ASH Highlights and Commentary: Additional Topics of Interest

Abstract 653

Efficacy and Safety of Pevonedistat Plus Azacitidine vs Azacitidine Alone in Higher-Risk Myelodysplastic Syndromes (MDS) from Study P-2001 (NCT02610777)

Mikkael A. Sekeres, Justin M. Watts, MD, Atanas Radinoff, Montserrat Arnan Sangerman, MD, PhD, Marco Cerrano, Patricia Font Lopez, Joshua F. Zeidner, MD, Maria Diez-Campelo, PhD, MD, Carlos Graux, Jane L. Liesveld, MD, Dominik Selleslag, MD, Nikolay Tzvetkov, MD, Robert J. Fram, Dan Zhao, Sharon Friedlander, Kevin Galinsky, Douglas V. Faller, and Ades Lionel

Visit https://ash.confex.com/ash/2020/webprogram/Paper135840.html for a complete list of contributor affiliations and full graphics.

Background: Pevonedistat (P), the first small-molecule inhibitor of the neural precursor cell expressed, developmentally downregulated 8 (NEDD8)-activating enzyme, disrupts proteasomal degradation of select proteins and has shown promising clinical activity and good tolerability in combination with azacitidine (A) in acute myeloid leukemia (AML).

Methods: 120 pts with higher-risk MDS/chronic myelomonocytic leukemia (Revised International Prognostic Scoring System [IPSS-R] risk >3, including intermediate- [≥5% blasts], high-, or very high-risk) or low-blast AML naïve to hypomethylating agents were randomized 1:1 to receive P 20 mg/m^2 intravenously (IV) on days (d) 1, 3, 5 + A 75 mg/m^2 (IV/subcutaneously) on d 1–5, 8, 9 (n=58), or A alone (n=62), in 28-d cycles until unacceptable toxicity, relapse, transformation to AML, or progression. The study was powered for event-free survival (EFS – time from randomization to death/transformation to AML, whichever occurred first). These analyses focus on clinical, cytogenetic, and genetic factors that could impact rate, depth, and duration of response, as well as EFS and overall survival (OS), in pts with higher-risk MDS.

Results: The 67 pts with higher-risk MDS were drawn from a larger intent-to-treat (ITT) population (n=120), in which EFS trended longer (median 21.0 vs 16.6 months [mos]; hazard ratio [HR] 0.67; 95% confidence interval [CI] 0.42–1.05; P = .076), and median OS was 21.8 vs 19.0 mos (HR 0.80; 95% CI 0.51–1.26; P =.334; median follow-up 21.4 vs 19.0 mos) with P+A vs A. In the higher-risk MDS pts, baseline characteristics were balanced between arms. Pts with higher-risk MDS received a median of 13.5 vs 10 cycles of P+A vs A, and EFS was longer with P+A vs A (median 20.2 vs 14.8 mos; HR 0.54; 95% CI 0.29–1.00; P = .045). Median OS was 23.9 vs 19.1 mos (HR 0.70; 95% CI 0.39–1.27; P = .240) with P+A vs A. Pts with MDS assessed as high-risk according to the combined Cleveland Clinic model formula [Nazha et al. *Leukemia* 2016;30:2214–20], which incorporates both clinical and genetic factors (n=16 in each arm), had a median EFS of 20.2 vs 11.7 mos (HR 0.39; 95% CI 0.17–0.90; P = .023) and a median OS of 24.2 vs 14.2 mos (HR 0.45; 95% CI 0.19–1.05; P = .056) with P+A vs A (Figure 1). In prespecified subgroup analyses of EFS among pts with IPSS-R-defined high- and very high-risk MDS, HRs favored P+A vs A (HR 0.47; 95% CI 0.19–1.18 and HR 0.53; 95% CI 0.17–1.72, respectively), as did overall response rate (complete remission [CR] + partial remission [PR] + hematologic improvement) in response-evaluable pts (79% vs 57%, with a CR rate of 52% vs 27% [P = .050] for P+A vs A). Median duration of response (CR + PR) was 34.6 vs 13.1 mos with P+A vs A (P = .106). Among pts with higher-risk MDS who were red blood cell (RBC) or platelet transfusion-dependent at baseline (P+A, n=13; A, n=19), 69.2% vs 47.4% became transfusion-independent (P = .228), and the median transfusion rate/month

