Myelodysplastic Syndromes: Recent Advancements in Risk Stratification and Unmet Therapeutic Challenges

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OVERVIEW

Significant advances have been achieved in understanding and treating myelodysplastic syndromes (MDS) in the past decade. For the first time, three drugs were approved specifically for this disease. Novel sequencing techniques have expanded our understanding of the molecular basis of MDS. Several clinically significant recurrent gene mutations have been identified. The classification and risk stratification of MDS continues to evolve in light of such advances. However, treatment options remain limited and novel therapeutic strategies are needed. In this review we address key questions for management of MDS. How do we better classify and risk stratify MDS, tailoring treatment accordingly? How do we diagnose and manage the challenging group of patients with MDS/myeloproliferative neoplasms (MPN) overlap? And finally, what is on the horizon for novel therapies?

MDS are a group of bone marrow (BM) failure disorders that share several key features. These include the presence of clonal hematopoiesis, inefficient differentiation resulting in cytopenias of the peripheral blood, and an increased risk of transformation to acute myeloid leukemia (AML). MDS are considered clinically heterogeneous conditions because they can present with widely varying degrees of severity and because patients with similar features at diagnosis can have large differences in how their disease evolves over time. In this review we highlight recent advancement in risk stratification, address the difficult-to-manage MDS/MPN, and overview the evolving novel strategies in treatment.

PART I: NEW MODELS OF CLINICAL- AND MOLECULAR-RISK STRATIFICATION IN MDS

MDS classification schemes have been created to identify subsets of patients that share disease features. The goal of these systems is to define MDS subtypes that have common molecular causes, responses to treatment, and similar prognoses. The current standard is the 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms. MDS subtypes are defined by the number of dysplastic cell lines, the proportion of myeloblasts, and in the case of patients with a sole deletion of chromosome 5q (5q-), by the presence of a cytogenetic abnormality. Molecular genetic abnormalities are not considered in the WHO classification.

Prognostic Scoring Systems

The WHO classification system for MDS defines disease subtypes that share prognostic features, but does not include many elements that contribute to the accurate determination of prognosis. A prognostic scoring system based on the WHO classification called WHO Prognostic Scoring System (WPSS) is in use today, namely in Europe. Several additional risk stratification models have been developed and validated (Fig. 1).

International Prognostic Scoring System (IPSS) and International Prognostic Scoring System Revision (IPSS-R). Since its release in 1997, IPSS has become the standard clinical tool used for risk assessment of patients with MDS. It has allowed for the comparison of different patient groups treated in clinical trials and has formed the foundation for clinical guidelines and therapeutic indications. Because it preceded the first WHO classification system, the IPSS was designed for a slightly different patient population. The IPSS included patients with up to 30% blasts in their BM (considered to have AML by WHO criteria). Several limitations of the IPSS have become evident over time. These include a relative over-weighing of blast percentage, underrepresentation of cytogenetic abnormalities, and an underestimation of risk in some patients, particularly those with severe cytopenias and few other risk factors.

A revision of the IPSS (IPSS-R) has recently been published (Fig. 2). It was created by examining data from over 7,012 patients (compared with 816 for the IPSS). As with the IPSS,
patients were risk stratified only at the time of diagnosis, could not have therapy-related disease, and could not have received disease-modifying treatments. The IPSS-R risk model addresses some of the deficiencies of the IPSS. Most importantly, the IPSS-R considers a much larger set of chromosomal abnormalities and better stratifies the prognostic risk associated with these. The relative weight of BM blasts is decreased and blast proportions between 2% and 5% are recognized as adverse. The IPSS-R considers cytopenias individually and weighs their severity instead of just their presence. Finally, the IPSS-R assigns patients to one of five risk groups instead the four in the IPSS. Like the IPSS, the IPSS-R does not consider age as an explicit variable. Instead, the cutoffs for risk groups can be adjusted by age once scores have been calculated. The net result is better risk stratification in the IPSS-R compared with IPSS without the need for additional testing. However, this improvement comes at the cost of much greater complexity that may slow the clinical adoption of the IPSS-R. Online calculators are available to facilitate the determination of IPSS-R risk groups (ipss-r.com).

**KEY POINTS**

- The successful adoption of the International Prognostic Scoring System has prompted the development of several prognostic models aimed at improving risk stratification for myelodysplastic syndromes (MDS). Recent discoveries into the genetic basis of MDS may limit the longevity of these prognostic models that do not include molecular features.

- Mutations of several genes in MDS have been shown to carry independent prognostic significance, and tests for these abnormalities are becoming clinically available. Future evidence that somatic mutations can improve the diagnosis and potentially predict response to therapy will drive the demand for genetic testing.

- Patients with MDS/MPN have their own distinct disease biology and outcomes than patients with a pure MDS or MPN. We are beginning to understand that diagnostic and treatment approaches will need to be tailored specifically for patients with MDS/MPN and likely their individual subtypes.

- Advances in the understanding of molecular genetics, epigenetics, and microRNA patterns may provide insights into the diagnosis, prognosis, and therapies in MDS/MPN. For example, the presence of SF3B1 mutations in 83% of patients with refractory anemia with ring sideroblasts associated with marked thrombocytosis offers the possibility of a synthetic lethal approach by using spliceosome inhibitors.

- Several novel agents for treating MDS are being explored. The better understanding of the disease underlying biology with the advent of new molecular technology will hopefully translate into identifying novel therapeutic targets.

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**FIG 1. Point values for elements of the WPSS, LR-PSS, and MDA-CSS. Each panel includes the proportion of patients in risk groups associated with these prognostic scores and their estimated median survival. Median survival ranges for the WPSS were estimated from the article describing this model.**

**MD Anderson Lower-Risk Prognostic Scoring System (LR-PSS).** This model is a secondary classifier in that it was created by examining 856 patients with MDS already assigned to the low- or intermediate-1 risk groups by the IPSS ("lower" risk). In the LR-PSS, lower-risk patients are reclassified on the basis of cytogenetic abnormalities, age, BM blast percentage, anemia, and thrombocytopenia with added weight for severe thrombocytopenia (Fig. 1). Patients are then assigned to one of three risk categories with nearly a third assigned to category 3, the group with the greatest risk. Patients
patients with category-3 disease have a median overall survival that is nearly identical with that predicted for patients with intermediate-2 disease by using the IPSS, thus identifying them as actually having “higher” risk disease. This is clinically important because practice guidelines for MDS recommend more aggressive disease-modifying therapies for patients with higher-risk disease while sparing lower-risk patients the potential morbidity of these treatments.

