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Aplastic Anemia & MDS International Foundation (AA&MDSIF): Bone Marrow Failure Disease Scientific Symposium 2018

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ABSTRACT

The bone marrow failure (BMF) syndromes are a group of rare disorders characterized by ineffective hematopoiesis resulting from deficiencies in the hematopoietic stem cell compartment. Although these diseases are typically acquired, some forms (e.g., Fanconi anemia, dyskeratosis congenita, Diamond Blackfan anemia, and Shwachman Diamond syndrome) are inherited. Patients with BMF syndromes can develop peripheral blood cytopenias and pancytopenia, and their disease can ultimately progress to acute myelogenous leukemia (AML).

Research around the world is shedding light on the biology of the BMF syndromes, their clinical effects, and novel treatments. The Aplastic Anemia and MDS International Foundation (AAMDSIF) is an independent non-profit organization whose mission is to help patients and family members cope with BMF syndromes. This report summarizes presentations on the latest scientific discoveries in BMF syndromes from the Sixth International Bone Marrow Failure Disease Scientific Symposium sponsored by AAMDSIF on March 22–23, 2018, in Rockville, Maryland.

1. Introduction

The bone marrow failure (BMF) syndromes are a group of rare disorders characterized by ineffective hematopoiesis resulting from deficiencies in the hematopoietic stem cell (HSC) compartment. Although these diseases are typically acquired, some forms (e.g., Fanconi anemia, dyskeratosis congenita [DC], Diamond Blackfan anemia, and Shwachman Diamond syndrome) are inherited. Patients with BMF syndromes can develop peripheral blood cytopenias and pancytopenia, and their disease can ultimately progress to acute myelogenous leukemia (AML).

The Aplastic Anemia and MDS International Foundation sponsored the Sixth International Bone Marrow Failure Disease Scientific Symposium in Rockville, Maryland on March 22–23, 2018. This article provides an overview of the meeting presentations on recent genetic, genomic, biologic, clinical, and translational discoveries in BMF syndromes.

2. Genetics and genomics of bone marrow failure

2.1. DNA changes that lead to inherited predisposition

Dr. Lucy Godley, University of Chicago, noted that researchers increasingly recognize that inherited predispositions can contribute to the development of myelodysplastic syndromes (MDS) and myeloid malignancies. Dr. Godley recommended that clinicians consider the

Abbreviations: BMF, bone marrow failure; DC, dyskeratosis congenita; AML, acute myelogenous leukemia; MDS, myelodysplastic syndromes; HSC, hematopoietic stem cell; HSCT, hematopoietic stem cell transplantation; PNH, paroxysmal nocturnal hemoglobinuria; OS, overall survival; GVHD, graft-versus-host disease; RBC, red blood cell; IST, immunosuppressive therapy; ATG, antithymocyte globulin; SAA, severe aplastic anemia; MUD, matched unrelated donor; EFS, event-free survival; iPSC, induced pluripotent stem cell; CMML, chronic myelomonocytic leukemia; HMA, hypomethylating agent; PD-1, programmed cell death protein 1; MPN, myeloproliferative neoplasm; FDA, U.S. Food and Drug Administration

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possibility of an inherited predisposition for every patient with a BMF syndrome. In her clinic, almost 20% of patients with a BMF syndrome have an inherited predisposition, and this proportion is likely to grow as research identifies more syndromes. The World Health Organization, National Comprehensive Cancer Network, and European Leukemia Net now recommend testing for germline predisposition mutations for patients with diagnosed MDS [1–3].

Dr. Sharon Savage, National Cancer Institute, discussed genetic and epigenetic changes beyond coding mutations [4,5]. Improving patient care for BMF syndromes requires integrated multidisciplinary approaches that combine etiology, basic science, and clinical research. Longitudinal follow-up is important for monitoring complex phenotype evolution and recognizing patterns. Abnormal telomere biology unites many complex phenotypes previously thought to be separate. Examples include DC, Hoyeraal Hreidarsson syndrome, Revesz syndrome, and Coats plus syndrome. Telomere biology disorders have expanded beyond BMF, and associated genes now include *TCAB1*, *PARN*, *TERT*, and *RTEL1*.

