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PERSPECTIVE

Myelodysplastic syndrome

Rethinking clinical trial endpoints in myelodysplastic syndromes

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Abstract

The myelodysplastic syndromes (MDS) are a heterogeneous collection of clonal, hematopoietic disorders primarily affecting an older population, making successful drug development a complicated process. A sole focus on response rate in clinical trials is likely not clinically meaningful if not accompanied by substantive response duration, improvement in quality of life, and ideally prolongation of survival. The process of receiving a new therapy should not be more burdensome than the MDS sequela it is intended to ameliorate. We review challenges in drug development in MDS with respect to aligning trial endpoints for lower and higher risk patients with treatment goals meaningful to patients.

The challenge of drug development for myelodysplastic syndromes

The myelodysplastic syndromes (MDS) are a tough bowl of nuts to crack. Diagnosis of MDS can be difficult, given inconsistency in bone marrow morphology and the presence of MDS "mimics" (i.e., non-neoplastic conditions causing cellular dysplasia identical to that seen in MDS) [1, 2], as well as the lack of a disease-defining molecular abnormality [3, 4]. Disease pathogenesis is enormously complicated, with more than 40 recurrent genetic mutations associated with MDS and tremendous allelic heterogeneity [5, 6]. No one genetic lesion is detectable in more than ~25% of patients, the most common being *SF3B1*, *DNMT3A*, and *TET2*, and DNA changes tell only part of the story: disordered epigenetic patterns are seemingly unique to each patient [7, 8]. Recent insights into pre-malignant clonal hematopoiesis have highlighted that multiple genomic lesions must occur, usually over many years, before MDS develops and by that time there may be no hematopoietic precursor cells left without initiating mutations [9, 10]. It is therefore no wonder that, unlike the "one-hit wonder", chronic myeloid leukemia, a mono-genetic neoplasm for which elegant preclinical and clinical work led to regulatory approval of several highly effective tyrosine-kinase inhibitors, there are only 3 drugs approved for messy MDS—and these 3 work, to put it generously, only fairly well and briefly [11–14].

Assessing the safety and efficacy of new drugs to treat MDS is equally complicated and challenging. Most people with MDS have been eligible for benefits through the American Association of Retired Persons for at least a decade [15, 16]. This means that not only do these people often have competing health risks ranging from cardiovascular disease to other cancers, they may also have impaired mobility, fixed income and limited ability to travel to a referral center for a clinical trial [17]. Additionally, patients may prefer to spend winters in warm beachfront climates or remote locations, where access to specialty medical care can be spotty. Probably because of this challenging disease biology and fragile patients, no new drugs have been approved by the U.S. Food and Drug Administration (FDA) for MDS since 2006.

Treatment goals in MDS

Patients with MDS can be broadly divided into two categories. In those with "lower-risk" MDS—commonly defined as the 2 lowest risk categories in the International Prognostic Scoring System (IPSS) or its revised version (IPSS-R)—therapeutic goals focus on minimizing or avoiding blood product transfusions and maximizing *quality-of-life*, a goal many patients value as much or more than living longer [18, 19]. Lower-risk patients often live at least 3–5 years and are bothered by burdensome symptoms,

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including fatigue, dyspnea on exertion, limited exercise capacity, and a tendency to bruise, bleed or get infected. Patients with "higher-risk" MDS, usually defined as the 2 highest risk categories within the IPSS/-R (but also including patients in IPSS/-R lower-risk categories with a high-risk genetic lesion, such as a *TP53* mutation) [6], share similar symptoms to lower-risk patients, but expected survival is shorter and the risk of progression to acute myeloid leukemia (AML) greater. Treatment objectives in these patients therefore include delaying disease evolution and improving survival, maximizing *quality-of-life* and reducing transfusions [20].

Trial endpoints should ideally meet MDS patients where they are. A focus on overall response rate (ORR) defined by improvement in blood counts or reduction in the proportion of bone marrow blasts is, by itself, not enough to validate a new drug's usefulness in MDS unless it correlates with improved *quality-of-life*, a meaningful reduction in transfusion frequency, or longer survival. To define valuable clinical trial endpoints we must also consider eligibility criteria to identify "the right patient for the job"—one who will derive benefit from the drug being studied with *benefit* aligned to the patient's goals.

