The wider perspective: twenty years of clinical trials in myelodysplastic syndromes

Summary

Most patients with myelodysplastic syndromes (MDS) require therapeutic intervention. However, there are few approved treatments for MDS. To explore reasons, we searched clinicaltrials.gov and clinicaltrialsregister.eu for MDS trials from 2000 to 2020. We assessed which agents were under investigation and analysed clinical trial characteristics and continuation rates from phase I to II to III to approval. As such, we identified 384 unique agents in 426 phase I, 430 phase II and 48 phase III trials. Success rates for phase III trials and agents were low, and MDS trials took markedly longer to complete than the average clinical trial. Although success rates were higher when MDS-specific phase I trials were conducted, 52% of the agents had not been evaluated in a phase I trial for MDS. MDS trials often failed to include quality of life, an especially important outcome for older MDS patients. Our work identifies factors potentially contributing to the paucity of available agents for MDS. We suggest a framework to improve clinical research in MDS that might ultimately augment the number of available agents.

Myelodysplastic syndromes (MDS) are myeloid malignancies characterized by bone marrow failure resulting in cytopenias. Severity of MDS is highly variable: while some patients experience an indolent disease course, others rapidly progress to acute myeloid leukaemia (AML). With only four agents — lenalidomide, luspatercept, azacytidine and decitabine — approved by the Food and Drug Administration (FDA), the number and clinical benefit of available treatments for MDS ranks among the lowest for all haematological malignancies. Allogeneic stem cell transplantation is a current, curative treatment option for some MDS patients, but the majority of MDS patients are too old and too frail to qualify for this intensive treatment. Although the pharmacological agents approved for MDS treatment provide temporary relief for subgroups of MDS patients, the development of novel agents that ensure durable therapeutic responses is highly warranted.

Presumably the paucity of available treatments is largely due to the heterogeneous biological nature of MDS and the lack of adequate preclinical models, hampering development of novel approaches. Although these unknowns must affect clinical research, it remains unclear whether the lack of efficacious treatment options is due to a low number of investigated agents in a clinical setting, a low success rate of the investigated agents, or both.

To explore reasons for the persistent scarcity of agents that improve quality and quantity of life for MDS patients, we investigated all clinical trials that were initiated from 2000 to 2020 and systematically analysed their characteristics. As such, we provide insights in the reasons for the lack of efficacious MDS agents, and provide data-driven suggestions to increase the number of available therapeutic agents for MDS patients.

Materials and methods

We conducted a retrospective review of all phase I, II and III clinical trials investigating (novel) drug regimens in MDS patients from 1 January 2000 through 31 December 2020 reported in clinicaltrials.gov and clinicaltrialsregister.eu. We excluded therapies that aimed to reduce side effects of treatment regimens for MDS, such as modulation of graft-versus-host disease after allogeneic stem cell transplantation and iron chelation therapy. To assess trial characteristics, we tabulated start date, completion date, investigated agent, drug type, diseases enrolled, MDS risk categories and trial endpoints from the trial documentation. Completion date is defined as the date the study has ended and participants are no longer being examined or treated (the last participant’s last visit has occurred). The collected trial characteristics are described in detail in Table I.

We examined whether agents progressed from phase I to phase II and from phase II to phase III, each within one year of finalization of the preceding study. If yes, agents were marked successful, if no, they were marked failed. Agents investigated in phase III were marked successful if the trial had met its primary end-point (based on publications available through PubMed); if not, the agent was marked failed. We classified the remainder as ongoing. To determine continuation rates, we divided the number of agents classified as successful by the sum of successful and failed agents. To detect differences in continuation rates, we used Fisher’s exact test with a two-sided significance level of 0.05. We did not adjust for multiple testing. The resulting clinical benefit of approved agents was assessed using the ESMO-MCBS (European Society for Medical Oncology-Magnitude of Clinical Benefit Scale) V1.1, evaluated for haematological malignancies, which takes into account the produced survival benefit or response rates as well as quality of life (QoL) and side effects of the therapy evaluated.
Results