Dr. Savage also discussed DC, a BMF syndrome caused by aberrations in telomere biology. Telomere length by fluorescence in situ hybridization in white blood cells is more than 95% specific and sensitive for distinguishing patients with DC from their unaffected relatives and those with other BMF syndromes [6]. This imaging technology is especially helpful in identifying older patients with less severe phenotypes and is significantly better than quantitative polymerase chain reaction [6,7].

Dr. Inga Hofmann Zhang, University of Wisconsin, and Dr. Jean Soulier, University of Paris Diderot, discussed what constitutes disease progression within the bone marrow. Dr. Zhang reviewed the reasons morphology matters, noting that blast count, dysplasia, and cytopenias can provide clues to underlying genetics. In addition, dyspoiesis and morphology can serve as reminders to test patients with MDS for inherited bone BMF syndromes. Many patients with inherited BMF syndromes have dyspoiesis, offering clues about underlying genetics. For example, patients with Fanconi anemia have low megakaryocyte counts.

Dr. Soulier discussed clonal changes and careful cytology in staging progression in Fanconi anemia. Ninety percent of patients with Fanconi anemia and dysplasia have genomic abnormalities that can be used in treatment decisions [8]. For example, isolated 1q duplication represents clonal hematopoiesis in Fanconi anemia rather than MDS. Dr. Soulier also reviewed ataxia-pancytopenia syndrome, a familial disorder resulting from a gain-of-function germline *SAMD9* mutation that can cause aplasia and myelodysplasia in children [9]. Most patients develop monosomy 7 that can be transient despite some myelodysplastic signs. This syndrome offers an example of clonal evolution with reversion and progression.

2.2. Genetics in the clinic: understanding and interpreting clonality

Dr. Luca Malcovati, University of Pavia, reviewed the significance of somatic mutations in cytopenias of undetermined significance. MDS arises from somatic mutations in HSCs, leading to proliferative advantage and clonal expansion. Additional external factors—such as abnormalities in the bone marrow niche, acute and chronic inflammation, and diminished stem cell pool—can contribute to MDS development by selecting clones and promoting their expansion.

Single mutations in splicing factor genes (*SF3B1*, *SRSF2*, *U2AF1*) can disrupt several cellular processes and might not require additional mutations to transform cells [10–12]. Patients with idiopathic cytopenias of unknown significance who carry somatic mutations have a greater than 90% risk of a myeloid neoplasm. Mutations that are highly predictive for myeloid neoplasm development with MDS include those in splicing factors and epigenetic regulators (e.g., *TET2*, *ASXl1*, and *DNMT3A*) [13]. These mutation patterns are highly specific for MDS and could provide evidence of MDS even without overt bone marrow dysplasia.

Dr. Akiko Shimamura, Dana-Farber Cancer Institute, discussed care for patients with BMF syndromes and known or potential germline predisposition syndromes. Early diagnosis of a germline predisposition syndrome can help determine the appropriate treatment. Certain diagnoses require modifications of transplant conditioning regimens to mitigate long-term effects, and screening is advisable of asymptomatic sibling donors who might carry the same mutation.

Clinicians should suspect germline mutations leading to BMF syndromes or MDS to decrease the number of unrecognized cases. Screening for BMF syndromes in patients with germline mutations is somewhat controversial, but general guidelines are available. For example, first-line screening should consist of complete blood counts. Bone marrow evaluations at baseline (even in patients with normal blood counts) help assess changes over time, but the need for repeat marrow evaluations for screening depends on the patient.

Dr. Alison Bertuch, Baylor College of Medicine, and Dr. Seth Corey, Virginia Commonwealth University, discussed whether to change management based on acquired mutations in patients with inherited BMF syndromes or leukemia. They agreed that the answer is generally no, but it might approach yes for certain mutations. For example, patients with *GATA2* deficiency have a 70% risk of MDS or AML and a risk of greater toxicity with AML-type therapy [14].