Clinical trial endpoints for lower-risk MDS

Almost everyone with MDS, even lower-risk patients, will have anemia. Some MDS clinical trials allow patients to enroll with a hemoglobin <10 g/dl even if un-transfused [21–23]. Although reasonable if the patient is symptomatic, it is less so if the patient otherwise feels well without compromise of daily tasks or *quality-of-life*. The only possible effect a new drug could have in this setting is to add adverse effects to an otherwise acceptable life (unless it delays progression to AML or prolongs survival). Better to enroll patients receiving RBC-transfusions or who have worsening quality-of-life attributed to MDS and not concomitant medical conditions such as congestive heart failure.

In such a patient, an increase in hemoglobin concentration, arbitrarily-defined such as 1.5 g/dl (a threshold for "erythroid hemoglobin improvement" in the 2006 International Working Group (IWG) MDS response criteria) [24] may make caregivers—and patients—appreciate the higher number, just as the band members in the movie *This is Spinal Tap* valued an amplifier whose dial could be turned to 11, a full 10% higher number than the dial capacity of other amplifiers. But the higher hemoglobin concentration is not clinically meaningful without a measurable increment in quality-of-life or fewer RBC- transfusions (Table 1). Delaying or preventing a future need for RBC-transfusions is a specious goal because thresholds for starting RBC transfusion are variable [21] and MDS patients may delay receiving transfusions for months or years without intervention and feel fine, or at least acceptably well [16].

For patients receiving RBC-transfusions to counter the physical misery attendant to anemia, what quantity and/or frequency justifies initiation? [25] And how much of a reduction is enough to declare a benefit? Although the threat of iron overload from frequent RBC transfusion may prompt some physicians to intervene, the vast majority of patients with MDS have much bigger concerns, as most are old and may not live long enough for iron accumulation to be an issue [26–28].

A RBC-transfusion frequency widely used to justify eligibility for clinical trials is ≥2 units every 4 weeks, averaged over an 8–16 week period (since intercurrent illness or bleeding may result in a temporary need for transfusions) [29, 30]. This has face validity and seems reasonable, as having to spend several hours in an infusion chair—plus the time spent traveling to a cancer center, paying for parking and gas, registering, having blood drawn to assess the hemoglobin concentration, enduring the pain of an intravenous line placement and waiting for an infusion chair to become available, every 28 days—is no fun.

The drug being studied should require no more, and preferably much less an investment in time and resources than the transfusions the drug is intended to mitigate. Complete freedom from RBC-transfusions in a RBC-transfusion-dependent patient is meaningful and, when durable, should be an approvable endpoint provided the interventions needed to achieve RBC-transfusion-independence are no worse (and hopefully much better) than the transfusions themselves. Randomized, placebo-controlled trials are still needed to demonstrate this, as control groups with myeloid disorders in such studies can achieve hematologic improvement up to 15–20% of the time even in the absence of a specific pharmacologic intervention [31]. A reduction in transfusion frequency is a slippery slope, as baseline transfusion needs vary widely [32].

Patients enrolled in trials could have the time invested in maintaining adequate hemoglobin concentrations, along with days in clinic or the hospital, measured at baseline, with a reasonable trial endpoint (complementing efficacy) being a meaningful reduction of these parameters from baseline. Patients might even define what is "meaningful" to them. Notably, an improvement in survival (the ultimate in "meaningful") has not been proved for any intervention in lower-risk MDS patients.