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was 0.7 vs 2. Median duration of RBC and platelet transfusion-independence was 23.3 vs 11.6 mos (P = .016) with P+A vs A. Median time to AML transformation (range) among pts with higher-risk MDS who transformed (P+A, n=5; A, n=9) was 12.2 (4.6–12.6) vs 5.9 (1.7–14.8) mos with P+A vs A. Median dose intensity of A was 98% in both arms. Overall, P+A had a comparable safety profile to A alone and did not increase myelosuppression. In higher-risk MDS, rates of adverse events (AEs), serious AEs (SAEs), and grade ≥3 AEs normalized by the mean number of cycles dosed of A were lower with P+A compared with A (Table 1). Clinical activity was observed with P+A in pts who had poor-risk cytogenetics and in pts with adverse-risk mutations, including TP53 (Figure 2).

Conclusions: In pts with higher-risk MDS, P+A led to longer EFS and a higher CR rate compared with A; the effect on EFS was particularly evident in pts with IPSS-R high- and very-high-risk disease. This finding was associated with longer duration of response, later transformation to AML, increased rate of transfusion-independence and lower transfusion rates with P+A vs A. AEs, SAEs, and grade ≥3 AEs per A cycle dosed appeared lower with P+A vs A. Clinical activity was observed in pts with a variety of adverse-risk mutations, and a prognostic risk model that incorporates both clinical and genetic risk factors revealed potential clinical benefit among pts with high-risk MDS. Further evaluation of P+A vs A is ongoing in a randomized phase 3 trial (NCT03268954).

Figure 1. Combined Cleveland Clinic model formula in patients with myelodysplastic syndromes. Improved event-free survival and overall survival in patients at risk category "High" with pevonedistat + azacitidine vs azacitidine

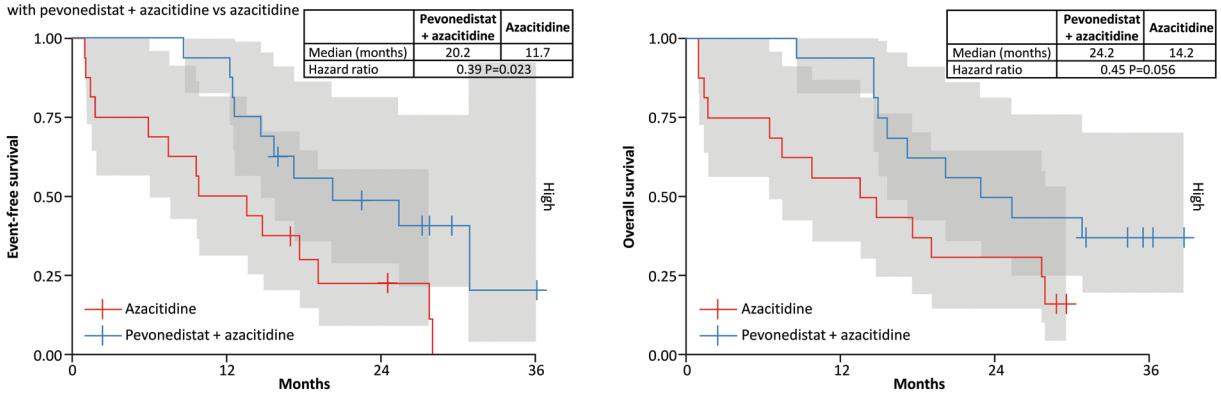

Figure 2. Clinical activity was observed with pevonedistat + azacitidine in patients with higher-risk myelodysplastic syndrome harboring poor-prognostic mutations. CR, complete remission; HI, hematologic improvement; ORR, overall response rate; PR, partial remission.

