive clotting of arterial and venous catheters, extravascular filters, and circuits also seem to be problematic. However, could the observation of excessive clotting events be due to clinicians being faced with an overwhelming number of patients? Or perhaps the thrombosis risk is, in fact, similar to that of other high-risk groups that are less prevalent? In a prospective study of 113 consecutive patients in the ICU with severe sepsis and septic shock, with all patients receiving i.v. antifibrinolytic therapy, the incidence of VTE was 37.2 percent (95% CI, 28.3-46.0).10 Science is still lagging behind in confirming the VTE observations in COVID-19, establishing risks of VTE in the spectrum of disease from mild to critical, and determining if these rates are higher than in other types of severe infection.10,11

Adding fuel to the fire, the news media has reported a higher incidence of stroke in young patients who have no underlying risk factors,12 and the possibility of antiphospholipid antibody syndrome (APS) in COVID-19 has been raised as a contributing factor to the hypercoagulability observed in these patients.13 It is worrisome that perhaps fear is feeding fiction. More robust evidence is desperately needed to help us provide evidence-based care to our patients.

The COVID Coagulopathy Conundrum

(Cont. from page 12)

Dr. Zaidi and Dr. Minniti indicated no relevant conflicts of interest.

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(Crit. from page 1)

with untreated patients or those treated later in the disease course.9 While such studies suggest a potential benefit for use of CP, the actual efficacy is difficult to assess due to lack of control groups, use of other therapies, and other confounders and biases. Nonetheless, meta-analyses of these case series did not reveal adverse effects.17

Studies Using CP in COVID-19

There have been six reports thus far on the use of CP for patients with COVID-19.14-18 These reports all included small numbers of patients, and approaches that were not uniform, making it difficult to compare results.

Potential Risks

Use of CP carries several potential risks beyond those associated with the transfusion of human blood products (e.g., infection with blood borne pathogens, allergic reactions, increase the entry of virus into cells expressing Fc receptors, and super-antigen mediated dissolution of lymphocytes).1}


Myel-Iennial Dilemma: What Are the Optimal Endpoints for Multiple Myeloma Clinical Trials?

About two years ago, our institution’s multiple myeloma (MM) group was discussing evidence-based maintenance regimens for high-risk MM. While the doublet regimen with a proteasome inhibitor and immunomodulator is appealing to us, the data are primarily from nonrandomized, single-center experiences, and results from randomized trials are not yet available to support our claim. As we debated, the following became very clear: By the time we get results from a randomized trial, those results are already clinically irrelevant. 1

How do we better design our trials to answer the key clinical questions, and how do we pick our clinical trial endpoints?

Challenging the Standard of Care

We have witnessed a rapid transition of several MM drugs from bench to bedside within the past decade. The pace of development is often faster than the pace of our clinical trial development, deployment, and analysis. The SWOG-0777 trial is an example of the challenging standard of care dilemma — a well-intentioned trial that began in 2007, designed to compare a three-drug induction to a two-drug induction. Unfortunately, the final results were published years after the three-drug regimens had already been adapted as standard of care by the National Comprehensive Cancer Network guidelines and after three-drug regimens had crept into common clinical usage. The same is true for phase III trials in the relapsed MM setting. This vicious circle will continue to hound investigators unless we break away from traditional study designs, especially with the new chimeric T- or natural killer–cell therapies, antibody-drug conjugates, and bispecific antibodies.

Picking Surrogate Endpoints for Future Trials: Pros

A wealth of MM literature demonstrates that depth of response (i.e., complete response [CR]) correlates with improved median progression-free survival or overall survival (FFSOS). 1 The postulated improvement of FFSOS led clinicians to quote regimens by their depth of response. 1 However, response kinetics are also important. Patients who achieved rapid response (< 3 months) and lost it early (< 24 months) have the worst outcomes. 2

The International Myeloma Working Group (IMWG) recognizes CR plus negative minimal residual disease (MRD; by flow or next-generation sequencing at 10^-3) as the deepest measurable response. Clinical trials already linked the achievement of MRD negativity with improved survival in newly diagnosed MM. 3 The group also defines sustained MRD as two MRD assessments deemed negative a year apart. This is an important concept to negate the risk of succumbing to an off-color surrogate endpoint. Sustained MRD negativity can be the right primary endpoint for treatment de-escalation questions in clinical trials for newly diagnosed MM, as well as smoldering MM.

Picking Surrogate Endpoints for Future Trials: Cons

Surrogate endpoints could be met and yet miss late-effects toxicity or death. Finally, all those clinical endpoints, whether they focus on survival or on quality of life, still miss the important concept of the “financial cost of survival.” 10

Conclusion

Investigators should not capitulate to the current ever-changing landscape when instead, we could subdue the dilemma of rapid synchronous drug development. We suggest using sustained MRD negativity as an endpoint for regimen development and approval. Simultaneously, we should continue to validate MRD as a tool, and only apply results from targeted therapy trials to targetable patients.

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Hematologic Therapies Being Studied for Coronavirus: Capitalizing on Progress

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As part of ASH’s online coverage of the COVID-19 pandemic, we have been regularly cataloguing the number of trials being launched as recorded at ClinicalTrials.gov. The number of newly registered studies grew rapidly early in the pandemic — following a curve that mirrors that of the disease — exponential for much of February, March, April, and May of 2020 (Figure). More than two-thirds of the studies are evaluating efficacy of treatments or assessing general outcomes of patients with COVID-19 infection. The remaining studies are investigating tele-medicine, testing, mental health, and more.

It should be no surprise to readers that scientific discoveries from the labs of hematologists are finding their way into clinical trials for the novel coronavirus. Infection often results in a profound dysregulatory effect on blood function and production, which is why there has been so much controversy over anti-coagulation strategies. It is also evident that the virus provokes, in some individuals, an unrestrained immune response. Hematologists are often called to treat conditions of immune dysregulation accompanied by organ dysfunction and profound immune response, including secondary hemophagocytic lymphohistiocytosis (sHLH) and the cytokine release syndrome (CRS) that can accompany chimeric antigen receptor T-cell therapy or the use of bispecific anti-neoplastic antibiotics. In early May 2020, we culled all coronavirus studies listed on ClinicalTrials.gov; approximately 10 percent (108/1,160 studies) were investigating agents that are also used in hematologic disorders. Generally, most of these overlap agents are being tested owing to their known ability to blunt the immune response.

Data show elevated levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-6 (IL-6) in patients with severe COVID-19. For this reason, one of earliest strategies has been to target GM-CSF or IL-6, given their shared use in dampening the excess immune response contributing to lung injury in the “second phase” of COVID infection. In summary, while we still have little definitive therapy that has been proven helpful in coronavirus, multiple innovative hematologic agents are being tested. We will see if the progress that we have seen in the past decade in managing blood cancers and high-risk disorders translates into control of this novel and devastating infection.