MD Anderson Comprehensive Scoring System (MDA-CSS). A more comprehensive prognostic model (MDA-CSS) that addresses several shortcomings of the IPSS was proposed. To create this model, a total of 1,915 patients with MDS were examined. The final model weighs several features not considered explicitly by the IPSS such as age, poor-performance status, and leukocytosis. Like the IPSS-R, the MDA-CSS considers anemia and thrombocytopenia separately, with added weight for patients with extremely low platelet counts (Fig. 1). Patients are assigned to one of five risk groups instead of the four included in the IPSS. Finally, the IPSS-R stratifies patients into five risk groups instead of the four included in the IPSS. This figure is adapted from Steensma DP. An updated risk model that improves prognostic forecasting in myelodysplastic syndromes. *Hematologist.* 2012. 9,6:10. Copyright American Society of Hematology, used with permission.

Abbreviations: IPSS, International Prognostic Scoring System; IPSS-R, a revision of IPSS.

**FIG 2.** Comparison of the (A) IPSS and (B) IPSS-R. The IPSS-R includes more cytogenetic risk groups and more chromosomal abnormalities. It decreases the relative weight of increased bone marrow blasts percentage. And, it considers cytopenias individually with additional weight given to more severe cytopenias. Finally, the IPSS-R stratifies patients into five risk groups instead of the four included in the IPSS. This figure is adapted from Steensma DP. An updated risk model that improves prognostic forecasting in myelodysplastic syndromes. *Hematologist.* 2012. 9,6:10. Copyright American Society of Hematology, used with permission.

Molecular Markers of Prognosis

Despite their utility, these scoring systems do not consider all of the variables that contribute to the prediction of prognosis. Other clinical features, such as comorbidities, have a significant influence on outcomes. There are also other features like ferritin, β2-microglobulin, and albumin levels that have been linked to survival in MDS. But the most notable elements missing from commonly used prognostic scoring systems are molecular genetic features, particularly mutations of individual genes.

Over 40 recurrently mutated genes have been identified in patients with MDS, including many found in more than 10% of cases. For example, mutations of splicing factor genes alone are present in over 50% of patients, making these lesions more common than cytogenetic abnormalities. It is likely that every patient with MDS carries one or more somatic mutations responsible for the development and progression of their disease. The diverse manner in which these driver mutations coexist can help explain the clinical variability associated with MDS and should therefore, aid in the classification and prediction of outcomes for patients.

In MDS, there is substantial evidence that single gene mutations provide prognostic information that is independent of the IPSS and other scoring systems. Several studies have identified prognostic significance for mutations of individual genes such as TET2, NRAS, TP53, RUNX1, ASXL1, DNMT3A, and SF3B1. However, mutations in these
genes can coexist and are often associated with clinical features, making it difficult to know how best to weigh each abnormality toward the determination of prognosis. This becomes particularly important if a mutation in one gene “trumps” the presence of another, thus altering its clinical relevance. This is true with regard to karyotype (e.g., 5q- is considered favorable even if it coexists with another abnormality, unless that second lesion is a deletion of chromosome 7).

In one study that examined 439 MDS BM samples for mutations in 18 genes, mutations of TP53, EZH2, ETV6, RUNX1, and ASXL1 were individually associated with an overall survival that was significantly shorter than predicted by the IPSS (Fig. 3). Nearly a third of patients harbored mutations in one or more of these genes. Patients with MDS with adverse mutations had a median survival that was closest to that of patients in the next-highest IPSS risk group, suggesting a simple way to incorporate mutational information into an existing prognostic system. This “upstaging” of patients by genetic testing has important clinical implications because MDS treatment guidelines are largely driven by the predicted prognosis.

Confirmation of these results in larger studies that include more recently discovered gene mutations will be required to adequately incorporate molecular genetics into clinical prognostic scoring systems. However, additional challenges will have to be addressed in parallel.

Challenges to the Clinical Use of Molecular Genetics in MDS

A major obstacle impeding the use of molecular genetic tests in the care of patients with MDS is a lack of availability. Only some academic centers and commercial interests have begun to offer sequencing-based tests capable of identifying mutations in recurrently mutated MDS genes. However, evidence for the utility of genetic markers across all cancer types continues to increase, and capacity to test for these abnormalities is becoming more widespread. The remaining challenge will be how to interpret the results of sequencing-based tests and incorporate them into the standard of care.

Genetic variants are not binary (i.e., simply present or absent). There are nuances that can affect their clinical relevance. Some mutations will be present in every diseased cell. Others might be found in subclones that expand during the evolution of disease. Therapies that target pathways affected by mutations might not be beneficial unless that mutation is in the dominant clone. Similarly, a mutation associated with drug resistance could predict poor outcomes even if it is found only in a tiny disease subclone. Another nuance involves variants that can be present in different configurations. Mutations of TP53 can be heterozygous to a normal (unmutated) allele, homozygous (from mitotic recombination replacing the remaining normal allele), hemizygous (from deletion of the remaining normal allele), or compound heterozygous with each allele carrying a different mutation. The disease phenotype, including prognosis, could vary between these configurations for some genes, but not for others. Even different types of mutations within the same gene could manifest differently. The TET2 gene, for example, can acquire very disruptive frameshift mutations, but often will carry a missense mutations predicted to be less damaging. Whether these types of abnormalities have different clinical significance is not known. Silent mutations that do not change the amino acid sequence and mutations known to be common germ line variants may be incidental and have little influence on disease phenotype, whereas frameshift mutations, premature stop codons, and amino acid changes at

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**FIG 3.** Patients with MDS with one or more mutations in TP53, EZH2, ETV6, RUNX1, or ASXL1 have a shorter overall survival than predicted by the IPSS. Panels A through C show the overall survival of patients in the low, Intermediate-1, and intermediate-2 risk groups, respectively, stratified by the presence and absence of mutation in one or more of the five genes shown have prognostic significance independent of the IPSS. The overall survival curve for patients in the next-highest IPSS risk group is included for comparison. From Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplastic syndromes. *N Engl J Med.* 2011;364:2496-2506. Copyright 2011 Massachusetts Medical Society. Reprinted with permission.