For the minority of patients who have lower-risk MDS, but where thrombocytopenia with bleeding episodes, or neutropenia with frequent infections, are the dominant problem [33], endpoints should again include concrete benefits that go beyond the Pyrrhic victory of simply

Table 1 Value of endpoints in MDS clinical trials

MDS type	Endpoint	Endpoint value	Comment
Lower-risk			
Lower-risk with anemia	Increase in hemoglobin concentration	Poor	Not clinically meaningful
	Increase in hemoglobin concentration and decrease in transfusion needs	Okay	Transfusion reduction amount associated with benefit not well defined Benefits of reducing iron overload not well defined
	Increase in hemoglobin concentration and decrease in transfusion needs with improved quality of life	Good	Time/resource/side effect impact of drug should be less than that for baseline transfusions Validated MDS quality of life instrument should be used and complemented with data from wearables
	Increase in hemoglobin concentration and decrease in transfusion needs with improved quality of life that is durable	Better	Days in clinic/hospital should be measured at baseline and improvement demonstrated Patients define meaningful duration
	Improvement in survival and quality of life	Best	
Lower-risk with thrombocytopenia and/or neutropenia	Increase in platelet or neutrophil counts	Poor	Not clinically meaningful
	Increase in platelet or neutrophil counts and decrease in transfusion needs	Okay	Transfusion reduction amount associated with benefit not well defined Time/resource/side effect impact of drug should be less than that for baseline transfusions
	Increase in platelet or neutrophil counts and decrease in transfusion needs with reduction in clinically important bleeding events and/or infections requiring antibiotics	Good	Time/resource/side effect impact of drug should be less than that for baseline transfusions or infectious episodes
	Increase in platelet or neutrophil counts and decrease in transfusion needs with reduction in clinically important bleeding events and/or infections requiring antibiotics that is durable	Better	Days in clinic/hospital should be measured at baseline and improvement demonstrated Patients define meaningful duration
	Improvement in survival and quality of life	Best	
Higher-risk	Overall response rate	Poor	Not clinically meaningful Certain response criteria (e.g., bone marrow complete response; stable disease) not associated with meaningful outcomes
	Delay in AML transformation or improvement in IPSS/IPSS-R category	Okay	Distinguishing AML from MDS biologically and clinically meaningless in some cases Patients can have “mixed responses”
	Co-endpoint: improvement in survival and ability to receive hematopoietic cell transplantation	Better	Complicated given the many steps and occasional subjectivity that contribute to successful transplantation
	Improvement in survival and quality of life	Best	

MDS myelodysplastic syndromes, *AML* acute myeloid leukemia, *IPSS/IPSS-R* International Prognostic Scoring System/-Revised

improved numbers, especially given the frequent but difficult to measure functional defects in neutrophils and platelets in MDS making an absolute increase in cell concentrations a poor predictor of infection and bleeding risk. Meaningful endpoints in these patients include reduction in clinically important bleeding events, reduction in platelet transfusion frequency, fewer clinic visits or hospitalized days and fewer infections requiring antibiotics [34–36]. As with the time and energy investment for RBC-transfusions, any drug being tested should not require more from patients than they are already undergoing at baseline as part of supportive care for their condition.

Although patients with higher hemoglobin concentrations have been shown to have an improved *quality-of-life* compared to those with lower concentrations [37, 38], patient reported outcome assessments accompanying clinical trials in patients with lower-risk MDS have not convincingly proved interventions intended to increase the hemoglobin concentration or other blood cell parameters make people feel better [39–41]. The cause of this may lie in using instruments not originally intended for an MDS population and which may not be sensitive to changes in an older population over time. Instruments such as the QUALMS [42], the first disease-specific Patient Reported Outcome tool for MDS validated in treated MDS patients with lower- and higher-risk disease, would be more appropriate, with clinically meaningful increments from baseline an endpoint of value to patients. This instrument is being explored as a companion study to a trial randomizing lower-risk MDS patients to reduced schedules of azacitidine or decitabine through the U.S. MDS Clinical Research Consortium that has almost completed accrual (Clinicaltrials.gov #NCT02269280). Another method of measuring improvement in functional state may be through wearable devices which can provide "hard" data about the amount of time a patient spends active compared to baseline.