A third category of agent familiar to hematologists, are inhibitors of the complement cascade. Trials are being done on eculizumab or raviluzumab, both as monotherapy, given in vivo evidence that the complement system was an important host mediator of SARS-CoV-2-induced disease. A recently published letter describes, for example, four cases of patients with paroxysmal nocturnal hemoglobinuria and COVID-19, and the differential outcomes of those on complement inhibition versus those who were not — though no conclusions can be made from their observations.

Small molecular inhibitors make up the second largest class of overlap drugs for coronavirus. Ruxolitinib, an inhibitor of the JAK/STAT signaling pathway is commonly used for higher-risk myelofibrosis and has also shown benefit in graft-versus-host disease. We found 11 studies using this drug to treat the immune storm of coronavirus, including in combination with other agents. The first trial to publish results was a prospective, randomized study of 5 mg ruxolitinib orally twice-daily in patients meeting criteria for severe infection. A total of 43 patients were randomized to this placebo-controlled study which had criteria for clinical improvement by day 14 as a primary endpoint. The study did not show a statistical improvement in outcomes in the interventional arm, though the authors point out that three of 14 patients in the control group died of respiratory failure, while no patients died in the ruxolitinib group.

Other small molecules being tested include agents to block phosphodiesterase 5-kinase (duvelisib), Bruton tyrosine kinase (acalabrutinib), and even three studies testing imatinib. A 2016 publication on SARS-CoV and MERS-CoV documented that inhibitors of Ab1-kinase, like imatinib, had in vitro activity against those coronavirus infections. Three studies are investigating inhibitors of the programmed-death pathway, employing nivolumab and pembrolizumab, along or in combination with IL-6 antagonists. Case reports on patients with receiving a programmed cell death protein-1 checkpoint inhibitor for cancer and contracting coronavirus have been mixed.

Finally, classical cytotoxic chemotherapy is also being investigated. Owing to its efficacy in the treatment of sHLH, one study is looking at etoposide as monotherapy. A second study will use methotrexate monotherapy in severe COVID infection due to its shared use in malignancy and autoimmune disease, presumed to assist in dampening the excess immune response contributing to lung injury in the “second phase” of COVID infection.


Dr. Monahan and Dr. Michaels indicated no relevant conflicts of interest.
Diffusion

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Quantified Morphology in Diagnosis of Hematologic Malignancies


MAHSHID RAHMAT, MD, AND IRENE GHOBRIAL, MD

In 1845, Rudolf Virchow described and named the disease of leukemia using light microscopy. He also emphasized that diseases including cancers, originated from normal cells. Since then, huge advances in cell-based cancer detection approaches revolutionized diagnosis and prevention of human cancers. Imaging methods, generation sequencing of cancer cells, and identification of circulating tumor cells from blood biopsies provide an opportunity to predict and monitor tumor progression and therapeutic responses. However, cancer detection still a major issue for pathologists and physicians, and in many cancers, light microscopy and immunophenotyping are still the gold standards of the initial diagnosis, especially for pediatric lymphomas and leukemias.

Microscopy and flow cytometry have been extensively used for diagnosis of hematologic malignancies, but these modalities have limitations that make them insufficient for a precise diagnostic classification. Microscopy is a skill-based and subjective approach that is considerably variable between pathologists, even those with years of training. In contrast to microscopy, flow cytometry can detect different cell types according to the expression of cluster of differentiation (CD) molecules on the cell surface. Although flow cytometry is a powerful method in detection of various cell types in normal samples, it cannot distinguish cells with similar or overlapping immunophenotypes, such as tumor cells that display similar surface markers to their normal counterparts.

Knowing the unique capacities and limitations of morphology and immunophenotyping, Dr. Albert G. Tsaï and colleagues developed a high-throughput and multiplexed morphometric assay that not only identifies different blood cell lineages in normal and malignant bone marrow samples but could distinguish tumor from normal cells using subcellular features. Investigators used antibody-measurable cellular antigens to quantify common cell morphological features such as chromatin, cytoplasm, and vesicles. To quantify the intracellular structures in hematopoietic and hematologic malignancies, authors selected 11 common structural components of cell morphology corresponding to chromatin quality, nuclear shape, nuclear size, granularity, granular color, cytoplasmatic color, and cell size; they tested these in the bone marrow of healthy donors and in a group of 31 diverse clinical samples including acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndromes, myeloproliferative neoplasm, B- and T-cell lymphoma, and multiple myeloma. Authors used CD markers to detect different cell types in a normal bone marrow, and then identified the morphometric signals in each. Although cellular structures are ubiquitously found in different cell types, morphometric analysis of bone marrow populations showed numerous differences between various lineages. Nuclear protein lamin-B1 and ribosomal 5.8s rRNA were highly common in blast (progenitor) cells. Cytoskeletal β-actin was enriched in neutrophils and monocytes, and heterochromatin protein 1 was found to be associated with neutrophil differentiation. Lymphocytes and erythrocytes were morphometrically similar; thus, authors used a CD45 marker to distinguish these populations. Being able to morphometrically define major cell types, Dr. Tsaï and colleagues analyzed the single-cell morphometric features of malignant samples and classified different cell populations with almost similar morphometry to normal samples. Although combination of morphometric markers could not distinguish normal from neoplastic cells, individual measurement of morphometric signatures revealed significant differences in normal and malignant bone marrow samples. Nuclear membrane proteins lamin A and C distinguished normal from neoplastic mature T cells, and a combination of lamin B1 and ribosomal RNA differentiated normal and leukemic blast cells independent of flow cytometric markers such as CD34 and CD117. They also identified the VAMP7-A morphometric maker as a substitution for light-based side scatter in diagnostic cytometry.

Combining multiple single-cell morphometric signatures with a machine learning approach (supervised dimensionality reduction by linear discriminant analysis (LDA)), authors generated a morphometric map (MM) that recapitulated and improved upon traditional light-scatter gating strategies. The morphometric LDA method was also able to visualize continuous and branching processes such as gradual differentiation, which is not detectable in diagnostic cytometry. Additionally, MM could distinguish tumor blasts from normal blasts in myeloid leukemias with much higher efficiency compared to flow cytometry and light microscopy, suggesting a clinically practical method that is easy to interpret and could be extended to other datasets.

The limited number of available cell-specific surface markers, similar expression of CD markers in normal and malignant cells, and downregulation of immunophenotypic markers by tumor cells to escape immunotherapies, highlight the importance of using common intracellular features in clinical diagnosis and therapeutic strategies. The authors of the discussed study have developed an automated and multiplexed morphology-based mass-cytometry assay to classify and diagnose hematologic disorders independent of known lineage-specific surface markers. This method requires further optimizations with respect to intracellular staining protocols and costs, but it is compatible with any antibody-based single-cell method such as cellular indexing of surface antibodies and epigenomes by sequencing (CITE-Seq), and if optimized and deployed, morphometry could be designed to aid hematologists in their cases.