These patients need HSC transplantation (HSCT) if they have marrow hypercellularity and refractory cytopenia in childhood or potentially after acquisition of *SETBP1* or *ASXL1* clonal mutations. Ultimately, HSCT should occur before these patients develop abnormal karyotypes, AML, severe immunodeficiency, or severe lung disease. Early HSCT is especially important for patients with *GATA2* deficiency and monosomy 7 or trisomy 8, who have poorer outcomes. Barriers to accurate predictions of MDS or AML in patients with an inherited BMF syndrome include lack of strong genotype-phenotype correlation, host factors (e.g., epigenetics and cooperating genes), clonal dynamics, and lack of certainty about when a clone becomes dominant.

3. PNH research update

Dr. Régis Peffault de Latour, Hôpital Saint Louis, discussed the clinical presentation of paroxysmal nocturnal hemoglobinuria (PNH), a rare acquired disorder related to a *PIG-A* mutation. The signs of PNH are hemolytic anemia, BMF, venous thromboembolism, or some combination [15]. Thrombotic events are the main life-threatening complications and can happen even without overt hemolysis [16–18]. HSCT for PNH showed acceptable overall survival (OS) for hemolysis and aplastic anemia, but results were poorer if thrombosis was present [15]. Moreover, graft-versus-host disease (GVHD) was frequent and affected quality of life. The development of eculizumab, an anti-C5 agent, has had a significant impact on classic PNH (hemolysis without overt BMF), improving long-term OS compared with HSCT and reducing thrombotic event incidence. However, hemolysis can still occur with eculizumab [18–20].

The standard treatment for overt aplastic anemia–PNH syndrome (evidence of intravascular hemolysis and BMF) should be similar to that for aplastic anemia without PNH if no hemolysis is present, although thrombotic risk is still high [21]. For the less frequent simultaneous hemolysis and severe BMF, clinical symptoms guide decision-making: eculizumab and IST can be prescribed using hemolysis or aplasia severity to guide initial treatment [22,23]. Antithrombotic primary prophylaxis has no role in PNH, and thrombotic events should be promptly treated with anticoagulation and eculizumab [15,21].

Dr. Antonio Risitano, Frederico II University of Naples, discussed next-generation complement inhibitors for PNH. The clinical spectrum of responses to eculizumab could range from a complete response to persistent red blood cell (RBC) transfusion dependency, residual anemia, secondary breakthrough hemolysis, or chronic C3-mediated extravascular hemolysis [20]. Genetic polymorphisms or mutations in

genes regulating complement cascade (*CR1* or *C5*) could explain this variability and can affect the degree of C3-mediated extravascular hemolysis resulting from eculizumab [19,20,24,25].

Dr. Risitano described several novel complement inhibitors, dominated by anti-C5 agents (terminal complement inhibitors) and agents targeting non-C5 components (proximal complement inhibitors). ALXN1210 (Alexion) is one of the most advanced terminal complement inhibitors and has a higher anti-C5 affinity and a longer half-life than eculizumab. Preliminary data from two phase III randomized studies in patients with untreated PNH or after eculizumab treatment showed noninferiority of this long-lasting anti-C5 monoclonal antibody [26,27]. Other terminal complement inhibitors under investigation include RO7112689 (Roche) [28], zilucoplan (A101495; Ra Pharma), coversin (Akari) [29], and cemdisiran (Alnylam) [30].

Proximal complement inhibitors include agents targeting the key component of the complement cascade C3 or upstream events involved in alternative pathway activation. The complement inhibitor AMY-101/Cp40 (Amyndas) inhibited lysis and C3 fragment opsonization of PNH erythrocytes in vitro [31]. Other proximal complement inhibitors include TT30 (Alexion) [32,33], compstatin [34], APL-1 and APL-2 (Appelis) [33], ACH-4471 (Achillion) [35,36], and LNP023 (Novartis). Currently, alternative anti-C5 agents have limited benefits compared with eculizumab (except in patients with *C5* mutations). However, these agents might be useful in preventing C3-mediated extravascular hemolysis and intravascular hemolysis.

4. Treatment options for aplastic anemia: are we ready for precision medicine?

Dr. Raul Urrutia, Medical College of Wisconsin, discussed the history of precision medicine, which is broader than genomic medicine. He described the roles of clinomics, pharmacogenomics, epigenomics, the microbiome, functional genomics, and bioinformatics in addition to genomics in the practice of precision medicine. Precision medicine requires use of all these components to diagnose, predict, and prevent diseases and to treat patients with precision. Wearable and portable devices contribute to precision medicine by enabling patients to transmit information passively and automatically to physicians.