Meaningful endpoints in lower-risk patients require a time component; interventions without durable benefit are less valuable than those where the benefits are sustained. The median RBC-transfusion freedom period in patients with del(5q) MDS who are treated with lenalidomide is more than 2 years, and more than 65% of patients become RBC-transfusion-independent. In contrast, in those without del(5q) receiving lenalidomide, the median duration is <1 year, and only one-quarter of patients benefit [43, 44]. Consequently, the FDA and European Medicines Agency approved lenalidomide only for del(5q) MDS. Viewing this from a patient's perspective, is it worth considering a drug with potential physical and fiscal adverse effects and where efficacy can only be determined after several months of therapy for a potential benefit such as freedom from RBC-transfusions of 2 or 3 months? Probably not. 6 or 8 months? Maybe, depending on the physical and fiscal toxicity. One year? Probably. As clinicians, we struggle with defining an acceptable duration of benefit, unnecessarily. Ideally, patients should define the duration of benefit that would make a specific intervention "worth it" to them.

Clinical trial endpoints for higher-risk MDS

In patients with higher-risk MDS, delaying, or decreasing transformation to AML is frequently promoted as a treatment goal. Co-endpoints of delayed transformation to AML, hematological response, and better survival led the FDA to approve decitabine for MDS [12, 14]. Yet, the distinction between higher-risk MDS and AML developing in someone with an antecedent hematologic disorder is artificial. Advancing from a bone marrow with 18% blasts to one with 21% blasts—thus crossing the Rubicon of 20% blasts which defines AML using World Health Organization (AML) criteria [4]—is biologically and clinically irrelevant (Table 1). Moreover, a 95% confidence interval of one value would include the other, highlighting the imprecision of such estimates. Someone whose blasts increase from <5% blasts to 40%, however, almost certainly has a real problem. Delay in AML transformation as a trial endpoint is also confounded by the frequency with which bone marrow aspirates and biopsies are assessed and consistency with which samples are performed across trial participants.

To address the arbitrary nature of the WHO-defined AML boundary some trials have defined AML progression as crossing the 20% Rubicon and having a 50% relative increase in blast, as well as a >5% absolute increment in blasts. Is having 18% blasts and 27% blasts substantively different? Likely no. In fact, survival curves in the IPSS and the IPSS-R for patients with 11–20% blasts and 21–29% blasts overlap (and thus the modification of the highest blast category in the IPSS-R to simply "≥10% blasts.") [18, 19].

Further complicating the notion of progression in MDS is so-called "mixed responses." Some patients may have an improvement in hemoglobin and/or blood cell concentrations but increased bone marrow blasts or the contrary. Did a patient progress because her percent bone marrow blasts increased from 15 to 25% blasts even when her platelets increased from 23 to $198 \times 10E+9$/L? Similarly, it is important not to use changes in IPSS or IPSS-R risk categories as an endpoint; these systems are not dynamic and have largely not been validated in treated patients [45–47].

Basing trial objectives on ORR carries with it the same problems in higher-risk MDS as it does with lower-risk MDS—namely, ORR in and of itself is not clinically meaningful absent meaningful improvement in quality-of-life, transfusion needs and/or survival. ORR includes unvalidated endpoints which may bolster the ORR without

providing real benefit (akin to moving the Spinal Tap amplifier dial from 11 to 12), such as bone marrow complete remission, which in some studies was shown to correlate with an outcome no different than stable disease [48]. In patients for whom hypomethylating drugs have failed, for example, rigosertib reduced bone marrow blasts in many patients without improving hematopoiesis or survival [49]. Including "stable disease" in ORR is an act of desperation for a drug that simply doesn't work well.

With the advent of routine next-generation sequencing (NGS) in clinical practice and increasing development of targeted agents other endpoints, such as decrease in variant allele frequency (VAF) of a clone with a somatic mutation, are starting to make their way into trials. Improvement in cytogenetics, including normalization or a major reduction in the proportion of abnormal metaphases, can be a similar, albeit less sensitive, measure of clonal reduction during therapy. Although clonal reduction may be useful in an early-phase trial, it is not yet proven to correlate with validated endpoints and should be a conditional endpoint suggesting a drug may warrant further study.