Dr. Rahmat indicated no relevant conflicts of interest. Dr. Ghobrial serves on advisory boards at Celgene, Takeda, Janssen, and BMS.
Taking the Brakes Off Programmed Cell Death: Will It Work for AML in Older Patients?


CLAUDIA BRUEDIAGAM, PHD, AND STEVEN LANE, MBBS, PHD, FRACP, FRCPA

Acute myeloid leukemia (AML) is primarily a disease of the older population, with a sharp spike in diagnoses seen in patients 80 years or older, and a median age of 70 years at disease onset. Current treatment outcomes for older patients with AML are limited by patient comorbidities, poor performance status, and altered drug metabolism. Additionally, disease-related factors include frequent adverse cytogenetic or molecular abnormalities. These factors contribute to low tolerability of treatments and overall reduced rates of clinical response to conventional treatments.

B-cell lymphoma-2 (BCL-2) is an apoptosis inhibitory molecule that is overexpressed in most AMLs, allowing leukemia cells to put a brake on programmed cell death. Venetoclax is a specific BCL-2 inhibitor that can unleash apoptotic responses when the remaining components of this pathway, such as TP53, BAX, and PMAI1P1, are functional.1 Clinical trials have revealed promising outcomes for AML patients. Although venetoclax as monotherapy showed only low response rates (19%) in relapsed/refractory AML, results dramatically improved when venetoclax was combined with low-dose cytarabine (LDAC; 54% complete response [CR]/CR with incomplete blood count recovery [CRi]; median overall survival, 10.1 months) or hypomethylating agents (DNMTi; 67% CR/CRI; median OS, 17.5 months) for older patients with de novo AML who were unfit for intensive chemotherapy.2,3 Unfortunately, relapse after venetoclax-based treatment remains common, and long-term cure remains elusive.

Dr. Courtney DiNardo and colleagues have investigated the genetic landscape underlying the clinical responses and resistance to venetoclax combination therapy for AML. Bulk AML as well as single-cell sequencing was performed on samples from 81 patients (median age 74 years) enrolled on two recently published trials of venetoclax in combination with either LDAC or DNMTi, taken at diagnosis, during remission, and at relapse.4 Survival was similar between the LDAC and DNMTi trials, and therefore, both cohorts were combined to increase statistical power. Patients were divided into three groups based on the quality of clinical response according to ELN2017 criteria: sustained remission (>12 months without relapse; n=18), initial clinical responses and resistance to venetoclax combination therapy for AML. Bulk AML as well as single-cell sequencing revealed dramatic complexity of polyclonal resistance. In one example, FLT3-ITD, CBL, and INVAS mutations were initially detected, with outgrowth of five additional kinase mutations.

The results demonstrate the importance of molecular studies to identify patterns of drug resistance and response. Here, NPM1 and IDH1 mutational status as favorable with minimal residual disease (MRD) monitoring and MRD-directed outcomes. Combination trials with relapse prevention strategies such as sequential or combination FLT3 inhibitors, or agents with activity in TP53-mutant AML, are urgently needed.

It will be of interest to see how we can tackle the molecular complexity of AML through trials of new drugs and combinations, risk stratification, precision-based monitoring, and finally, molecularly guided risk-adaptive therapy.


Molecular risk stratification in acute myeloid leukemia to identify patients with favorable responses to venetoclax combinations versus those with high-risk genetics who may benefit from additional targeted therapies. MRD, minimal residual disease.

The Hematologist: ASH News and Reports
1. Loss of the Y chromosome (LOY) is one of the more common cytogenetic abnormalities in myeloid malignancies. Its biological relevance has been understudied, with a lower risk proportion within the IPSS-R. Additionally, LOY is a common age-related phenomenon in men. Cytogenetic abnormalities signify underlying clonal hematopoeisis (CH) and are associated with adverse outcomes, independent of concomitant disease processes. The researchers performed a multivariate analysis controlling for CH-associated mutations and found that LOY remained a significant, independent predictor of developing a myeloid neoplasm. Furthermore, patients with LOY were significantly more likely to harbor CH-associated mutations than patients without LOY. In fact, the prevalence of CH-associated mutations in patients with the highest quartile of LOY burden was comparable to that observed in patients with true MDS. Lastly, they analyzed patients with sequential samples and found that some patients who developed myeloid neoplasia developed increased LOY burden over time, though the sample size was too small for statistical analysis.

2. In summary, the data here show that LOY burden is associated with the burden of CH-associated mutations and, after controlling for the presence of these mutations, remains an independent predictor of myeloid neoplasia. This study highlights the striking similarities between clonal hematopoeisis of indeterminate potential (CHIP), as defined by the presence of pathogenic somatic mutations and isolated LOY. Both entities are markers of CH, increase in prevalence with age, and are associated with an increased risk of developing myeloid neoplasms. Interestingly, LOY is also associated with a variety of nonhematologic disease states, including cardiovascular disease and nonhematologic malignancies. This study adds to the growing evidence that LOY is related to CHIP and should be included in the definitions of CHIP in clinical and research settings. LOY is present in up to 30% of older men, a prevalence that is comparable to that of all other CHIP-associated mutations combined. Overlooking cytogenetic data could result in misclassifying a large subset of male patients who are at higher risk of developing MDS than their female counterparts. Furthermore, the clustering of LOY with CHIP-associated mutations suggests a shared role in leukemogenesis. Understanding how these various genetic lesions develop and interact with one another is critical to better understanding this process.

3. These findings are also clinically relevant. In a patient with cytopenias and bone marrow morphology that is nondiagnostic for myeloid neoplasia, how should the finding of isolated LOY be interpreted? Should it raise concern for evolving myeloid neoplasia or be disregarded as an incidental, age-related finding? By Dr. Ouseph and colleagues, it might be tempting to rely solely on the results of NGS testing, which have shown a high positive predictive value for patients developing myeloid neoplasia; however, this is premature. The study argues that some patients with LOY can provide additional insights into whether cytopenias are related to a developing myeloid neoplasia. The possibility that longitudinal trends in LOY might be even more informative is provocative but should be assessed further. Overall, these findings reinforce the continued relevance of cytogenetic analysis, even in the age of NGS, to the diagnostic process and to prognosis prediction at the bedside.