Abbreviation: IPSS, International Prognostic Scoring System.
commonly mutated hotspot codons are more likely to be disease related.

Comprehensive sequencing reports will need to include the mutation profile of several MDS-related genes, the nature of the mutations present, the frequency at which they were detected, and ideally, a prediction about their overall clinical relevance. This may require the interpretation of a pathologist or expert in cancer genetics.

**PART II: DIAGNOSIS AND TREATMENT OF MDS/MPN**

Myeloid hematologic cancers with overlapping features of MDS and MPN are classified into MDS/MPN overlap neoplasms. These include CMML, atypical chronic myeloid leukemia, juvenile myelomonocytic leukemia, and MDS/MPN-unclassifiable (MDS/MPN-u), which includes the provisional entity of refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T).26

### TABLE 1. Diagnostic Criteria for Myelodysplastic/Myeloproliferative (MDS/MPN) Neoplasms according to the 2008 World Health Organization Classification

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<th>Criteria</th>
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| CMML | 1) Persistent peripheral blood monocytosis (>1 × 10^9/L).  
2) No Philadelphia chromosome, bcr-abl fusion gene, PDGFRα or PDGFRβ gene rearrangement.  
3) Peripheral blood or bone marrow blasts of < 20% (blasts in the context includes myeloblasts, monoblasts, and promonocytes).  
4) Presence of dysplasia in ≥ 1 hematopoietic lineages. |
| JMML | 1) Presence of peripheral blood monocytosis (>1 × 10^9/L).  
2) Presence of blasts which includes promonocytes accounting for < 20% of the total WBC count in the PB and BM.  
3) Absence of the Philadelphia chromosome or bcr-abl fusion gene plus two or more of the following: a) hemoglobin F increased for age. b) presence of immature granulocytes in the PB. c) WBC count > 10 × 10^9/L. d) presence of the clonal cytogenetic abnormality (including −7), and/or. e) in vitro hypersensitivity of myeloid progenitors to GM-CSF. |
| Atypical CML | 1) Peripheral blood leukocytosis (WBC ≥ 13 × 10^9/L) due to increased neutrophilic precursors and mature neutrophils with prominent dysgranulopoiesis.  
2) Peripheral blood or bone marrow blasts is ≥ 20%.  
3) No Philadelphia chromosome, bcr-abl fusion gene, PDGFRα or PDGFRβ gene rearrangement.  
4) Neutrophil precursors (promyelocytes, myelocytes, metamyelocytes) ≥ 10% of leukocytes.  
5) Minimal absolute basophilia (< 2% of leukocytes).  
6) No or minimal absolute monocytosis (< 10% of leukocytes).  
7) Presence of a hypercellular BM with granulocytic proliferation and dysplasia; with or without an accompanying dysplasia of the erythroid and megakaryocytic lineages. |
| MDS/MPN unclassifiable (RARS-T as a provisional entity) | MDS/MPN unclassifiable | 1) The case has clinical, laboratory, and morphological features of one of the categories of MDS and peripheral blood and BM blast percentages does not fulfill the criteria for AML, and  
2) has prominent myeloproliferative features exemplified by thrombocytosis (≥ 450 × 10^9/L) associated with megakaryocytic proliferation or PB leukocytosis (WBC ≥ 13 × 10^9/L) with or without splenomegaly, and  
3) has no preceding history of an underlying MPN or MDS, no history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic or myeloproliferative features, no Philadelphia chromosome, bcr-abl fusion gene, PDGFRα or PDGFRβ gene rearrangement, and absence of isolated del(5q), t(1;3)(q21;q26) or inv(3)(q21q26), or  
4) the patient has de novo disease with mixed myeloproliferative and myelodysplastic features and cannot be assigned to any other category of MDS, MPN, or of MDS/MPN. |
| RARS-T | 1) A minimum platelet count of ≥ 450 × 10^9/L  
2) Presence of ring sideroblast (RS) in the BM (≥ 15% RS)  
3) Presence of megakaryocytic atypia resembling those of essential thrombocythemia or myelofibrosis |

Abbreviations: CMML, chronic myelomonocytic leukemia; JMML, juvenile myelomonocytic leukemia; WBC, white blood cell; PB, peripheral blood; BM, bone marrow; GM-CSF, granulocyte-macrophage colony-stimulating factor; CML, chronic myelogenous leukemia; RARS-T, refractory anemia with ring sideroblasts associated with marked thrombocytosis; MDS, myelodysplastic syndromes; AML, acute myeloid leukemia; MPN, myeloproliferative neoplasms.
Relatively little is known about the clinicopathologic behavior of MDS/MPN and treatment of those patients is based on extrapolation from MDS or AML studies, resulting in limited responses, inaccurate prognosis, and variability in survival outcomes. The increasing number of biologic studies supporting the distinction of MDS/MPN from other myeloid neoplasms has brought greater awareness about the need to study MDS/MPN as its own entity. In this review we focus on CMML and MDS/MPN-u.

**Chronic Myelomonocytic Leukemia**

CMML is the most common MDS/MPN subtype. The median age at diagnoses is age 65 to 75. It is more common in males (1.5–3:1:1).27

**Diagnosis.** Most patients eventually diagnosed with CMML initially present with increased white blood cell (WBC) counts with or without concomitant anemia, and persistent monocytosis. The diagnosis is made on the basis of the 2008 WHO classification criteria (Table 1).

Persistent monocytosis (>1 × 10⁹/L) in the peripheral blood (PB) is an essential finding. Leukocytosis with neutrophilic and monocytic predominance can be seen, along with dysplasia, although some may present with normal or low WBC counts. Eosinophils may also be increased, and if absolute eosinophils count was 1.5 × 10⁹/L or greater may suggest a diagnosis of CMML with eosinophilia. Molecular testing for chromosomal abnormalities in PDGFRA, PDGFRB, or FGFR1 will be needed, as these findings can dictate therapy with tyrosine kinase inhibitors (TKI). Platelet counts can be decreased or normal in numbers. Anemia is commonly observed.