We are left, then with improvement in *quality-of-life* and survival as the most meaningful endpoints in higher-risk MDS. Only azacitidine has shown a survival benefit in this setting [11]. Hematopoietic cell transplants are increasingly used in older persons with higher-risk MDS. Consequently, a co-endpoint of survival and ability to receive a transplant is possible, albeit complicated given the many steps and occasional subjectivity that contribute to successful transplantation. Longer survival may not be sexy, and it certainly isn't particularly innovative, but it is of real value to patients, as is a better quality-of-life. Ongoing trials investigating combinations of drugs that include those recently approved by the U.S. Food and Drug Administration for older adults with AML (such as glasdegib and venetoclax), which is biologically and clinically similar to higher-risk MDS, may have the best potential for meeting valued outcomes.

Particularly for people with higher-risk disease, endpoints short of living longer and living better sell our patients short and inflate the promise of a drug. And if interim endpoints that don't clearly correlate with more meaningful endpoints constitute the goals of clinical trials, we are bound to disappoint the people with MDS for whom the new drugs are intended.

Conflict of interest M.A.S. serves on Advisory Boards for Celgene, Takeda, and Syros and on a DSMB for Opsona. D.P.S. consults for Novartis and Otsuka; serves on DSMBs for Onconova, Janssen, and Takeda; and his institution receives research funding from Celgene and H3Bioscience.

References

1. Foran JM, Shammo JM. Clinical presentation, diagnosis, and prognosis of myelodysplastic syndromes. Am J Med. 2012;125 (7 Suppl):S6–13.
2. Naqvi K, Jabbour E, Bueso-Ramos C, Pierce S, Borthakur G, Estrov Z, et al. Implications of discrepancy in morphologic diagnosis of myelodysplastic syndrome between referral and tertiary care centers. Blood. 2011;118:4690–3.
3. Vardiman J, Thiele J, Arber D, Brunning R, Borowitz M, Porwit A, et al. The 2008 Revisions of the WHO classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009;114:937–51.
4. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127:2391–405.
5. Makishima H, Yoshizato T, Yoshida K, Sekeres MA, Radivoyevitch T, Suzuki H, et al. Dynamics of clonal evolution in myelodysplastic syndromes. Nat Genet. 2017;49:204–12.
6. Bejar R, Stevenson K, Abdel-Wahab O, Galili N, Nilsson Br, Garcia-Manero G, et al. Clinical Effect of Point Mutations in Myelodysplastic Syndromes. N Eng J Med. 2011;364:2496–506.
7. Zhao X, Yang F, Li S, Liu M, Ying S, Jia X, et al. CpG island methylator phenotype of myelodysplastic syndrome identified through genome-wide profiling of DNA methylation and gene expression. Br J Haematol. 2014;165:649–58.
8. Taskesen E, Havermans M, van Lom K, Sanders MA, van Norden Y, Bindels E, et al. Two splice-factor mutant leukemia subgroups uncovered at the boundaries of MDS and AML using combined gene expression and DNA-methylation profiling. Blood. 2014;123:3327–35.
9. Steensma DP, Bejar R, Jaiswal S, Lindsley RC, Sekeres MA, Hasserjian RP, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood. 2015;126:9–16.
10. Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371:2488–98.
11. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009;10:223–32.
12. Kantarjian H, Issa JP, Rosenfeld CS, Bennett JM, Albitar M, DiPersio J, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. Cancer. 2006;106:1794–803.
13. List A, Dewald G, Bennett J, Giagounidis A, Raza A, Feldman E, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med. 2006;355:1456–65.
14. Steensma DP, Baer MR, Slack JL, Buckstein R, Godley LA, Garcia-Manero G, et al. Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndromes: the alternative dosing for outpatient treatment (ADOPT) trial. J Clin Oncol. 2009;27:3842–8.
15. Sekeres MA. Epidemiology, natural history, and practice patterns of patients with myelodysplastic syndromes in 2010. J Natl Compr Canc Netw. 2011;9:57–63.
16. Sekeres MA, Schoonen WM, Kantarjian H, List A, Fryzek J, Paquette R, et al. Characteristics of US patients with myelodysplastic syndromes: results of six cross-sectional physician surveys. J Natl Cancer Inst. 2008;100:1542–51.
17. Zipperer E, Tanha N, Strupp C, Kundgen A, Nachtkamp K, Neukirchen J, et al. The myelodysplastic syndrome-comorbidity