4. A recent meta-analysis of five pooled prospective studies (555 adult participants) demonstrated that mental stress–induced myocardial ischemia led to a doubling of the risk of adverse cardiac events or total cardiac mortality among individuals with coronary artery disease. Proposed mechanisms include that mental stress results in coronary artery vasodilation, reduced myocardial oxygenation, myocardial electrical instability, impaired endothelial function, and an exaggerated sympathetic nervous system response. This study confirmed that psychological stress is associated with pain and health care use in adults and adolescents with SCI, and this is believed to be mediated by autonomic nervous system (ANS) pathways. Individuals with SCI are believed to have enhanced autonomic nervous system function, and this may underlie the mechanism of pain in SCI, including pain, hypoxia, and sighing. In an elegant study by Dr. Maha Khaleel and colleagues, investigators demonstrated that individuals with SCI had an exaggerated vasocostriction response to the combination of direct and indirect application of painful heat stimuli to one arm, with a decreased microvascular perfusion in both arms. While subjective measures of pain threshold and pain tolerance were similar between SCI and controls, there was a significantly higher vasoreactivity in SCI in the microvascular flow response to thermal pain in SCI (p=0.0028). They postulated that this exaggerated global vasocostriction response in SCI increases red cell transit time through circulation and increases propensity for vaso-occlusion.

5. Results showed a significant drop in regional microvascular blood flow during experimentally induced mental stress (cognitive tasks and PA tasks). Pain anticipation yielded a greater drop in regional blood flow than baseline. Baseline differences were not detected in the magnitude of response between individuals with SCI and controls. Once vasocostriction occurred, it remained throughout the whole task regardless of task difficulty. The degree of vasocostriction in SCI was independent of the avoidant strategy the patient used. The authors concluded that there was no effect on blood flow response in SCI patients versus controls (p=0.03) and having vertebral artery disease in SCI was found to be an independent risk factor for pain anticipation (p=0.002). Investigators found that highly anxious patients with SCI tended to have lower mean baseline blood flow and were therefore already vasocostricted at baseline. As a result, reactivity (parasympathetic withdrawal as well as sympathetic activation) was also noted in all subjects.

6. What does all this mean? Taken together, it is clear that individuals with SCI have or are at high risk of developing MDS due to age-related risk factors. If these individuals have additional risk factors such as smoking, obesity, or a family history of myeloid neoplasia, they may be at increased risk of developing myeloid neoplasia. The study by Dr. Ouseph and colleagues highlights the importance of considering the presence of CH-associated mutations and LOY burden in the evaluation of patients with unexplained blood counts. Overall, these findings underscore the continued relevance of cytogenetic analysis, even in the age of NGS, to the diagnostic process and to prognosis prediction at the bedside.

7. The take-home message is that not only do we, as a community of providers, need to identify a patient’s triggers of VOEs and prescribe their disease modification therapy (such as hydroxyurea, anagrelide, and other anti-platelet agents), but the clinician has to be aware of the potential for patients to identify and test efficacy of interventions that can ameliorate stress and distress in this vulnerable population.
Unmasking the Immunopathological Characteristics of COVID-19: Monocytes Grow With the Flow and Lymphocytes Shelter in Place?


On December 1, 2019, the World Health Organization was informed of cases of pneumonia with unknown etiology in Wuhan City, China. A novel beta coronavirus, Sars-CoV-2, was soon identified as the causative agent of the outbreak, termed COVID-19. By May 5, 2020, there were more than 3.5 million documented cases worldwide. The clinical course ranges from asymptomatic carrier to rapid and fatal respiratory failure. Initial reports revealed lymphopenia and dramatically elevated cytokine production, sometimes referred to as cytokine storm, in severely ill patients. Importantly, the degree of lymphopenia and cytokine production correlates with disease severity and mortality, suggesting that immune dysfunction may drive tissue pathology. Careful elucidation of the nature of both innate and adaptive immune dysfunction in patients with COVID-19 is therefore essential.

Evidence suggests that excessive macrophage activation may drive dysregulation of the innate response. Dr. Dan Zhang and colleagues demonstrated that macrophages and monocytes express ACE2, the surface receptor for SARS-CoV-2 and SARS-CoV-2 in agreement with previous data. They then used flow cytometry to identify aberrant populations of monocytes and macrophages in COVID-19–positive patients. They found a relative decrease in classical monocytes (CD14 bright, CD16 dim/ negative) in patients with COVID-19, and a concomitant increase in nonclassical monocytes (CD14 dim, CD16 bright). This skewing of monocyte populations was associated with the abnormal presence of macrophages with high forward scatter properties in the peripheral blood of patients with COVID-19 (Figure 1A). These macrophages were present in 28 (100%) of 28 COVID-19–positive individuals, but in none of the healthy controls (0/18 controls), or in those persons with other infections (HIV, tuberculosis, H1N1 influenza A, or Hantaan orthohantavirus). They represented a mix of the proinflammatory M1 subtype (expressing CD80 and typically associated with high IL-6 production) and the anti-inflammatory M2 subtype (expressing CD163 and CD206 and associated with IL-10 secretion). IL-6 in particular has been implicated as a key effector masterminding the cytokine storm found in patients with COVID-19. Peripheral blood smears from infected patients morphologically supported this finding, demonstrating increased numbers of macrophages with large, coalescent vacuoles (Figure 1B). Intriguingly, Dr. Zhang and colleagues also identified reductions in CD19+ B cells as well as CD16+ CD56+ natural killer cells, but not CD16+ CD56+ CD3+ natural killer cells, and CD8+ T cells are reduced, their cytokine products are paradoxically increased. These findings may point to significant production of monocytes and T lymphocytes and their inflammatory cytokines with concomitant destructive, consumptive, or sequestrative processes, resulting in the particular cytopenias.

There seems to be a relative increase in T regulatory cells, which may also be associated with dysregulated inflammation. However, while the broad phenotypic patterns of innate and adaptive responses have now been mapped, the specific functional subsets that compose these populations, and their contribution to viral clearance versus tissue pathology, remain unclear. Does the degree of vacuolization correlate with specific macrophage phenotypic or functional subsets, or is it a general property of effective responses? Even the origin of the monocyteemia and lymphopenia in the setting of a hyperinflammatory antiviral state is not clear. Evidence indicates SARS-CoV-2 induces a type III response dominated by Th17 cells despite the lymphopenia and the key mediator IL-6 typically results in skewing of CD4+ T cells away from regulatory T cells towards Th17 type cells – the opposite of what was found in these studies. Additionally, while other CD4+ and CD8+ T cells are reduced, their cytokine products are paradoxically increased. These findings may point to significant production of monocytes and T lymphocytes and their inflammatory cytokines with concomitant destructive, consumptive, or sequestrative processes, resulting in the particular cytopenias.