The BM is typically hypercellular with prominent granulocytic hyperplasia. Monocytic proliferation may be noted, as can dysplasia of one or more hematopoietic lineages. Reticulin fibrosis is present in 30% of patients. Mature plasmacytoid dendritic cells may be present in the core biopsy. Patients diagnosed with CMML can be further subdivided into CMML-1 (with a peripheral blast count of less than 5% with no Auer rods, or BM blasts less than 10%) and CMML-2 (with PB blast counts from 5% to 19%, the presence of Auer rods, or BM blasts less than 10%). Also patients can be divided into proliferative CMML (WBC >13,000) or dysplastic CMML (WBC <13,000).

**Cytogenetics/molecular genetics.** Traditional metaphase cytogenetic techniques and fluorescent-in situ-hybridization can detect chromosomal abnormalities in 20% to 40% of patients with CMML. The changes include +8, −7, −7q, −X, −Y and 12p abnormalities and may affect prognosis (Table 1).28 The cytogenetic detection rate can be further improved to 60% by single nucleotide polymorphism arrays29 and may affect prognosis.30 Careful attention to exclude monotypic cases caused by either t(9;22; q34;q11.2) or PDGFRA/PDGFRB rearrangements needs to be made. Patients with features of CMML but with the rare t(5;12) are best categorized as myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRB. These conditions are responsive to TKI.

Molecular genetics has advanced our understanding of CMML biology. After the initial identification of RAS gene mutations, the molecular profile of CMML continues to grow and includes TET2 (49% to 61%), ASXL1 (43% to 44%), DNMT3A (10%), UTX (8%), EZH2 (6% to 10%), IDH1/2 (4%), CBL (14% to 19%), KRAS (7% to 11%), NRAS (4% to 16%), RUNX1 (22%) and JAK2V617F (1% to 7%).29,31 Mutations are not always mutually exclusive; the presence of three or more genetic mutations are found more frequently in advanced phases of CMML: AML evolving from CMML (25%) versus CMML-2 (19%) versus CMML-1 (6%)32 RAS with RUNX1 mutations32 and RUNX1 with Flt-3, NRAS, or KRAS can occur together.33 Spliceosome mutations like SRSF2 (36% to 47%), U2AF1 (13%), and SF3B1 (6%) are also frequent in CMML.31 Mutations in SETBP1 were also noted in 4% of patients with CMML.34

**Treatment.** Therapy for CMML begs, borrows, and steals from therapies for MDS and AML. Treatments are divided into cytotoxic and epigenetic therapies. Although topotecan-based regimens or low-dose cytarabine can lead to complete response (CR) rates of 27% to 40%, median survival remains short, usually less than 12 months.35 Similarly, hypomethylating agents have been used with some success in CMML, with overall response rates generally around 40%, but again with typical survival being less than 2 years. Hydroxyurea may be used palliatively. Clinical trials specifically directed toward patients with CMML are needed (Table 2). Furthermore, recent data on the importance of molecular mutations in predicting response to therapy in MDS, such as molecular abnormalities along methylation pathways such as TET2 and DNMT3A may be useful in identifying patients with CMML more responsive to hypomethylating agents.36

Despite being the most common subtype of MDS/MPN, data on allogeneic hematopoietic stem-cell transplantation (AH SCT) in CMML is limited. To date, there has not been a prospective trial designed for this group, so the ideal conditioning regimen and optimal time of transplant is unclear. One report of 197 patients with CMML gathered from several AH SCT studies reported a long-term survival of 18% to 75% at 2 to 10 years and relapse rate at 2 to 4 years of 17% to 63% in earlier studies and 25% to 57% in later studies. This is unfortunate considering that the median survival is only approximately 20 months for patients with CMML, and the curative potential of AH SCT for patients with CMML (Table 3).37 Improved prognostication in patients with CMML complemented by understanding disease biology may allow better identification of patients best managed with AH SCT.38

**MDS/MPN-u Provisional Entity RARS-T**

The true incidence of MDS/MPN-u and RARS-T is not known. In one study, MDS/MPN-u that included RARS-T accounted for 12% of the total MDS and MDS/MPN cohort and 43% of the MDS/MPN cohort. RARS-T, on the other
hand, accounted for just 5% of the total MDS and MDS/MPN group and 17% of the MDS/MPN cohort.30

Diagnosis. Cytopenias, specifically anemia, is common and, in general, is the primary presenting feature, along with the thrombocytosis. With time, some patients with RARS-T may develop normal or low platelet levels, similar to what can occur with patients with essential thrombocytosis. Hepatosplenomegaly may also occur. An increased rate of thromboses was observed in RARS-T with SF3B1 mutations.39 RARS-T remains a provisional entity in the 2008 WHO classification, the explanation being that RARS-T is not a distinct disease and rather just an MDS or MPN that subsequently acquired RS as a secondary form of dysplasia40 or the occurrence of two rare diseases in the same patient (Table 1).

Most patients with MDS/MPN-u have either a normocytic or macrocytic anemia. The WBC count can be either low or mildly increased with variable heterogeneity in the differential. PB blasts if present are less than 20%. With RARS-T, features of RARS (anemia, absence of PB blasts, dysplastic changes in the erythroid lineage, presence of ≥ 15% RS in the BM, and the presence of < 5% BM blasts) are accompanied by platelet counts of 450 x 10^9/L or higher and the presence of atypical megakaryocytes. There are no specific immunophenotypic or IHC features associated with MDS/MPN-u or RARS-T.