Dr. Shinji Nakao, Kanazawa University, discussed the role of glycosylphosphatidylinositol-anchored protein (PNH-type) cells as a prognostic indicator in treating aplastic anemia. The presence of PNH-type cells has proved useful in decision making about treatment for patients with BMF of unclear pathophysiology. Dr. Nakao presented data showing an increased response to immunosuppressive therapy (IST) with cyclosporine and antithymocyte globulin (ATG) in the presence of PNH-type cells, even when clones are small [37]. The clinical threshold for defining the presence of a PNH-type clone is less than 0.01%. Identification of PNH-type cells in patients with late graft failure also predicts improved response to subsequent IST.

Dr. Danielle Townsley, National Heart, Lung and Blood Institute (NHLBI), gave an update on the expanded eltrombopag study [38]. All cohorts received ATG and cyclosporine for 6 months along with eltrombopag starting on day 1 for 6 months or starting on day 14 for 3 or 6 months.

A review of the initial study results show that response rates improved for patients from all cohorts compared with historical controls treated with IST without eltrombopag. Response rates from the cohort treated with eltrombopag for 6 months were highest and led to the cohort's expansion. To date, 88 patients have completed treatment with a response rate of 79% and a complete response rate of 44%. A subset analysis revealed a lower response rate, 72%, in patients younger than 18 years, with 31% achieving a complete response, which is similar to historical data for IST alone. This finding led to the conclusion that adding eltrombopag results in the same improved response rates in children as in adults. A large, randomized controlled trial (NCT02099747) in Europe is following up on Dr. Townsley's results.

Dr. Tom Winkler, NHLBI, presented unpublished results from the most recent study of extended dosing with eltrombopag in 40 patients with refractory severe aplastic anemia (SAA). Twenty patients (50%) responded at 6 months, and most have maintained a hematologic response after eltrombopag discontinuation. Rates of clonal evolution were similar to those in prior studies. These evolutions occur within 3 to 6 months after eltrombopag initiation, are not usually associated with dysplasia, and can be transient in patients lacking high-risk mutations (non–chromosome 7 abnormalities). Numbers of somatic mutation variants did not increase with eltrombopag treatment. Dr. Winkler also reported the results of a study on eltrombopag treatment for moderate aplastic anemia, which found a 52% response rate at 4 months and stable responses in most patients after eltrombopag discontinuation. The only two clonal evolutions were transient. Finally, in Fanconi anemia patients, eltrombopag can stabilize hematopoietic stem and progenitor cells in the presence of interferon-gamma. Based on this concept, a new clinical trial (NCT03206086) using eltrombopag in patients with Fanconi anemia patients will soon accrue patients.

Dr. David Margolis, Medical College of Wisconsin, discussed the history of bone marrow transplantation in SAA. Initially, with the exclusive use of matched sibling donors, the survival rate before the 1980s approached 75% [39]. However, unrelated donor transplant outcomes did not begin to increase toward that number (50–60%) until the 1980s with increased-intensity pretransplant regimens [40]. In the modern era, the survival rate for SAA with bone marrow transplantation is 80% with the addition of pretransplant fludarabine [41]. However, these patients face the same issues as in the 1970s: graft rejection, infection, and GHVD. Newly published data regarding haploidentical transplantation show that these transplants are becoming more common [42]. These advances continue to make cure a possibility for more patients with aplastic anemia.

5. Unrelated donor HSCT as primary therapy for newly diagnosed SAA

Dr. Carlo Dufour, Istituto Giannina Gaslini, compared IST and matched unrelated donor (MUD) HSCT as front-line therapy for children with newly diagnosed SAA. To date, MUD HSCT has been used as a rescue treatment for children after IST failure with excellent outcomes in the most recent studies [43]. In a retrospective controlled study, OS was similar for front-line MUD HSCT (96%) and IST (94%) [44]. However, the event-free survival (EFS) rate was much lower in those treated with IST (40%) than those who underwent HSCT (92%; $p = 0.0001$). Outcomes for up-front MUD HSCT were similar to matched sibling donor HSCT with no statistically significant difference (OS and EFS rates were approximately 90% in both groups). The 2-year OS and EFS rates with up-front MUD HSCT were significantly higher than for MUD HSCT after IST failure (95% vs. 74% for both OS and EFS; $P = 0.02$), suggesting that there may be no point in waiting for IST failure to initiate MUD HSCT.