Regardless, these distinct changes in the peripheral blood may be hallmarks of the dysregulated inflammatory state and may help stratify those patients who are likely to need more intensive care, as well as encourage investigations into adjuvant therapeutic options.
Complements and Catastrophe: How Complement Activation Affects Clinical Phenotype in Antiphospholipid Syndrome


ERIC TSENG, MD, MS, CH, FRCPC

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ntiphospholipid syndrome (APS) is an autoimmune disease characterized by thrombosis and pregnancy morbidity in the persistent presence of antiphospholipid antibodies (APL). A rapidly progressive form of catastrophic APS (CAPS) may also occur with multorgan thrombosis and thrombotic microangiopathy. The pathogenesis of thrombosis and pregnancy morbidity in APS is not completely understood, and it remains unclear why some patients have more severe phenotypes including recurrent thrombosis or CAPS. Those who are triple positive for lupus anticoagulant, anti-cardiolipin antibody, and anti-β2-glycoprotein-1 antibody are at highest risk of recurrent thrombosis despite anticoagulant therapy.

In this article, Dr. Shrut Chaturvedi and colleagues investigate the role of complement dysregulation in the pathophysiology of thrombosis and CAPS in APS. Patients with thrombotic APS (n = 59) and CAPS (n = 22) from three tertiary centers were prospectively recruited, along with patients with systemic lupus erythematosus with APS (n = 41) for comparison. Serum samples were collected and assessed for evidence of complement activation using a modified Ham’s (nM/am) assay to test killing of PIGA-negative cells after exposure to patient sera. The mHam assay was also performed with the addition of both euclumalum (terminal complement blockade) and novel factor D inhibitor (selective inhibition of alternative complement pathway). Evidence of cell-surface complement (C5b-9) deposition was confirmed via flow cytometry. Finally, targeted sequencing for germline mutations of 15 genes involved in complement regulation (including C1r, C1s, C1s, C1r, C4, C5, C6, C7, C8, C9, CFH, CD55, and CD59) was done along with samples from patients with atypical hemolytic uramec syndrome (aHUS).

The mHam assay was positive in a greater proportion of patients with CAPS (86%) than those with thrombotic APS (36%) and SLE (7%). mHam positivity was also more strongly associated with triple positivity (60%) than with patients who were double-positive (26%). Increased mHam positivity was more likely in those who had a recurrent thrombotic event despite therapeutic anticoagulation (43%) than those with a single event (33%).

APS patient sera were found to induce C5b-9 deposition seen by flow cytometry on the test PIGA-negative cells. Moreover, the addition specifically of anti-β2-glycoprotein-1 antibodies to body fluids was also shown to induce C5b-9 deposition. This complement activation induced by patient sera was inhibited by mHam blocking with both euclumalum but not inhibited by a factor D inhibitor (selective inhibitor for alternative pathway), suggesting that complement activation in APS occurred via the classical pathway. Finally, germline mutations in complement regulatory genes were seen in a higher proportion of patient with APS (6/10, 60%) compared to SLE (1/5, 22%) and mLEL (1/10, 29%). The rate of germline mutations in CAPS was similar to that of a sample of patients with aHUS (17/33, 52%).

These data were initially presented during the Plenary Scientific Session at the 2019 ASH Annual Meeting to evaluate the significance of these findings. They confirm that complement activation likely plays an important role in the pathogenesis of thrombosis in APS, particularly in more severe phenotypes including recurrent thrombosis and CAPS. This complements several previous reports where increased mHam positivity was more likely in those who had a recurrent thrombotic event despite therapeutic anticoagulation (43%) than those with a single event (33%).

The limitations of this study include referral bias, as these cases were highly selected for referral to tertiary care. There was also no control group matched for patient characteristics or treatments, limiting the ability to draw comparisons. Nevertheless, these data provide important insight into the pathogenesis of immunothrombosis in APS. They also highlight the importance of the use of complement blockade in treating refractory CAPS, which has been reported in case series after the failure of standard therapy with steroids, plasma exchange, anticoagulation, or other treatments. These studies should focus on functional significance of germline mutations and investigating complement blockade in CAPS.

Cancers evolve through a process of Darwinian evolution driven by heritable variation at the cellular level. A plethora of somatic alterations occurring within the DNA of a cell leads to an aberrant phenotype characterized by increased proliferation and growth, resistance to apoptosis, and immune surveillance. Characterizing the mutational landscape of cancer has been a major aim of the past 50 years of research. Initial efforts were able to identify numerous mutations occurring in specific genes promoting tumor development and proliferation. With the advent of new technologies, it has been possible to perform whole-genome sequencing (WGS) to catalogue changes occurring within any given cancer genome. The Pan-cancer Analysis of Whole Genomes (PCAWG) Consortium was created with the goal of identifying somatic events driving common cancer development across all tumor types. A team of researchers, counting more than 700 groups, is divided across 16 working groups analyzing 2,658 genomes from 38 tumor types. Their discoveries are illustrated in 52 articles published across Nature journals.

The findings presented in their flagship article, supervised by Drs. Peter Campbell and Gad Getz (among others), highlight shared abnormalities between cancer types and the importance of using WGS data, compared to targeted approaches, to analyze cancer genomes. After carefully benchmarking the pipeline to call single-nucleotide variants (SNVs), indels, copy number alterations (CNAs), and structural variants (SVs), the researchers show that 96 percent of cases had a driver event. On average there are 4.6 driver events per tumor, for coding point mutations the average was 2.6 per tumor. Non–coding point mutations were less frequent. A coding driver mutation and/or a CNV was identified in 76 and 73 percent of tumors, respectively. In B-cell lymphomas, there was a higher prevalence of SNV driving events compared to SVs. Not surprisingly, the guardian of the genome, the tumor suppressor TP53, was the most frequently altered gene, with both alleles mutated in 77 percent of TP53-mutated cases (usually a somatic point mutation on one allele and a somatic deletion of the other allele).

Across samples initially identified not to have any driving mutations, the authors identified numerous technical reasons for missing driver mutations. For example, failure of bioinformatic algorithms affected 35 myeloproliferative neoplasms where JAK2V617F point mutation was missing as a result of the conflation by JAK2V617F clones in matched normal or "panels of normal" samples. This highlights the challenge of applying WGS to study certain transformation problems (e.g., non-Hodgkin’s lymphoma). For technical shortfalls, 5.3 percent of cases still had no identifiable somatically altered driver. The authors conclude that, despite the scale and sophistication of the analyses, cancer driver discovery is not yet complete.