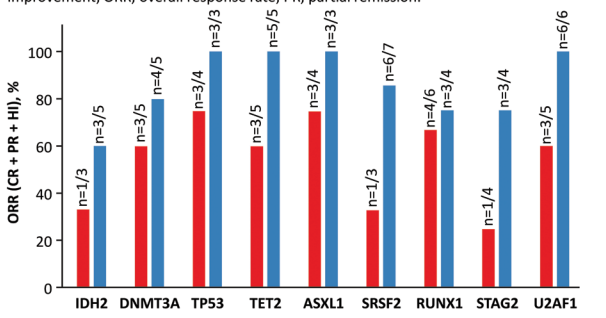

Table 1. Adverse events in patients with higher-risk myelodysplastic syndromes normalized by mean number of azacitidine cycles dosed. Normalized n=AE (n)/azacitidine cycles dosed (mean). AE, adverse event; SAE, serious adverse event.

	Pevonedistat + azacitidine n=32	Azacitidine alone n=35
Azacitidine cycles dosed (mean)	16.3	10.7
Any AE, n (normalized n)	32 (1.96)	35 (3.27)
Treatment-related AE, n (normalized n)	22 (1.35)	27 (2.52)
SAE, n (normalized n)	24 (1.47)	20 (1.87)
Treatment-related SAE, n (normalized n)	4 (0.25)	3 (0.28)
Grade ≥3 AE, n (normalized n)	30 (1.84)	29 (2.71)

The Advanced Practitioner Perspective: Sara Tinsley, PhD, APRN, AOCN®

This abstract presented the efficacy of pevonedistat in combination with azacitidine, with a focus on response rates and safety. Pevonedistat is a small-molecule inhibitor that targets the neddylation pathway, a protein homeostatic pathway that is essential for the growth and survival of cancer cells.

120 patients with higher-risk myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML) were randomized 1:1 to receive azacitidine or azacitidine in combination with pevonedistat. The dose of pevonedistat was 20 mg/m^2 intravenously on days 1, 3, and 5 with azacitidine (IV/subcutaneously) on days 1 to 5, 8, and 9 (n = 58). For the azacitidine alone group (n = 62), patients received azacitidine in 28-day cycles until unacceptable toxicity, relapse, transformation to acute myeloid leukemia, or progression.

The study was powered for event-free survival (EFS = time of randomization until death or transformation to acute myeloid leukemia, whichever came first). The patients with higher-risk MDS received a median of 13.5 vs. 10 cycles of pevonedistat with azacitidine vs. azacitidine alone. Event-free survival was longer with pevonedistat with azacitidine vs. azacitidine alone. The median overall survival for pevonedistat with azacitidine was 23.9 months compared with 19.1 months with azacitidine alone, although the difference was not statistically significant. Other meaningful responses included transfusion independence from red blood cell or platelets transfusions with the combination, and delayed transformation to acute myeloid leukemia. There was also activity in patients with poor-risk cytogenetic and adverse mutations, including *TP53*. The safety profile of the combination was similar with the safety profile of azacitidine alone.

Implications for the Advanced Practitioner

This treatment utilizing pevonedistat in combination with azacitidine is moving into phase III clinical trials. Stay tuned for updates on this new small-molecule inhibitor, as there is a need for therapies that improve outcomes in our higher-risk MDS and CMML patients.

Disclosure: Dr. Tinsley has served as a consultant for Agios, Celgene, Incyte, Jazz Pharmaceuticals, and Novartis, and on the speakers bureaus for Astellas Pharma, Celgene, Incyte, and Jazz Pharmaceuticals.

Abstract 313

COVID-19 in Patients With Hematological Malignancies: High False Negative Rate With High Mortality

Alex Niu, MD, Bo Ning, PhD, Francisco Socola, MD, Hana Safah, MD, Tim Reynolds, Moayed Ibrahim, MD, Firas Safa, MD, Tina Alfonso, Alfred Luk, MD, David M. Mushatt, MD, Tony Hu, PhD, and Nakhle S. Saba, MD

Visit https://doi.org/10.1182/blood-2020-138611 for a complete list of contributor affiliations and full graphics.