After idiopathic SAA diagnosis, if no matched sibling donor is available, an unrelated donor search should begin immediately. If a MUD is likely to be available and HSCT is performed within 2–3 months after diagnosis, this option should be pursued after the clinician clearly explains the pros and the cons. Conversely, if transplantation within 2–3 months is unlikely, clinicians should proceed directly to IST.

Dr. Michael A. Pulsipher, Children's Hospital of Los Angeles, commented that the improved MUD HSCT outcomes raise the question of whether to change the current SAA treatment paradigm. Some children do not respond to up-front IST and might require HSCT relatively early. Some of the majority who do respond have a relapse or need long-term IST [45]. Eventually, these children can develop secondary MDS or AML. Only a randomized controlled trial will show whether the current treatment approach needs to change. A pilot clinical trial (NCT02845596) that will enroll 40 patients is now open at 10 centers in the United States.

Dr. Risitano presented data on MUD HSCT in adults. If an HLA-identical sibling is available, the standard SAA treatment in patients younger than 40 is MUD HSCT, and the standard treatment for older patients is IST with or without eltrombopag. On November 16, 2018, the U.S. Food and Drug Administration (FDA) extended the approval of eltrombopag in combination with standard IST to newly diagnosed adults and children 2 years and older with SAA. MUD HSCT is usually considered in patients aged 20 to 40 years or older only after front-line IST failure. Ten-year OS rates range from 85% for ages 1 to 10% to 49% for those older than 40 years [46]. Dr. Risitano recommended starting the search for a MUD as soon as the patient is diagnosed and considering MUD HSCT 3–6 months after the patient does not respond to IST.

Patients who do not have a suitable MUD could be eligible for a cord blood graft if the nucleated cell dose is adequate, but the 3-year OS rate is only 38% [47]. Other options include HSCT with 9/10 or 7/8 HLA antigen-matched donors (3-year OS rate = 57% for both) and haploidentical HSCT, whose 3-years OS rate is similar to that of cord blood transplantation [48–50].

Dr. Amy DeZern, Johns Hopkins University, discussed haploidentical HSCT with post-transplant cyclophosphamide for refractory or relapsed SAA. The conditioning regimen used at John Hopkins includes rabbit ATG, fludarabine, cyclophosphamide, and total body irradiation. After transplantation, the patient receives two doses of intravenous cyclophosphamide, oral mycophenolate mofetil, and tacrolimus to prevent GVHD. All 20 patients with SAA treated with this regimen are alive with no clonality [51]. Only one patient had graft failure. No patients had an aplastic anemia relapse, two patients developed acute grade 2 GVHD, and one patient developed extensive chronic GVHD.

Haploidentical HSCT is reserved for relapsed or refractory aplastic anemia and should be done in an experienced center as part of a clinical trial designed to prevent graft rejection and GVHD [48–50]. The main advantage of haploidentical HSCT is that virtually every patient has a donor who can be available quickly.

Dr. Phillip Scheinberg, Hospital Beneficência Portuguesa de São Paulo, presented three case reports showing the need for a comprehensive approach in treatment algorithms for SAA. He described ways to integrate clinical information and biological data to better treat SAA. Dr. Scheinberg then moderated a roundtable discussion in which participants identified other factors to consider in choosing aplastic anemia treatment, such as genetic mutations, telomere length, reticulocyte count, and presence of a PNH clone. These factors are associated with response to IST [52], long-term complications, and/or disease progression.