Cytogenetics/molecular genetics. There are no specific cytogenetic findings in MDS/MPN-u or RARS-T. However, cytogenetics is important in the exclusion of diseases like chronic myelogenous leukemia (CML), 5q- syndrome, and myeloid neoplasms with rearrangements of PDGFRA, PDGFRB, or FGFR1. SNP-A lesions are also found in MDS/MPN-u and RARS-T.30

The most frequently identified molecular mutations in RARS-T are SF3B1 (72%) and JAK2V617F (60%).27,13,39 Other frequent molecular mutations include MPL (23%) and DNMT3A (17%). Less frequent mutations are in ASXL1, TET2, and LNK genes.39

Treatment. The treatment for patients with MDS/MPN-u and RARS-T are usually extrapolated from data or experience in treating patients with MDS or CMMML. Allogeneic hematopoietic cell transplantation is potentially curative. The recent identification of SF3B1 mutations in RARS-T may help in the identification of novel therapies for this disease.41 A case report of two patients with RARS-T demonstrated responsiveness to lenalidomide, even correlating with elimination of the JAK2 clone in one patient.42

PART III: NOVEL THERAPIES FOR MYELODYSPLASTIC SYNDROMES

Treatment for MDS remains an unmet medical need. AHSCRT remains the only curative option for MDS.43 There is no question that available current treatment modalities could be helpful for selected subset for patients. Unfortunately, short of lenalidomide for treatment of 5q-. MDS most of those options have 30% to 40% response rate with median duration of response ranging from 12 to 24 month.44 Figure 4 summarizes current algorithm of MDS management in 2013. The strategies to improve outcome in MDS may include (1) better selection of patients with MDS with higher chance of response to “biomarker driven therapies” (Table 4), (2) improve response rate or duration of response by combination strategies, (3) and finally introducing novel agents on the basis of understanding of the underlying biology and critical disease pathways.

Combination Strategies

In patients with higher-risk MDS, encouraging results of combining azacitidine (75 mg/m^2 day 1 through 5 every 28 days) with lenalidomide (10 mg daily day 1 through 21) were reported. Among 36 patients with higher-risk MDS in a phase II study, the overall response rate was 72% (modified international working group criteria) and 44% achieved CR. The most common grade 3/4 nonhematologic adverse event was febrile neutropenia (22%).45 Several studies examined combination of azacitidine with histone deacetylase inhibitors (HDACi). The only randomized clinical trial combining azacitidine with HDACi (entinostat) did not yield in better outcome.46 The most promising HDACi to be combined with azacitidine are vorinostat and pracinostat.47,48 There is ongoing randomized SWOG S1117 study between three arms: azacitidine, azacitidine/lenalidomide, or vorinostat/vorinostat.

In patients with lower-risk MDS, combination of lenalidomide and ESA yielded erythroid responses (HI-E) in a group of patients whose MDS did not respond to either agents alone.49 The MDS response rate to combined therapy after failing ESA and lenalidomide monotherapy was 21%. The benefits of lenalidomide plus erythropoietin-stimulating agent (ESA) are currently under investigation in a phase III intergroup study. Ezatiostat is a glutathione analog prodrug glutathione S-transferase P1–1 (GSTP1–1) inhibitor reported 40% HI-E rate in azanucleoside-naive, lenalidomide failures.50 In a phase I study, ezatinostat recommended for phase II dose (R2PD) was 2,000 mg combined with lenalidomide 10 mg daily in patients with nondel (5q-). The HI-E reported on this phase I study was 43%.51

Novel Therapies for Treatment of MDS

There are currently 348 interventional studies recruiting patients with MDS (clinicaltrials.gov, accessed February 12, 2013). The section is by no means conclusive for all the ongoing efforts.