index provides additional prognostic information on patients stratified according to the revised international prognostic scoring system. Haematologica. 2014;99:e31–2.
18. Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89:2079–88.
19. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120:2454–65.
20. Sekeres MA, Gerds AT. Established and novel agents for myelodysplastic syndromes. Hematol Am Soc Hematol Educ Program. 2014;2014:82–9.
21. Platzbecker U, Symeonidis A, Oliva EN, Goede JS, Delforge M, Mayer J, et al. A phase 3 randomized placebo-controlled trial of darbepoetin alfa in patients with anemia and lower-risk myelodysplastic syndromes. Leukemia. 2017;31:1944–50.
22. Gabrilove J, Paquette R, Lyons RM, Mushtaq C, Sekeres MA, Tomita D, et al. Phase 2, single-arm trial to evaluate the effectiveness of darbepoetin alfa for correcting anaemia in patients with myelodysplastic syndromes. Br J Haematol. 2008;142:379–93.
23. Raza A, Galili N, Smith SE, Godwin J, Boccia RV, Myint H, et al. A phase 2 randomized multicenter study of 2 extended dosing schedules of oral ezatiostat in low to intermediate-1 risk myelodysplastic syndrome. Cancer. 2012;118:2138–47.
24. Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006;108:419–25. Epub 2006 Apr 11.
25. Gale RP, Barosi G, Barbui T, Cervantes F, Dohner K, Dupriez B, et al. What are RBC-transfusion-dependence and -independence? Leuk Res. 2011;35:8–11.
26. Steensma DP, Gattermann N. When is iron overload deleterious, and when and how should iron chelation therapy be administered in myelodysplastic syndromes? Best Pract Res Clin Haematol. 2013;26:431–44.
27. Sekeres MA. How to manage lower-risk myelodysplastic syndromes. Leukemia. 2012;26:390–4.
28. Steensma DP. Myelodysplasia paranoia: iron as the new radon. Leuk Res. 2009;33:1158–63.
29. Platzbecker U, Germing U, Gotze KS, Kiewe P, Mayer K, Chromik J, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. Lancet Oncol. 2017;18:1338–47.
30. Komrokji R, Garcia-Manero G, Ades L, Prebet T, Steensma DP, Jurcic JG, et al. Sotatercept with long-term extension for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes: a phase 2, dose-ranging trial. Lancet Haematol. 2018;5:e63–e72.
31. Tefferi A, Al-Ali HK, Barosi G, Devos T, Gisslinger H, Jiang Q, et al. A randomized study of pomalidomide vs placebo in persons with myeloproliferative neoplasm-associated myelofibrosis and RBC-transfusion dependence. Leukemia. 2017;31:1252.
32. Ramsey SD, McCune JS, Blough DK, McDermott CL, Beck SJ, Lopez JA, et al. Patterns of blood product use among patients with myelodysplastic syndrome. Vox Sang. 2012;102:331–7.
33. Kantarjian H, Giles F, List A, Lyons R, Sekeres MA, Pierce S, et al. The incidence and impact of thrombocytopenia in myelodysplastic syndromes. Cancer. 2007;109:1705–14.
34. Platzbecker U, Sekeres MA, Kantarjian H, Giagounidis A, Mufti GJ, Jia C, et al. Relationship of different platelet response criteria and patient outcomes in a romiplostim myelodysplastic syndromes trial. Leukemia. 2014;28:2418–21.
35. Kantarjian H, Fenaux P, Sekeres MA, Becker PS, Boruchov A, Bowen D, et al. Safety and efficacy of romiplostim in patients with lower-risk myelodysplastic syndrome and thrombocytopenia. J Clin Oncol. 2009;28:437–44.
36. Giagounidis A, Mufti GJ, Fenaux P, Sekeres MA, Szer J, Platzbecker U, et al. Results of a randomized, double-blind study of romiplostim versus placebo in patients with low/intermediate-1-risk myelodysplastic syndrome and thrombocytopenia. Cancer. 2014;120:1838–46.