6. Biology of MDS and secondary AML

Dr. Coleman Lindsley, Dana-Farber Cancer Institute, described genetic pathways of disease progression in myeloid malignancies. The landscape of common, recurrent somatic alterations in the coding genome of myeloid malignancies has been extensively characterized, revealing a central role for specific mutations in driving the distinctive features of disease biology. Other mechanisms probably contribute to disease pathogenesis, including alterations in the noncoding genome, epigenome, and bone marrow microenvironment [43]. When a clone acquires a driver mutation that causes a selective growth advantage, this mutated cell's progeny gain clonal dominance and may cause clinically apparent disease. Within this dominant clone, additional mutations can cooperate to drive further clonal advantage and define genetically distinct subclones. During progression, mutations become more common and more diverse, leading to increased size of the dominant clone, whose alterations may or may not sweep awau previous clones [44].

Dr. Eirini Papapetrou, Mount Sinai School of Medicine, described the generation of patient-derived induced pluripotent stem cells (iPSCs) covering diverse stages of myeloid malignancies. Dr. Papapetrou identified phenotypes of different disease severities and/or stages, thus delineating a roadmap of disease progression [53]. Both disease progression and reversal can be modeled in Dr. Papatretou's system using genetic correction or introduction of mutations via CRISPR/Cas9. Therefore, iPSCs can be used to assess disease-stage–specific responses to drugs. Dr. Papapetrou used this model to screen 2000 drugs in MDS and healthy cells.

Dr. Britta Will, Albert Einstein College of Medicine, discussed the mechanism of action of eltrombopag in MDS. Eltrombopag stimulates thrombopoietin signaling and formation of megakaryocytes in MDS cells [46]. The drug also increases numbers of immature blood cells without promoting AML development, kills leukemia cells or inhibits their growth, and induces myeloid differentiation. Two randomized studies in low-risk and high-risk MDS achieved their shared primary objective of alleviating thrombocytopenia and reducing clinically relevant thrombocytopenic events, without safety concerns [50,52]. A randomized phase III clinical trial of eltrombopag plus azacitidine vs azacitidine alone in MDS was stopped early because the combination worsened platelet recovery, induced lower response rates, and showed a trend toward increased rates of progression to AML [54]. These findings might reflect inhibition of the effects of azacitidine by eltrombopag.

Dr. Zuzana Tothova, Dana-Farber Cancer Research Institute, described cohesin mutations in MDS. Cohesin forms a multimeric protein complex and plays important roles in many different processes, including DNA replication and repair. Mutations in genes that control the cohesin complex (including *STAG2*) are mutually exclusive and develop early in MDS progression. Cohesin defects are associated with poor OS [55]. The *STAG2*-mutated cohesin complex interferes with DNA replication and repair, chromatin binding, and gene expression. Cells with these mutations are, in vitro and in vivo, more sensitive to poly-ADP ribose polymerase inhibitors than wild-type cells, suggesting the potential for a phase I clinical trial with these agents in MDS.

Dr. Stephanie Halene, Yale University, reviewed the challenges of studying MDS biology, including the poor growth in culture of MDS HSCs, limited ability of genetically modified mouse breeds to fully recapitulate human disease, and poor engraftment of MDS HSCs in immunodeficient mice. Synergy between multiple humanized cytokines might enable the full recapitulation of human myeloid development and function in mice. Dr. Halene generated immunodeficient *Rag2-/-Il2rg-/-* mice in which the genes encoding human macrophage colony-stimulating factor, human interleukin-3, granulocyte-macrophage colony-stimulating factor, and human thrombopoietin (human cytokines essential for hematopoiesis) are knocked out [56]. These mice permit human hematopoiesis, efficiently engraft all subtypes of MDS, and can be used to compare MDS HSC function and activity with those of normal HSCs. This model is ideal for studying and developing new MDS treatments.

Dr. Robert Bradley, Fred Hutchinson Cancer Research Center, focused on recurrent but rare splicing factor mutations in MDS. Collectively, these mutations are the most common class in MDS, occurring in more than 50% of patients [57]. Most studies focus on the highest-frequency mutations, but each mutated protein has multiple mutational hotspots. Splicing factor mutations might be better classified by molecular mechanism than cellular phenotype because animal studies cannot be conducted for all splicing mutations and these mutations alone do not induce malignant transformation. For example, *SRSF2* mutations alter recognition of exonic motifs to drive MDS, and *U2AF1* mutations alter 3′ splice site recognition [57]. Many low-frequency *SRSF2* mutations act as drivers with biological effects similar to those of more common mutations.