The advantage of using WGS compared to simply assessing the coding genome (i.e., targeted exome sequencing) is the opportunity, firstly, to identify SNVs (CNA and chromosomal rearrangement) and clusters of mutations (hotspots), and secondly, to investigate whether these are early or late events in cancer development. The authors show that chromoplexy (a double-strand break–induced chromosomal rearrangement) was found in 17.8 percent of cases, while kataegis (generation of a hypermutated hotspot with locally clustered nucleotide substitutions) was found in 60.5 percent, and chromothripsis (chromosomal shattering followed randomly stitched back together) was found in 22.3 percent. The latter was also shown to be associated with TP53 mutation and an early event occurring at the clonal level, suggesting a prominent driving role in those tumors. This increased clonal heterogeneity may be given the statistic of the white blood cell panel assessing a few hundred genes is often instead used of WGS, which will miss such chromosomal clustering of mutations and SNVs. For instance, extreme kataegis burden (more than 30% of clones) was only found in a small percentage of WGS-H Hodgkin's lymphoma. Understanding the analysis of telomeric sequences to gain further insights into telomere maintenance – a well-known mechanism of cancer – and gain replication history, the authors found that 16 percent of the tumors have somatic mutations altering either the function or the expression of either TERT, ATXR1, or DAXX genes, which are all known to be responsible for telomere maintenance. However, an association with alterations in the retinoblastoma 1 (RB1) gene was also observed, possibly representing a novel pathway for telomere length preservation. Finally, the study also describes many novel germline variants that determine rates and patterns of somatic mutation.

The PCAWG consortium reported the integrated genetic analysis of more than 2,600 genomes, describing common genetic features across 38 tumor types. This is a truly remarkable achievement, requiring computational analysis at a staggering scale, achieved through cloud computing. Only a relatively small number of somatic driver events are typically found in important cancer development, and the majority of these are either SNVs within the coding genome or CNAs, with a smaller number of somatic driver mutations occurring in non-coding regions of the genome and frequent occurrence of clusters of mutations, including SVs. These highly recurrent events can potentially be comprehensively characterized by using WGS. While undoubtedly some driver mutations remain to be discovered, the occurrence of certain tumors without any detectable driver mutations suggests WGS also raises the possibility of other mechanisms of tumor development that may play a role. For instance, the involvement of tumor microenvironment is also a common feature among cancer types, but it may not be detectable by somatic mutations detected in numerous blood cancer model systems. The next herculean effort, as highlighted by the authors, will be to focus on translating WGS-based cancer genomic clinical practice. The same team led the way as part of the 100,000 Genome England initiative. The long-term ambition is for WGS to become a routine clinical assessment tool in order to apply precision medicine. As the authors acknowledge, the dramatic patient-to-patient variability and even cell-to-cell heterogeneity within a tumor will necessitate “knowledge banks” comprising tens of thousands of patient tumors to analyze and will require analysis of detailed clinical and large international consortia. This PCAWG resource article, despite its impressive scale, represents only the first early steps in this process.

Dr. Orlando and Dr. Mead indicated no relevant conflicts of interest.
Data from randomized control trials examining edoxaban and rivaroxaban, published in 2018, changed the landscape of anticoagulation for cancer-associated venous thromboembolism (VTE). These drugs were welcome alternatives to low-molecular-weight heparins, the previously established optimal therapy over warfarin. The use of fondaparinux has been limited by the observed increase in major bleeding with edoxaban and a clinically relevant nonmajor bleeding (CRNMB) with rivaroxaban in comparison to dalteparin. After publication of the Hokusai VTE Cancer and SELECT-D® studies, the International Society for Thrombosis and Haemostasis published guidelines with recommendations for these drugs, but with a notable concern regarding the potential for higher risk of bleeding, especially in patients with luminal gastrointestinal malignancies.

The Caravaggio study was an open-label, randomized, multinational clinical trial studying apixaban compared to dalteparin for cancer-associated VTE. Participants had active cancer and symptomatic (or incidental, up to 20%) proximal deep vein thrombosis (DVT) or pulmonary embolism. Patients who had received initial nonstatistical parenteral anticoagulation for a minimum of 72 hours before enrollment. The primary outcome of recurrent VTE was defined as proximal DVT (symptomatic or incidental), symptomatic upper extremity DVT, or pulmonary embolism (symptomatic, incidental, or fatal) within six months. The principal safety outcome was major bleeding occurring during the study period and within 72 hours of last study drug administration.

At 119 sites, 1,170 patients were randomized, making it the largest study of cancer-associated VTE. A total of 1,155 patients, 576 treated with apixaban and 579 treated with dalteparin, were included in the modified intention to treat analysis. The primary efficacy outcome of recurrent VTE occurred in 5.6 percent with apixaban and 7.9 percent with dalteparin after six months (HR, 0.69; 95% CI, 0.37-1.01; p<0.001 for noninferiority, p=0.09 for superiority). The primary safety outcome of major bleeding occurred in 9.8 percent with apixaban and 4.0 percent with dalteparin (HR, 0.82; 95% CI, 0.40-1.69; p=0.60). Major gastrointestinal bleeding (not a prespecified outcome) was similar between apixaban and dalteparin, occurring in 1.9 percent and 1.7 percent of patients, respectively. CRNMB was not statistically different and occurred in 9.0 percent of apixaban- and 6.0 percent of dalteparin-treated patients (HR, 1.42; 95% CI, 0.88-2.30).

Apixaban now has robust data to support its use in patients with cancer-associated VTE and must be put into perspective with previous studies (Table 1), but there are limitations to the conclusions we can draw from these comparisons. While each drug was compared against the same regimen of dalteparin, differences in inclusion or exclusion criteria, and recruitment of patients at different times in different settings led to small, but potentially meaningful differences in patient populations. For example, the Caravaggio study excluded patients with primary brain tumors, known cerebral metastases and acute leukemia, and the SELECT-D® study excluded patients with upper gastrointestinal malignancies after initial safety analyses demonstrated a concern for higher bleeding rates with rivaroxaban. Patients with atypical VTE (upper extremity, cerebral venous sinus, and splanchic vein thrombosis), which is seen more commonly in patients with cancer, were excluded from all studies except the ADAM-VTE study. Heterogeneity in the studies can also be observed by examining the percent treated who had colorectal cancer, which varied up to 10 percent between studies. The rates of major bleeding with dalteparin were very similar between most of the studies, but interestingly there was more variability with recurrent VTE across the studies. Now that a robust arsenal of agents is available for the treatment of cancer-associated VTE, studies should focus on refining the use and selection of these drugs for specific cancers and specific circumstances as a means to optimize benefits and minimize harm.