Introduction: Patients with hematological malignancies (HM) are uniquely immunocompromised and considered at high risk for COVID-19. However, data regarding the diagnosis, clinical course, treatment, and outcomes of these patients is sparse. In particular, the ability to successfully detect SARS-CoV-2 in patients with HM remains unknown. We have previously reported 2 cases of allogeneic stem cell transplant (SCT) diagnosed with COVID-19 using clustered regularly interspaced short palindromic repeats (CRISPR) technique, following multiple negative nasopharyngeal RT-PCR testing (Niu et al. *Bone Marrow Transplantation - Nature*). Here we examine 29 patients with a variety of HM with high suspicion for COVID-19 based on clinical presentation, lab results, and imaging, whom were tested with CRISPR and/or RT-PCR based techniques. From 3/31/20 to 7/17/20, 29 patients (age 24 to 82) with a variety of HM (20 lymphoid, 9 myeloid; Table 1), 24 of which presented with an undiagnosed respiratory illness and 5 presented while asymptomatic for testing prior to chemotherapy, were evaluated for COVID-19. While 16 patients tested positive for COVID-19 with guideline-directed nasopharyngeal RT-PCR testing (including the 5 asymptomatic patients), 13 patients tested negative with the

same technique. However, based on their clinical history, imaging, and disease course, concern for COVID-19 infection remained in these 13 patients. We then used CRISPR technology available at our institution (Huang et al. *Biosensors and Bioelectronics*) to test 8 patients who initially tested negative by RT-PCR. Surprisingly, 7 of the 8 patients tested positive for COVID-19 with either a blood sample and/or nasal swab for the SARS-CoV-2 specific N gene and ORF1ab gene. Excluding the patients who were negative by RT-PCR and not tested by CRISPR, the rate of false negativity with RT-PCR testing is significantly elevated at 29% (7/24) in our cohort of HM, which compares unfavorably with the expected false negative rates of RT-PCR techniques.

A very high fatality rate was observed with 9 out of the 29 patients (31%) ultimately dying. Fifteen patients were undergoing active chemotherapy, 4 had received an autologous SCT, 6 had received an allogeneic SCT, and 4 were on surveillance. Of the 23 COVID-19 positive patients (by RT-PCR or CRISPR), 8 patients received COVID-19-directed therapy with either hydroxychloroquine/azithromycin, remdesivir, and/or Covid-19 convalescent plasma (CCP) depending on their clinical status, and 4 patients expired. Of the 8 treated patients, 7 improved while 1 patient expired. For the 5 patients who were negative for RT-PCR with no CRISPR completed, 1 patient received hydroxychloroquine/azithromycin proactively due to symptoms and imaging and recovered, while 3 patients expired at outside facilities due to unknown causes. Breakdown of testing and treatment is shown in Fig. 1.

The majority of our patients had undergone SCT or were actively on chemotherapy, notably lymphodepleting chemotherapy. Associated with the fact that COVID-19 is known to worsen lymphopenia, our patient's symptoms and immune response to COVID-19 is likely to differ from immunocompetent hosts. This translated into an overall worse outcome as seen by the high mortality with our patients. In our limited dataset, patients presented with a variety of symptoms ranging from asymptomatic to acute respiratory failure. Intriguingly, the 5 asymptomatic patients had lymphoid malignancies and were on chemotherapy.