P38-MAPK inhibitors. The hallmark of lower-risk MDS is accelerated apoptosis, which explains the paradoxical finding of peripheral cytopenia and hypercellular BM. The accelerated apoptosis is result of intrinsic clone susceptibility, Proinflammatory cytokines that suppress the normal and MDS clone as well.52 P38 mitogen-activated protein kinase
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<th>Study Phase</th>
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<td><strong>High-Intensity Chemotherapy</strong></td>
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<tr>
<td>Beran et al. Leuk Lymphoma. 1998;31:521–531.</td>
<td>II</td>
<td>60 (30 MDS, 30 CMML)</td>
<td>Induction course: Topotecan 2 mg/m² IV over 24 hrs D1-5 q 4-6 wks</td>
<td>CR = 27%, HI = 12%</td>
<td>10.5 mo</td>
<td>Mucositis, diarrhea, nausea, vomiting, febrile neutropenia, infections</td>
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<tr>
<td>Beran et al. J Clin Oncol. 1999;17:2819–1230.</td>
<td>II</td>
<td>86 (MDS/CMML = 59, CMML = 27)</td>
<td>Topotecan 1.25 mg/m² IV and cytarabine 1 g/m² IV D1–5 every 4–8 wk</td>
<td>CR = 44%</td>
<td>9.4 mo</td>
<td>Mucositis, diarrhea, fever (63%), infections (49%)</td>
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<tr>
<td>Bennet et al. Am J Hematol. 2001;66:23–27.</td>
<td>II</td>
<td>10 (RAEB/RAEB-t = 8, CMML = 2)</td>
<td>Intermediate dose cytarabine IV D1,2,8,9 and mitoxantrone 10 mg/m²/d IV D3,4,10,11 plus sargramostim†</td>
<td>Bone marrow CR = 20%</td>
<td>36 mo</td>
<td>Hepatic toxicity (hyperbilirubinemia) = 70%, Infection (70%)</td>
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<td>Qunitas-Cardama et al. Cancer. 2006;107:1525–1529.</td>
<td>II</td>
<td>44 (CMML = 32, MDS = 12)</td>
<td>9-Nitro-camptothecin 2 mg/m² PO D1–5/week q 4–6 wk</td>
<td>CR = 11%, PR = 16%, HI = 16%</td>
<td>2 yr survival = 25%</td>
<td>Nausea, vomiting, diarrhea, GI and GU toxicities</td>
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<td>Siverman et al. J Clin Oncol. 2002;20:2429–2440.</td>
<td>III</td>
<td>191 (CMML = 14)</td>
<td>5-azacitidine (AZA) 75 mg/m²/d SC D1-7 versus supportive care</td>
<td>AZA: ORR = 60% (CR = 7%, PR = 16%, HI = 37%) versus Supportive: HI = 5%</td>
<td>20 mo versus supportive care = 14 mo</td>
<td>Myelosuppression is the most common toxicity with AZA.</td>
</tr>
<tr>
<td>Kantarjian et al. Cancer. 2006;106:1794–1803.</td>
<td>III</td>
<td>170 (CMML = 14)</td>
<td>Decitabine 15 mg/m² IV q 8 x 3 d versus supportive care</td>
<td>Decitabine: ORR = 28% (CR = 8%, PR = 7%, HI = 13%) versus supportive: HI = 6%</td>
<td>Decitabine = 14 mo versus supportive care = 14.9 mo</td>
<td>Myelosuppression is the most common toxicity with decitabine. Grade 3/4 febrile neutropenia with decitabine = 28%</td>
</tr>
<tr>
<td>Aribi et al. Cancer 2007;109:713–717.</td>
<td>II</td>
<td>19 (all CMML)</td>
<td>Decitabine 100 mg/m² per course in 3 different schedules repeated q 4 wk</td>
<td>CR = 58%, HI = 11%</td>
<td>19 mo</td>
<td>Myelosuppression related complications (8%)</td>
</tr>
<tr>
<td>Wijermans et al. Leuk Res 2008;32:587–591.</td>
<td>II &amp; III</td>
<td>31 (all CMML)</td>
<td>Decitabine 15 mg/m² IV 3x/d x 3 d q 6 wk</td>
<td>CR = 10%, PR = 16%, HI = 19%</td>
<td>15 mo</td>
<td>Nausea and vomiting (42%, pneumonia (29%)</td>
</tr>
<tr>
<td>Costa et al. Cancer. 2011;117:2690–2696.</td>
<td>retrospective</td>
<td>38 (all CMML)</td>
<td>AZA 75 mg/m²/d SC fx D1-7 or 100 mg/m²/d SC D 1-5 q 28 d</td>
<td>ORR = 39% (CR = 11%, PR = 3%, HI = 25%)</td>
<td>12 mo</td>
<td>Cytopenia is the most frequent side effects (24%). Fatigue occurred in 16% of patients.</td>
</tr>
<tr>
<td><strong>B. Histone Deacetylase Inhibitors</strong></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Siitonen et al. Haematologica. 2007;92:1119–1122.</td>
<td>II</td>
<td>19 (CMML = 4, MDS = 15)</td>
<td>Valproic acid PD to achieve serum concentration of 500-700 μmol/L and 13- cis retinoid acid 10 mg PO BID and Vitamin D3 1 μg PO/day for 16 wk.</td>
<td>CR = 0%, HI = 16%</td>
<td>NA</td>
<td>Cheilitis and dry skin. The most common side effect is fatigue.</td>
</tr>
</tbody>
</table>
(MAPK) pathway is divergence pathway for several inflammatory signals. It is overactivated in lower-risk MDS. SCIO-469 (P38-MAPK inhibitor) was tested in 62 patients with lower-risk MDS in a phase I/II clinical study. Hematological improvement was reported in 29% (18% erythroid, 12% platelets, and 25% neutrophil). Array 614 is potent dual inhibitor of P38-MAPK and Tie 2. In a phase I multicenter study, single daily dose was escalated to 1,200 mg orally daily with no MTD reached. The twice-a-day dose cohort was discontinued given dose-limiting toxicities at 300 mg twice daily. The most common side effects were rash and diarrhea. Overall hematological improvement was 30% (erythroid 20%, platelets 32%, and neutrophils 31%). The response rate were higher at 1,200 mg dose (38%) and 67% had bilineage response. There is ongoing trial with improved oral formulation.

Transforming growth factor-beta (TGF-β) inhibitors. Myelosuppressive cytokines such as TGF-β are important regulators of hematopoiesis. The levels of TGF-β were found to be increased in the plasma and bone marrow progenitors of patients with MDS. Studies have shown SMAD2 is constitutively activated in primary MDS bone marrows. Furthermore, studies have shown that SMAD7, a negative regulator of the TGF-β receptor I kinase, is significantly reduced in MDS bone marrow progenitor. Pharmacologic and genetic (siRNA mediated) inhibition of TGF receptor I leads to increased hematopoietic colony formation from primary MDS hematopoietic progenitors in vitro. LY2157299 is a novel compound that specifically inhibits the kinase activity of TGF-β type I receptor and its downstream signaling pathway. LY2157299 has been shown to increase hematocrit levels in a mouse model of bone marrow failure induced by constitutive expression of TGF-β.

Activin and its receptors are part of the TGF-β superfamily. Sotatercept (ACE011) is a fusion protein consisting of the extracellular domain of activin receptor IIA linked to the human IgG1 Fc domain and ACE536 is the same for activin type IIB. Treatment with sotatercept resulted in increased hemoglobin and absolute red cell number in both nonclinical and clinical studies. The rapid and sustained increases were observed in two phase I studies in healthy volunteers, as well as

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**TABLE 2. Results of Pharmacologic Trials in Patients with Chronic Myelomonocytic Leukemia (cont’d)**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Phase</th>
<th>Cohort Size</th>
<th>Treatment</th>
<th>Response</th>
<th>Survival</th>
<th>Side effects</th>
</tr>
</thead>
</table>
| **C. Farnesyl Transferase Inhibitors**
Feldman et al. Leukemia. 2008;22:1707–1711. | II | 67 (CMML = 35) | Lonafarnib 200 mg PO BID | ORR = 24% (CR = 3%, PR = 2%, HI = 19%) | NA | Gastrointestinal toxicities = 19% |
| **D. Immuno Modulatory Agents (Thalidomide, Arsenic Trioxide, Dexamethasone, Ascorbic Acid)**
Bejanyan et al. 2011; Cancer. | II | 28 (CMML-I = 8) | a. Thalidomide 50 mg/d PO x 2 wk then 100 mg/d PO x 6 mo | ORR = 29% (PR and HI) | 21 mo | 25% experienced grade 3/4 hematologic toxicity. Fatigue was the most common non-hematologic toxicity (82%) |
| b. Arsenic 0.25 mg/kg x 5 d IV and 0.25 mg/kg twice a week IV x 11 wk |
| c. Dexamethasone 4 mg/d x 5 d PO q 4 wk |
| d. Ascorbic acid 1000 mg 2-3 h PO prior to each arsenic dose |
| **E. Others**
Wattel et al. Blood 1996;88:2480–2487. | III | 105 (all CMML) | Hydroxyurea (HU) 1-4 g/day PO versus etoposide 150-600 mg/wk PO* | HU (60%) versus etoposide (36%) p = 0.02 | HU (20 mos) versus etoposide (9 mos) | More patients treated with etoposide developed alopecia |

Abbreviations: MDS, myelodysplastic syndromes; CMML, chronic myelomonocytic leukemia; IV, intravenously; CR, complete response; HI, hematological improvement; HU, hydroxyurea; PO, oral; PR, partial response; GI, gastrointestinal; GU, genitourinary; SC, subcutaneously; ORR, overall response rate; NA, not available.