Table. Direct Oral Anticoagulant Randomized Controlled Trials in Cancer-Associated VTE

<table>
<thead>
<tr>
<th>Study</th>
<th>Published Date</th>
<th>Study Drug</th>
<th>Study Size (No. of Patients)</th>
<th>Follow-up (Months)</th>
<th>Comparison of Selected Maligancies Among DOAC-Treated Groups</th>
<th>Recurrent VTE</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>Caravaggio</td>
<td>4/2020</td>
<td>Apixaban</td>
<td>1,155</td>
<td>6</td>
<td>Colorectal – 21%</td>
<td>Upper GI – 4.0%</td>
<td>Lung – 18.2%</td>
</tr>
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<tr>
<td>ADAM-VTE®</td>
<td>10/2019</td>
<td>Apixaban</td>
<td>300</td>
<td>6</td>
<td>Colorectal – 12.2%</td>
<td>Upper GI – 4.8%</td>
<td>Lung – 21.8%</td>
</tr>
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<tr>
<td>SELECT-D®</td>
<td>7/2018</td>
<td>Rivaroxaban</td>
<td>406</td>
<td>6</td>
<td>Colorectal – 27%</td>
<td>Upper GI – 8.1%</td>
<td>Lung – 11%</td>
</tr>
<tr>
<td>Hokusai VTE Cancer®</td>
<td>2/2018</td>
<td>Edoxaban</td>
<td>1,046</td>
<td>12</td>
<td>Colorectal – 15.9%</td>
<td>Upper GI – 6.3%</td>
<td>Lung – 14.8%</td>
</tr>
</tbody>
</table>

Abbreviations: DOAC, direct oral anticoagulant; GI, gastrointestinal; VTE, venous thromboembolism.

Allogeneic HSCT After PD-1 Blockade

blockade prior to transplantation to that of patients who did not. Prior exposure to PD-1 blockade did not lead to excess toxicity in the post-transplant course, and most likely, the incorporation of PTCy as GVHD prophylaxis can ameliorate the risk of moderate to severe chronic GVHD. Whether PD-1 blockade prior to allo-HSCT improves relapse rates remains to be determined, but it is clear that remission status at time of transplantation is an important predictor of long-term outcome. Prospective trials specifically designed to address optimal transplant strategies are needed. Finally, ongoing follow-up of the Checkpoint 205 trial has identified a subset of patients with cHL who received PD-1 blockade as salvage therapy after autologous BMT relapse and have remained in CR for more than three years without further therapy. Thus, future studies will likely investigate whether subset of patients can be cured with checkpoint blockade alone and do not need to proceed to allo-HSCT.


Dr. Alpert and Dr. O’Dwyer indicated no relevant conflicts of interest.
APRIL 16, 2020
Recurrence isplateral deep vein thrombosis has major clinical ramifications, but is often difficult to distinguish from residual clot by ultrasound. Dr. Lisette F. van Dam and colleagues demonstrated that magnetic resonance direct thrombus imaging can accurately distinguish the two, with a low risk of venous thromboembolism recurrence after a negative study.

In this month’s CME article, Dr. Laetitia Vercellino and colleagues report results of a secondary analysis of patients with diffuse large B-cell lymphoma in the REMARC trial who had baseline positron emission tomography scans, thereby demonstrating that metabolic tumor volume combined with performance status allowed risk stratification of patients before treatment and predicted survival independent of response to chemoinmunotherapy.

APRIL 30, 2020
Dr. Steffen Boettcher and colleagues analyzed clonal hematopoiesis (CH) in 42 donor-recipient pairs of long-term survivors of allogeneic stem cell transplantation. CH is prevalent among both donors and recipients, including a small number of patients with engraftment of donor CH; these clones vary significantly between donor and recipient.

MAY 14, 2020
Molecular analysis has modified the view of complete remission in acute myeloid leukemia (AML) to include consideration of measurable residual disease. In this Perspective, the authors highlight the complexity of interpreting clonal hematopoiesis to distinguish residual AML from ancestral clones of uncertain significance, new or emerging clones, or donor-derived clones in patients undergoing stem cell transplantation.

MAY 21, 2020
The International Lymphoma Radiation Oncology Group (ILROG) provides evidence-supported options for adjusting radiation therapy timing and delivery for patients with selected hematologic malignancies in the COVID-19 pandemic, while maintaining efficacy and safety.

A key question for many patients when first diagnosed with early-stage chronic lymphocytic leukemia is, “When will I need therapy?” Dr. Adalgisa Condoluci and an international consortium report a validated algorithm comprising clinical and laboratory measures to estimate the probability of requiring therapy within five years for individual patients.

MAY 28, 2020
Increasing fetal hemoglobin expression is an important clinical approach to the treatment of hemoglobinopathies, but the mechanism of upregulation of hemoglobin F (HbF) is still not clear. Dr. Eugene Khandros and colleagues demonstrated by elegant transcriptional and proteomic profiling studies that F cells and A cells are virtually identical, suggesting that HbF expression and nonexpression reflect identical transcriptional changes in the b-globin locus.

In anticipation of possible blood shortages during the current COVID-19 pandemic, Dr. Michael DeBaun proposes rapid initiation of administration of low, fixed doses of hydroxyurea for children with sickle cell anemia (SCA) who receive regular prophylactic transfusions for stroke prevention.

JUNE 4, 2020
Wiskott-Aldrich syndrome (WAS) is an X-linked disease manifesting with thrombocytopenia, eczema, recurrent infections, autoimmune disease, and malignancy. Hematopoietic cell transplantation (HCT) is potentially curative. Dr. Lauri Burroughs and colleagues from the Primary Immune Deficiency Treatment Consortium (PIDTC) report excellent outcomes for WAS patients with modern allogeneic HCT and high-level myeloid engraftment.

JUNE 11, 2020
In a study reported in a Plenary Paper, Dr. Peng Huang and colleagues used a CRISPR screen to identify ATF4 as a critical species-specific protein regulating fetal hemoglobin. ATF4 downregulates γ-globin through activating transcription of BCL11A, a silencer of the γ-globin gene locus.

Dr. Andrew Henry Wei and colleagues report the results of a randomized trial of low-dose cytaracline (LDAC) combined with venetoclax versus LDAC alone in elderly “ unfit” patients with acute myeloid leukemia (AML), demonstrating that venetoclax increases complete remission rate and overall survival.

JUNE 18, 2020
Perspective, the authors highlight the complexity of interpreting clonal hematopoiesis to distinguish residual AML from ancestral clones of uncertain significance, new or emerging clones, or donor-derived clones in patients undergoing stem cell transplantation.

JUNE 23, 2020
In anticipation of possible blood shortages during the current COVID-19 pandemic, Dr. Michael DeBaun proposes rapid initiation of administration of low, fixed doses of hydroxyurea for children with sickle cell anemia (SCA) who receive regular prophylactic transfusions for stroke prevention.
ASH Members Respond to COVID-19 Challenges

The COVID-19 pandemic has upended all facets of life, including both hematology research and clinical practice. ASH has been working to ensure that the concerns of hematologists and their patients are considered by federal policy makers in COVID-19 relief legislation. To better understand and address the impact of the COVID-19 crisis, and Washington’s response to it, The Hematologist spoke with three ASH members: Dr. Julie Kanter (member, ASH Committee on Government Affairs and the Sickle Cell Disease [SCD] Work Group on Health Care Professional Education and Training), Dr. Chancellor Donald (Chair, ASH Committee on Practice), and Dr. Ross Levine (Chair, ASH Committee on Scientific Affairs).