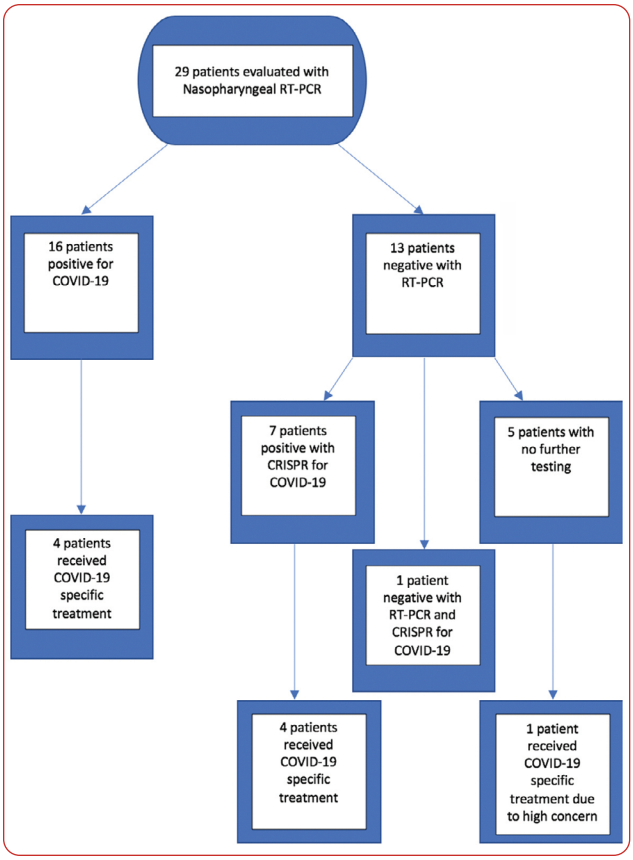

Figure 1. Pathway showing patients who tested positive and negative for COVID-19 via Nasopharyngeal RT-PCR.

It is thus imperative to establish the diagnosis of COVID-19 quickly, as faster initiation of treatment has been associated with better outcomes. The 8 patients who were diagnosed and treated improved substantially. However, as seen by our dataset, a strikingly high false negative rate was observed. Thus, a high clinical suspicion must guide further workup and therapy in patients with HM who present with an undiagnosed respiratory illness consistent with COVID-19. Patients with HM can have a wide variety of presentations when infected with COVID-19. For this select patient population we must establish an algorithm to diagnose COVID-19 efficiently as we reported a high number of initial false negative COVID-19 tests before the more sensitive CRISPR revealed a positive test. In addition, treatment pathways need to be instituted to not only treat COVID-19 infection, but also provide the best treatment for these patient's underlying HM.

The Advanced Practitioner Perspective: Sandra E. Kurtin, PhD, ANP-C, AOCN®

It is hard to believe that the Human Genome Project started in October 1990 and was completed in April 2003 (National Human Genome Research Institute, 2021). Over the past two decades, we have come to better understand that cancers are a result of either germline or somatic genetic and epigenetic alterations with variable incidence and severity based on individual promoting factors. Therapies exploiting genomic targets, transcription processes, or pathways have changed the natural history of many malignancies. Yet, progress in other malignancies have been limited. The unrelenting exploration of the human genome, characterizations of human illness, and the elements of the immune response to illness has led to the more recent development of immunotherapies.

These discoveries would not have been successful without development and standardization of technologies and techniques to elucidate and characterize the genome and the immune system. Pharmacogenomic testing, predictive testing, and prognostic testing using peripheral blood, bone marrow samples, and in some cases saliva, have changed the way we diagnose, risk stratify, and treat malignancies. From this work, precision medicine became the standard way we practice.

Fast forward to 2020, and the unforeseen and devastating COVID-19 pandemic occurs. The application of the knowledge gained through the years of genomic discovery allowed Niu and colleagues to use one of these new techniques, clustered regularly interspaced short palindromic repeats (CRISPR), to interrogate DNA to rapidly detect SARS-CoV-2 in patients with hematologic malignancies where polymerase chain reaction (PCR) testing was negative.

In order to replicate, viruses require an intact DNA viral genome (Redman et al., 2016). CRISPR technologies allow for genomic editing using a single guide RNA (sgRNA) and Cas9, a DNA endonuclease (Redman et al., 2016). CRISPR directs the Cas9 protein to cut a specific DNA (genomic) sequence allowing manipulation of genes involved in viruses and in carcinogenesis (Chen et al., 2019). The potential for benefit to cancer patients includes genome editing of cancer cells, combating carcinogenic viruses, development of therapies that target stromal cells, anticancer drug development, expanding cancer immunotherapy, and oncolytic virotherapy (Chen et al., 2019).