† In the original study performed in patients with AML, the dose defined as intermediate dose cytarabine depends on the age of the patient (1 g/m² was given to patients younger than 60 years and 500 mg/m² was given to patients age 60 or older).§

‡ - etoposide dose are doubled for patients with visceral involvement.

Σ - Etoposide data provided are just for patients with CMML.
in a phase IIa study in patients with multiple myeloma.\textsuperscript{60,61} There is ongoing phase II clinical study with sotatercept for lower risk MDS (NCT01736683). Preclinical work in murine MDS model demonstrated efficacy of ACE-536 in improving the hematologic parameters through enhancing maturation of terminally differentiated erythroid cells.\textsuperscript{62}

**Indoleamine 2,3-dioxygenase inhibitors.** IDO is a rate-limiting enzyme in breakdown pathways of tryptophan. IDO is over-activated in different cancers and blocks tumor specific cytotoxic T cells activity, which is key element for induction of tumor immune tolerance.\textsuperscript{63} In MDS, there is expansion of regulatory T cells particularly effective memory subtype.\textsuperscript{64} In addition, in MDS there is expansion of inflammation-related immature myeloid-derived suppressor cells (MDSC) that display direct cytotoxic and suppressive effects on hematopoietic progenitor cells. In mice model, expansion of MDSCs led to MDS-like phenotype.\textsuperscript{65} IDO1 inhibition will increase T-cell proliferation, and decrease regulatory T cells. IDO inhibition also decreases MDSC suppressive activity. INCBO24360 represents a novel, potent, and selective inhibitor of the enzyme IDO that will be tested in a phase II study in patients with MDS.

**Mouse double minute 2 homolog (MDM2)-p53 pathway modulation.** In 5q- MDS, haploinsufficiency of RSP14 ribosomal protein is a key contributor to the anemia. MDM2 is an E3-ubiquitin ligase and key negative regulator of protein 53. MDM2 directly binds to the DNA binding domain of p53 where it ubiquitinates p53 thereby targeting it for proteasomal degradation. Disruption of ribosome assembly results in the liberation of free RPs that interact with MDM2 preventing its negative regulation of p53. The resultant stabilization of p53 appears responsible for senescence and apoptosis of erythroid precursors in the 5q- syndrome, manifested clinically as hypoplastic anemia. Treatment with lenalidomide results in hyperphosphorylation of MDM2 via auto-ubiquitination and stabilizes MDM2 and promotes p53 degradation. Development of resistance to lenalidomide is associated with over expression of PP2A and restoration of MDM2 directly binds to the DNA binding domain of p53.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cohort Size (No. of Patients)</th>
<th>Disease Types</th>
<th>Median Age (y)</th>
<th>Type of Transplant</th>
<th>Conditioning Regimen</th>
<th>Survival Outcomes</th>
<th>Relapse Rate</th>
<th>Therapy Related Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mittal et al, Bone Marrow Transplant. 2004;33:1005-1009.</td>
<td>20</td>
<td>CMML = 8 Ph\textsuperscript{neg} CML = 7 MF = 5</td>
<td>51 (20-64)</td>
<td>MSD = 15 MUD = 5</td>
<td>MA = 11 RI = 9</td>
<td>2 yr OS = 47% 2 yr DFS = 37%</td>
<td>30%\textsuperscript{f} 10%</td>
<td></td>
</tr>
<tr>
<td>Elliott et al. Bone Marrow Transplant. 2006;37:1003-1008.</td>
<td>17</td>
<td>CMML to AML = 11 NA = 6</td>
<td>50 (26-60)</td>
<td>MSD = 14 MUD = 3</td>
<td>MA = 16 RI = 1</td>
<td>3 yr OS = 18% 3 yr DFS = 18%</td>
<td>41% 41%</td>
<td></td>
</tr>
<tr>
<td>Ocheni et al. Bone Marrow Transplant 2009;43:659-661.</td>
<td>12\textsuperscript{†}</td>
<td>CMML-1 = 7 CMML-2 = 3 NA = 2</td>
<td>56 (37-66)</td>
<td>MSD = 1 MUD = 11</td>
<td>MA = 7 RI = 6</td>
<td>2 yr OS = 75% 2 yr DFS = 67%</td>
<td>17% 25%</td>
<td></td>
</tr>
<tr>
<td>Krishnamurthy et al. Bone Marrow Transplant. 2010;45:1502-1507.</td>
<td>18</td>
<td>CMML = 10 CMML/MPD = 1 CMML to AML = 7</td>
<td>54 (38-66)</td>
<td>MSD = 7 MUD = 11</td>
<td>MA = 1 RI = 17</td>
<td>3 yr OS = 31% 3 yr DFS = 47% (if &lt; 5% blasts) and 20% (if &gt; 5% blasts)</td>
<td>44% 31%</td>
<td></td>
</tr>
<tr>
<td>Eissa et al. Biol Blood Marrow Transplant. 2011;17:909-915.</td>
<td>85</td>
<td>CMML-1 = 57 CMML-2 = 26 Inconclusive = 2</td>
<td>52 (0-69)</td>
<td>MSD = 38 MUD = 47</td>
<td>MA = 58 RI = 27</td>
<td>10 yr OS = 40% 10 yr DFS = 40% 10 yr PFS = 38%</td>
<td>27% at 10 yr 34% at 10 yr</td>
<td></td>
</tr>
<tr>
<td>Park et al. Eur J Haematol. 2013.</td>
<td>73</td>
<td>CMML-1 = 45 CMML-2 = 28</td>
<td>53 (29-47)</td>
<td>MSD = 41 MUD = 31 HPI = 1</td>
<td>MA = 30 RI = 43</td>
<td>3 yr OS = 32% 3 yr DFS = 29%</td>
<td>35% 36%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CMML, chronic myelomonocytic leukemia; CML, chronic myelogenous leukemia; MF, myelofibrosis; MSD, matched sibling donor; MUD, matched unrelated donor; MA, myeloablative; RI, reduced intensity conditioning; OS, overall survival; DFS, disease-free survival; AML, acute myeloid leukemia; NA, not available; MPD, myeloproliferative disorders; RFS, relapse-free survival; PFS, progression-free survival; HPI, haploidentical; EFS, event-free survival.