Research on cause. Dr. Levine, a physician scientist at Memorial Sloan Kettering Cancer Center, recently convened leaders to discuss the impacts of research projects that have been halted because of required physical distancing measures. While acknowledging the necessity of such measures, Dr. Levine remains concerned about long-term consequences. “The ‘pause’ in laboratory research is a well-considered, appropriate step but has innumerable consequences on the pace of scientific discovery, the progress of specific scientific projects, and the careers of all investigators including trainees and junior faculty,” he said.

ASH has been working to inform Congress of the effects of closing research labs. In April, members of the ASH Grassroots Network sent hundreds of letters to Capitol Hill urging legislators to join bipartisan “Dear Colleague” letters authored by Reps. Diana DeGette (D-CO) and Fred Upton (R-MI), and Sens. Thom Tillis (R-NC) and Ed Markey (D-MA). These letters ultimately included signatures from more than 175 members of the House and more than 30 members of the Senate from both parties urging congressional leaders to include $26 billion in supplemental funding for federal research agencies in any future COVID-19 supplemental relief package. These emergency supplemental resources would allow federal research agencies, including the National Institutes of Health (NIH), to mitigate COVID-19-related disruptions and restore momentum across the full range of the nation’s research enterprise as quickly as possible once the crisis subsides.

The Society has developed a COVID-19 Research Agenda in Hematology in response to the hematology-related complications that have emerged in many patients. This document explores the key underlying research questions that, to date, lack scientific evidence to inform clinical practice and treatment efforts and which are of top priority for patients. ASH leaders have been sharing the new research agenda with numerous institutes and centers at NIH, including the National Heart, Lung, and Blood Institute (NHLBI) Director Dr. Gary Gibbons and leaders from other federal, state, and blood organizations, where she shared highlights from ASH’s new COVID-19 Research Agenda (www.hematology.org/research-agenda), as well as information on the ASH Research Collaborative Data Hub’s COVID-19 Registry for Hematology.

Navigation an altered health care system. ASH, working with Committee on Practice Chair Dr. Donald, has been disseminating updates on the numerous regulatory changes issued by the Centers for Medicare and Medicaid Services (CMS) during the crisis. These changes aim to help hospitals address issues with capacity, to provide flexibility in how physicians see patients and supervise trainees, and to expand the limits of where physicians can treat patients. “The Committee on Practice has worked to engage CMS regarding reimbursement issues for telehealth,” Dr. Donald said. Not only did Committee members lobby U.S. Senators for reimbursements, but a webinar was conducted with panelists well versed on the delivery of care for patients with hematologic disorders via telemedicine. ASH was pleased when CMS established new reimbursement rates for telephone-only evaluation and management (E/M) services to align with the comparable office/outpatient E/M codes.

“Our patients need us now more than ever!” As with other hematology patients, telemedicine has changed the way individuals living with SCD receive care. “We have switched 90 percent of ‘well visits’ to telemedicine and that has been very successful,” said Dr. Kanter, a professor of hematology and director of the Adult Sickle Cell Program at the University of Alabama in Birmingham. “We have also tried to call patients getting chronic treatments to ensure they know it is safe to come in and important to continue their transfusions, apheresis, infusions, etc. to ensure they remain healthy.”

ASH is working with members of Congress to authorize a Medicaid demonstration program to improve preventive and primary outpatient care for individuals living with SCD so that the unique medical needs of SCD patients, including those patients dealing with COVID-19, are taken into consideration. Recent data show that individuals with SCD are at higher risk for severe illness from COVID-19 due to a suppressed immune system and comorbid conditions of the heart, lungs, and other major organs. In April, ASH Grassroots Network members urged their federal representatives to join Rep. Danny Davis’ (D-IL) “Dear Colleague” letter to congressional leadership to support an amendment to the next COVID-19 relief package that would create a demonstration project at CMS to improve access to comprehensive outpatient care for individuals with SCD. The effort ultimately generated nearly 500 letters from ASH members to Capitol Hill and led to 35 of Representative Davis’ colleagues joining him in sending the letter to congressional leaders. ASH also led the creation of a letter from nearly 70 organizations in support of the effort.

Hematology patients also face acute challenges including limitations to receiving blood donations due to the pandemic. ASH worked with the U.S. Food and Drug Administration (FDA) and other partners to address the significant challenges of maintaining the national blood supply during the pandemic and to raise awareness to the shortage. Specifically, in March, ASH Grassroots Network members contacted their elected officials about the urgent need for safe, organized, and ongoing blood donations during this time of crisis. ASH has also supported the FDA’s updated guidance on blood donor eligibility to address the pressing need for blood donations during the pandemic.

For information on opportunities to advocate on behalf of hematology, visit the ASH Advocacy Center at www.hematology.org/advocacy.

OLGA POZDNYAKOVA, MD, PhD,1 AND ANNETTE S. KIM, MD, PhD2
1. Associate Pathologist, Brigham and Women’s Hospital; Medical Co-Director, Hematology Lab; Medical Director, Brigham and Women’s Harvard Physician Diagnostics Lab; Associate Professor, Harvard Medical School, Boston, MA
2. Associate Professor of Pathology, Harvard Medical School; Associate Pathologist, Brigham and Women’s Hospital Boston, MA

A 65-year-old woman with end-stage renal disease status post renal transplant 19 months ago was admitted with cough, fevers, and shortness of breath. Complete blood count (CBC) on admission showed the following: white blood cell (WBC) count, 1.41 K/Ml; hemoglobin, 12.9 g/dL; mean corpuscular volume, 90 fl.; and platelets, 163 K/Ml. WBC differential was as follows: neutrophils, 55 percent; lymphocytes, including large granular forms, 30 percent; monocytes, 15 percent. Chest X-ray showed ill-defined pleural opacities in the lungs. Infectious work-up was positive for SARS-CoV-2 (the virus that causes COVID-19) by reverse transcriptase–polymerase chain reaction and negative for all other infections. The figure shows three images from the peripheral blood.

What are the inclusions in the patient’s neutrophils?
A. Anaplasma spp. morulae
B. Döhle bodies
C. May–Hegglin anomaly
D. Howell–Jolly body–like inclusions
E. Blue-green inclusions

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

Dr. Pozdnyakova and Dr. Kim indicated no relevant conflicts of interest.

Read The Hematologist online at www.hematology.org/thehematologist, and catch up on the latest news in the field of hematology right on your desktop, mobile phone, or tablet.