Implications for the Advanced Practitioner

The challenge to maintain a working knowledge of technologic and therapeutic approaches to battle cancer is unrelenting. This abstract by Niu and colleagues provides important information about the limitation of PCR testing for COVID-19 in patients with hematologic malignancies, in particular in patients with lymphopenia. It also explores the impact of the CRISPR-Cas9 system more fully and its application to oncology. Importantly, genomic editing also raises important ethical concerns and will need continued scrutiny to effectively balance therapeutic benefit with any unknown or known potential harm.

As this technology grows, advanced practitioners in oncology will need to know enough about these technologies to be able to describe it to our colleagues and to our patients, and effectively manage patients receiving therapies developed using the CRISPR-Cas9 system.

Disclosure: Dr. Kurtin has no conflicts of interest to disclose.

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Abstract 151

Longitudinal Analysis of Anemia Severity, Treatment and Healthcare Resource Utilization Among Patients With Primary Cold Agglutinin Disease in a Large US Database

Amanda Wilson, Florence Joly, Gandarvaka Miles, Kammy Kuang, and Huy P. Pham, MD, MPH

Visit https://doi.org/10.1182/blood-2020-139637 for a complete list of contributor affiliations and full graphics.

Introduction: Cold agglutinin disease (CAD) is a serious and rare autoimmune hemolytic anemia driven by cold agglutinin autoantibodies, which bind to red blood cells and activate the classical complement system to initiate hemolysis and anemia (Berentsen S. *Hematology Am Soc Hematol Educ Program* 2016). There is limited evidence on the individual and societal impact of CAD. A retrospective study of 27 patients in a US healthcare institute demonstrated fluctuations in severity of anemia over the course of the disease, and significant utilization of healthcare resources (Mullins M et al. *Blood Adv* 2017). The objective of this study was to understand the long-term characteristics and disease burden in patients with primary CAD from a large US Electronic Health Record (EHR) database.

Methods: This retrospective observational cohort study included adult patients from the Optum© EHR database between January 1, 2007 and September 30, 2019 who had ≥1 medical encounter with an autoimmune hemolytic anemia-related diagnosis code, ≥3 documentations (on different dates) of CAD and ≥1 hemoglobin (Hb) value <12 g/dL. The index date was defined as the first mention of CAD; all patients were required to have a 12-month baseline period prior to this. To limit the study to patients with primary CAD, patients were excluded if they had ≥1 medical encounter with mycoplasma, cytomegalovirus and Epstein-Barr at the index date, or ≥1 medical encounter with lymphoma, MALT lymphoma, chronic lymphoid leukemia, Waldenstrom macroglobulinemia or myeloma during the baseline period.

Anemia severity (defined as the lowest Hb value in each study period), utilization of CAD-related therapies, blood transfusions and all-cause healthcare resource utilization (HCRU) were analyzed at baseline and at 6-month follow-up intervals. Although no treatment is approved in CAD, corticosteroids, immunoglobulin, rituximab, immunosuppressants, antineoplastic and biologics were considered as CAD-related therapies to reflect usual practice. Results were stratified by anemia severity category (severe [Hb <8 g/dL], moderate [Hb 8.0-10 g/dL], mild [Hb 10.1-<12 g/dL] or no anemia [Hb ≥12 g/dL]) during each follow-up interval. Severe hemolysis was defined as elevated LDH and/or elevated bilirubin.

Results: A total of 610 adults with primary CAD were included in the study (mean [SD] age 67.9 [14.5] years, 65.4% female). The mean (SD) duration of follow-up was 48.1 (30.6) months; 90% of patients had ≥12 months of follow-up. At baseline (0-6 months prior to first mention of CAD), 47.6% of patients had elevated bilirubin levels and 63.1% had elevated lactate dehydrogenase (LDH) levels.