7. Nontransplant treatments for MDS and secondary AML

Dr. Olatoyosi Odenike, University of Chicago, described next-generation hypomethylating agents (HMAs) in high-risk MDS and AML.

Current HMAs, such as azacitidine, provide important clinical benefits for patients with high-risk MDS, but the overall response rate is about 50% and only 10–20% of patients have a complete response. Furthermore, almost all responders subsequently relapse [58].

Guadecitabine, a dinucleotide of decitabine and deoxyguanosine linked by a phosphodiester bond, is resistant to deamination by cytidine deaminase, the main enzyme responsible for degrading its active metabolite, decitabine, resulting in prolonged drug exposure in vivo [59]. In a phase II clinical trial in treatment-naive patients with intermediate- or high-risk MDS or chronic myelomonocytic leukemia (CMML), this drug was active and well tolerated, even in the presence of adverse biological features [60]. A phase III clinical trial (NCT02907359) is evaluating guadecitabine in high-risk MDS or CMML following failure or relapse after treatment with azacitidine, decitabine, or both. Oral HMAs should enable extended administration and prolonged hypomethylation, but these drugs are rapidly cleared in the gut and liver by cytidine deaminase. A phase I study of oral decitabine plus an oral cytidine deaminase inhibitor showed encouraging preliminary results [61]. Oral formulations of azacitidine are also being studied in patients with low-risk MDS or those who do not respond to subcutaneous azacitidine [62].

Dr. Guilermo Garcia-Manero, MD Anderson Cancer Center, discussed the importance of HMA schedules and doses. A phase II, multicenter, open-label study found that three different azacitidine dosing schedules were safe and resulted in RBC transfusion independence [63]. The recommended dose of decitabine for MDS is 20 mg/m^2/day for 5 consecutive days. A recent study demonstrated that patients with AML and MDS who had high-risk cytogenetic abnormalities, *TP53* mutations, or both had positive clinical responses and consistent, but incomplete, mutation clearance after serial 10-day courses of 20 mg/m^2/day decitabine [64]. Lower doses of decitabine per cycle can also be effective in lower- or intermediate-risk MDS [65]. For patients with untreated, lower-risk MDS, Dr. Garcia-Manero proposed using lower doses of HMAs or lenalidomide and, for untreated high-risk MDS, standard doses of HMAs, a similar regimen to that for AML, or HSCT.

Dr. Naval Daver, MD Anderson Cancer Center, described numerous new treatments for MDS and secondary AML. Monoclonal antibodies in AML therapy include naked antibodies against AML surface antigens, such as CD33 (e.g., lintuzumab) or CD38 (e.g., daratumumab); anti-CD33 antibodies conjugated to toxins (e.g., gemtuzumab); anti-CD123 formulations (e.g., SL-401); and antibodies conjugated to radioactive particles (e.g., I- or Ac-labeled anti-CD33) [66]. Approaches to harness the body's own T cells against AML include antibodies that recruit and induce cytotoxicity of tumor cells by T cells (e.g., bispecific T-cell engagers) or that block immune checkpoint receptors CTLA4 (e.g., ipilimumab) or programmed cell death protein 1 (PD-1)/programmed death receptor ligand-1 (e.g., nivolumab) on T cells, unleashing patients' T cells against leukemic cells [67].

Single-agent immune checkpoint inhibitor therapy has shown modest clinical efficacy in AML and MDS [68]. HMAs both enhance antitumor immune response and dampen immune response by upregulating inhibitory immune checkpoint molecule expression. Immune checkpoint molecule upregulation might be an important mechanism of azacitidine resistance. Multiple clinical trials combining HMAs with immune checkpoint blockade have shown encouraging and durable responses [68].