37. Bailey RA, Reardon G, Wasserman MR, McKenzie RS, Hord RS. Association of anemia with worsened activities of daily living and health-related quality of life scores derived from the Minimum Data Set in long-term care residents. Health Qual Life Outcomes. 2012;10:129.
38. Platzbecker U, Hofbauer LC, Ehninger G, Holig K. The clinical, quality of life, and economic consequences of chronic anemia and transfusion support in patients with myelodysplastic syndromes. Leuk Res. 2012;36:525–36.
39. Casadevall N, Durieux P, Dubois S, Hemery F, Lepage E, Quarre MC, et al. Health, economic, and quality-of-life effects of erythropoietin and granulocyte colony-stimulating factor for the treatment of myelodysplastic syndromes: a randomized, controlled trial. Blood. 2004;104:321–7.
40. Steensma DP, Heptinstall KV, Johnson VM, Novotny PJ, Sloan JA, Camoriano JK, et al. Common troublesome symptoms and their impact on quality of life in patients with myelodysplastic syndromes (MDS): results of a large internet-based survey. Leuk Res. 2008;32:691–8.
41. Santini V, Almeida A, Giagounidis A, Platzbecker U, Buckstein R, Beach CL, et al. The Effect of Lenalidomide on Health-Related Quality of Life in Patients With Lower-Risk Non-del(5q) Myelodysplastic Syndromes: Results From the MDS-005 Study. Clin Lymphoma Myeloma Leuk. 2018;18:136–44.e7.
42. Abel GA, Efficace F, Buckstein RJ, Tinsley S, Jurcic JG, Martins Y, et al. Prospective international validation of the Quality of Life in Myelodysplasia Scale (QUALMS). Haematologica. 2016;101:781–8.
43. List AF, Bennett JM, Sekeres MA, Skikne B, Fu T, Shammo JM, et al. Extended survival and reduced risk of AML progression in erythroid-responsive lenalidomide-treated patients with lower-risk del(5q) MDS. Leukemia. 2015;29:2452.
44. Santini V, Almeida A, Giagounidis A, Gropper S, Jonasova A, Vey N, et al. Randomized Phase III Study of Lenalidomide Versus Placebo in RBC Transfusion-Dependent Patients With Lower-Risk Non-del(5q) Myelodysplastic Syndromes and Ineligible for or Refractory to Erythropoiesis-Stimulating Agents. J Clin Oncol. 2016;34:2988–96.
45. Nazha A, Al-Issa K, Hamilton BK, Radivoyevitch T, Gerds AT, Mukherjee S, et al. Adding molecular data to prognostic models can improve predictive power in treated patients with myelodysplastic syndromes. Leukemia. 2017;31:2848–50.
46. Nazha A, Komrokji RS, Garcia-Manero G, Barnard J, Roboz GJ, Steensma DP, et al. The efficacy of current prognostic models in predicting outcome of patients with myelodysplastic syndromes at the time of hypomethylating agent failure. Haematologica. 2016;101:e224–7.
47. Zeidan AM, Sekeres MA, Garcia-Manero G, Steensma DP, Zell K, Barnard J, et al. Comparison of risk stratification tools in predicting outcomes of patients with higher-risk myelodysplastic syndromes treated with azanucleosides. Leukemia. 2016;30:649–57.
48. Komrokji RS, DeZern AE, Zell K, Al Ali NH, Estling C, Zimmerman C, et al. Validation of International Working Group (IWG) Response Criteria in Higher-Risk Myelodysplastic Syndromes (MDS): A Report on Behalf of the MDS Clinical Research Consortium (MDSCRC). Blood. 2015;126:909.
49. Garcia-Manero G, Fenaux P, Al-Kali A, Baer MR, Sekeres MA, Roboz GJ, et al. Rigosertib versus best supportive care for patients with high-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, phase 3 trial. Lancet Oncol. 2016;17:496–508.