\textsuperscript{f} Within CMML only – relapse rate is 62%.

\textsuperscript{†} There were 0.12 patients, but 13 allogeneic transplants performed.

**Thrombopoietin-stimulating agents (TPO) stimulators.** Thrombocytopenia is common in MDS and associated with poor in patients with MDS.

**References:**

outcome. Two TPOs that are approved for immune thrombocytopenia are being investigated in MDS. Romiplostim, a TPO peptide agonist was tested in a randomized placebo controlled study in patients with lower-risk MDS with platelets $20 \times 10^9$/L or less or $50 \times 10^9$/L or less with a history of bleeding. Romiplostim was administered as 750 mcg

**TABLE 4. Biomarkers That Predict Response to Current Available Therapies**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Positive Predictor</th>
<th>Negative Predictor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide</td>
<td>5q- in lower risk</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Erythroid-stimulating agents</td>
<td>Serum epo &gt; 500</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Two units RBC transfusion per month</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aberrant myeloblast immunophenotype detected by flowcytometry</td>
<td></td>
</tr>
<tr>
<td>Azacitidine</td>
<td>TET-2 mutation</td>
<td>Prior low-dose cytarabine</td>
</tr>
<tr>
<td></td>
<td>Complex karyotype</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$&gt; 15%$ myeloblasts</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressant therapy</td>
<td>Age &lt; 60</td>
<td>Long duration of disease</td>
</tr>
<tr>
<td></td>
<td>HLA-DR 15 +</td>
<td>Heavy transfusion burden</td>
</tr>
<tr>
<td></td>
<td>CD4:CD8 ratio &gt; 2</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: epo, erythropoietin; RBC, red blood cell.
subcutaneous weekly. In terms of efficacy romiplostim was associated with reduced clinically significant bleeding events in patients with platelets 20 to 50 and only reduced platelets transfusion in those with platelets less than 20. The study was terminated early because of concerns of increased myeloblasts and AML. On romiplostim, 15% of the patients had increase in the myeloblasts and in 56% of those cases decreased at end of study. On longer follow-up, there was no difference in rate of AML transformation (8.9% with romiplostim compared with 8.5% with placebo).70

Eltrombopag is an oral nonpeptide TPO agonist that binds to transmembrane domain different from TPO binding site, antileukemic effect of eltrombopag was reported in vitro. Encouraging results were reported from phase II placebo controlled study in patients with lower-risk MDS with platelets less than $30 \times 10^3/L$. Eltrombopag was started at 50 mg daily and dose increased every 2 weeks up to 300 mg. Responses were seen in eight/nine patients compared with zero/five patients on the placebo in early preliminary report. No drug-related adverse events were reported nor cases of disease progression.71 The role of TPOs in treatment of thrombocytopenia remains investigational. Future combinations with disease modifying treatments is appealing.

TKI. Rigosertib is a nonadenosine-triphosphate–competitive small–molecule multi–TKI including polo–like kinase 1. Several studies with intravenously dosing formulation were reported demonstrating activity in reducing myeloblasts, inhibiting cyclin D1 particularly in trisomy eight patients. In a phase I study with oral formulation, 560 mg was the R2PD.72-75 A randomized clinical study with intravenously dosed rigosertib is currently the only randomized clinical study available for higher-risk patients after azanucleosides failure. Studies with oral formulation are ongoing in lower-risk patients.

Erlotinib oral small–molecule TKIs that inhibit intracellular epidermal growth factor receptor tyrosine kinase had off–target activity reported preclinically in MDS and AML. Anecdotal responses in patients with concomitant–treated MDS/AML and lung cancer were reported. In a phase II single–institution study of patients with higher–risk MDS in which azanucleosides failed, 15% over all response rate (marrow CR and platelet response) were reported. Erlotinib may have synergistic effect with azacitidine and future combination is being explored.76 Dasatinib had very modest activity in pilot phase II study after azanucleosides failure.77

Aminopeptidase inhibitors. Inhibition of aminopeptidase enzyme depletes intracellular amino acids pool that is crucial for tumor cell survival. Tosedostat an oral inhibitor was tested in phase I/II studies in MDS/AML and was well tolerated, thrombocytopenia was most common toxicity, R2PD was 130 mg daily. Overall response rate reported was 27%.78 In a phase II AML study, overall response was 22% as single agent.79 There is ongoing study testing tosedostat in combination with decitabine or cytarabine (NCT01567059).

Hedgehog inhibitors. In hematologic malignancies, the Hh pathway appears to be active, but mutations have yet to be described.80 Hedgehog signaling is active in AML stem cells and showed that its expression contributed to drug resistance.81 In MDS, overexpression of the HH target gene, BMII, is a prognostic biomarker for disease progression and increases according to IPSS score and BM blast percentage.82 A first in–human phase I study of PF–04449913 in patients with AML, primary myelofibrosis, CML, and MDS demonstrated efficacy in all four diseases. One of the three patients with low–risk MDS achieved a reduction in spleen size and a hematologic improvement in platelets and neutrophils. Among the 18 patients with AML, one had a decrease in BM blasts from 92% to 1% without hematologic improvement. An additional five patients had at least a 50% reduction in the BM blasts.83 A phase II single–agent PF–04449913 in patients with MDS after azanucleosides failure is on the way.

Disclosures of Potential Conflicts of Interest

Relationships are considered self–held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.


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