Dr. Mikkael Sekeres, Cleveland Clinic, reviewed HMA-based combination therapy. Drugs studied in combination with HMAs include romiplostim, a thrombopoietin mimetic that increases platelet counts, and histone deacetylase inhibitors (e.g., entinostat, pracinostat, and vorinostat) [69]. The combination of HMAs and histone deacetylase inhibitors increased side effects while offering response rates similar to those of each agent alone [70]. Dr. Sekeres reviewed the rationale for PD-1 blockers plus azacitidine: HMAs induce PD-1 expression on T cells in the MDS microenvironment, likely hampering the immune response to MDS blasts [71]. Thus, activation of the PD-1 checkpoint during HMA treatment might be a resistance mechanism that could be overcome by combination therapy with a PD-1 pathway inhibitor.

Dr. Aristoteles Giagounidis, Marien Hospital Düsseldorf, described novel therapies for anemia in low-risk MDS. Erythropoiesis-stimulating agents are the top choice. A double-blind, placebo-controlled study showed that epoetin-α in lower-risk MDS reduced the need for RBC transfusions and increased the time to first transfusion compared with placebo [72]. Lenalidomide is the first and only MDS therapeutic agent that targets a cytogenetically defined disease subset, MDS with chromosome 5q deletion [73]. This drug results in RBC transfusion independence in about 25% of patients with lower-risk MDS with del(5q) by suppressing the malignant clone to restore effective erythropoiesis. In non-del(5q) MDS, lenalidomide restores effective erythropoiesis by enhancing erythropoietin receptor–initiated transcriptional response and is a second-line therapeutic option for these patients [74]. Luspatercept, a novel fusion protein, blocks the transforming growth factor β superfamily inhibitors of erythropoiesis. In a phase II study in lower-risk MDS, the overall response rate for luspatercept was 73%. Luspatercept could therefore provide a novel therapeutic approach in this setting [75].

Dr. Eric Padron, H. Lee Moffitt Cancer Center, reviewed therapeutic strategies for CMML. This disease is characterized by peripheral blood monocytosis, marrow dysplasia, cytopenias, frequent extramedullary involvement by clonal cells with mutations in a small group of genes (e.g., *TET2*, *ASXL1*, and *SRSF2*), and a propensity for progression to AML [76]. On average, survival after diagnosis is 32 months [77]. Upfront HSCT is recommended for higher-risk CMML, based on 10 retrospective studies showing that this procedure prolongs survival [78]. Hydroxyurea and other cytoreductive agents have been used to control myeloproliferative neoplasm (MPN)-like features in CMML, and epigenetic modifiers (e.g., azacitidine or decitabine) have been used for MDS-like features [79]. Newer drugs exploiting molecular and epigenetic abnormalities in CMML (e.g., ruxolitinib, a JAK2 inhibitor) are being developed [80]. CMML-specific response criteria are needed to improve clinical outcomes.

Dr. Geoffrey Uy, Washington University, described emerging agents for secondary AML, which occurs after MDS/MPN or as a complication of cytotoxic chemotherapy or radiotherapy for an unrelated disease. Patients with secondary AML have a higher frequency of adverse-risk karyotype and more comorbidities, and they tend to be older and have poorer performance status than those with de novo AML. Therefore, intensive chemotherapy, the standard treatment for primary AML, is inappropriate for secondary AML. Several novel therapies that are different from HMAs are being studied. In a phase III study in 309 older patients with newly diagnosed secondary AML, CPX-351, a combination of liposomal daunorubicin and cytarabine, significantly improved median OS and had a significantly higher overall remission rate [81]. CPX-351 is now the only treatment for secondary AML with FDA approval. In a phase I/II open-label trial, a combination of venetoclax, a BCL-2 selective inhibitor with FDA approval in CMML, with low-dose cytarabine in treatment-naïve patients led to a complete response rate of 26% [82].

Glasdegib, a hedgehog pathway smoothened inhibitor, reduced leukemia stem cells from patients with AML, downregulated hedgehog target genes involved in leukemia stem cell maintenance, and significantly reduced tumor burden [83]. In a phase II study [84], 132 patients with previously untreated AML or high-risk MDS who were ineligible for intensive chemotherapy were treated with low-dose cytarabine and oral glasdegib or cytarabine alone. Complete response rates were significantly higher for the combination treatment. Therefore, adding glasdegib to low-dose cytarabine might be an option for AML or high-risk MDS.

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