A high proportion of patients with CAD experienced severe or moderate anemia at baseline and in the 6 months post-baseline; this proportion tended to be lower, but still substantial, throughout the follow-up period (Table). Frequency of moderate/severe anemia or severe hemolysis events per patient year was also higher in the first 6 months: 5.70 (95% CI: 5.00, 6.49), compared with 2.92 (2.30, 3.71) and 2.43 (1.89, 3.11) events at months 19-24 and months 31-36, respectively.

The median number of CAD-related treatments per patient was high in all CAD patients at 6 months and remained high during the follow-up period (Table). The most common therapies used (excluding blood transfusion) were corticosteroids, antineoplastics and biologics. The mean number of blood transfusions per patient was higher in the severe anemia category at all follow-up intervals. The number of hospitalizations and emergency room visits were generally higher in patients with increased anemia severity; outpatient visits were high in all CAD patients and remained so over the study period (Table).

Conclusion: This observational cohort study followed a large sample of primary CAD patients with a 4-year mean follow-up. The results highlight the long-term substantial burden of CAD on patients and healthcare systems, which generally increased with higher severity of anemia. Three

years after diagnosis, the number of moderate to severe anemia or hemolysis events remained high in CAD patients, despite off-label CAD management. The need for blood transfusions was still substantial in the severe anemic population 3 years after diagnosis. This longitudinal analysis illustrates the unmet medical needs in primary CAD.

The Advanced Practitioner Perspective: Sandra E. Kurtin, PhD, ANP-C, AOCN®

Cold agglutinin disease (CAD) is among a heterogeneous group of complement-mediated hemolytic anemias with variable underlying etiologies. The incidence of CAD is estimated to be 16:1,000,000, representing approximately 20% of all autoimmune-mediated anemias (Mullins et al., 2017). The most common feature of CAD is anemia due to the chronic hemolysis resulting from cold agglutinins that bind to red blood cells causing agglutination (Berentsen, 2018). However, patients with CAD may also be at risk for thromboembolic events, acral cyanosis, and in some cases Raynaud phenomenon, particularly when exposed to cold temperatures (Berentsen, 2018). Importantly, primary CAD should be differentiated from secondary cold agglutinin syndrome that is a result of underlying diseases including certain infections, B-cell malignancies, and less commonly other malignancies.

Wilson and colleagues conducted a retrospective observational cohort study to describe the disease burden of primary CAD among a population represented in a large electronic health record database. Retrospective review of claims data offers a way to analyze attributes in rare diseases where prospective trials are not feasible. This analysis included records over a 22-year period, yielding 610 adults meeting criteria for primary CAD, emphasizing the rarity of this disease.

Descriptions of the long-term disease burden for primary CAD, including moderate to severe anemia, hospitalizations, emergency room or urgent care visits, and the frequency of outpatient visits to monitor or treat the disease, offer insights into the patient experience. Current treatments for CAD are largely focused on B-cell inhibition, including anti-CD20 monoclonal antibodies. Sutimlimab, a monoclonal antibody targeting C1s, a serine protease within the C1 complex, and the first step in activating the classical complement pathway of the immune system, is in phase III trials and would represent the first therapy designated for the treatment of primary CAD.

Implications for the Advanced Practitioner

Rare diseases, including CAD, present a unique challenge to advanced practitioners in oncology. The first step is in making the diagnosis. Understanding the differential diagnosis for anemia is key. Learning to ask the right questions in a review of systems and analyzing the chronicity of symptoms and clinical data is essential.

Patients with rare diseases should always be referred to the National Organization for Rare Disorders (NORD) rare disease database and CAD resources (https://rarediseases.org/rare-diseases/cold-agglutinin-disease/). This site also provides resources for clinicians, including a summary of clinical trials, critical for continued characterization of and therapeutic advancement for rare diseases.

Disclosure: Dr. Kurtin has no conflicts of interest to disclose.

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