Clinical trial characteristics in MDS

We identified 904 trials, investigating 384 distinct drugs (Fig 1 and Table SI). A total of 426 phase I trials were initiated. Among these, 76% investigated drugs for higher-risk MDS (HR-MDS) and 79% included both patients with MDS and other diseases. While the majority (~60%) of MDS patients have lower-risk disease, only 6% of phase I studies evaluated treatment for lower-risk-MDS (LR-MDS) patients. The remaining trials (18%) did not specify risk categories or included all MDS types. ‘Targeted’ agents (defined in Table I), were the most frequently investigated agent types (45%) followed by hypomethylating agents (17%). The median duration of a finished phase I trial was 41 months (range: 7–175). The number of initiated phase I trials increased from a mean of 20 per year in 2000–2010 to 46 per year in 2010–2020, mainly reflecting an increase in targeted agents evaluated for HR-MDS patients (Fig 2A).

In all, 430 phase II studies were initiated of which 50% only included MDS patients, while the other 50% included both MDS patients and patients suffering from other diseases [e.g. AML or chronic myelomonocytic leukaemia (CMML)]. Similar to the phase I trials, most studies included HR-MDS patients (58%). Again, targeted agents were the most frequently investigated agent type (31%), followed by chemotherapy (18%). The median duration of a phase II trial was 43 months (range: 8–156). From 2000 to 2010, the number of phase II trials increased, but subsequently stabilized (Fig 2B). Response rates (such as 'overall response rate', 'complete response rate', 'partial response rate', 'response rate' and 'haematological response rate') were reported by 69% of studies as primary end-point. In HR-MDS, 62% reported general response rates, and in LR-MDS, 59% of the primary end-points were haematological response rates or transfusion independence, which were heterogeneously defined among the studies included.

Of the 78 phase III trials (Fig 2C), 46% included HR-MDS and 36% LR-MDS, and the remaining trials did not specify which MDS subgroups were included. All trials investigating LR-MDS only included MDS patients. Forty-five percent of the trials involving HR-MDS were limited to HR-MDS patients; the remaining 55% also included AML patients. The median duration of a phase III trial was 45 months (range 17–137). Primary end-points in phase III were survival (35%), transfusion independence (29%) and haematological improvement (13%). In 78% of trials including LR-MDS patients, transfusion independence was the primary end-point. In HR-MDS, survival was the most frequently (72%) reported primary end-point of which 62% reported overall survival and 38% reported surrogate survival end-points such as leukaemia-free survival and progression-free survival. Combining HR and LR, 73% of studies reported survival parameters and 52% reported QoL.

Progression rates of agents under investigation

Fifty-eight percent of agents under investigation in phase I progressed to phase II (top-50 shown in Fig 3). Progression rates were 72% for LR (n = 18) and 59% for HR (n = 171; P = 0.32, 95% CI 0.56–6.7). Agents investigated in studies including only MDS patients had a 72% succession rate compared to 60% for trials that additionally included other diseases (P = 0.13, 95% CI 0.29–1.191). Due to the low number of studies investigating LR-MDS, further stratification was possible only in HR-MDS. Agents investigated in trials that included only HR-MDS patients and no other diseases had a continuation rate of 76% compared with 59% in HR-MDS trials also including other diseases (P = 0.11, 95% CI 0.84–5.70).

The progression rate of agents from phase II to phase III was 32%: 44% for LR and 36% for HR (P = 0.37, 95% CI 0.33–1.60). Agents investigated in HR-MDS studies only including MDS patients had continuation rates of 50%, compared with 36% in HR-MDS studies that also included other diseases (P = 0.13, 95% CI 0.80–4.00). Strikingly, 52% of all investigated agents in phase II did not appear in a phase I study enrolling MDS patients. The success rate of these agents was 21%, compared with 43% for agents that were evaluated in a prior phase I MDS trial (P = 0.009, 95% CI 1.35–0.74).

Table I. Description of analysed trial characteristics.

| Trial characteristics | Specifications |
|-----------------------|---------------|
| Start year            | 2000–2020     |
| Investigated agent    | Generic name  |
| Type of agent         | Cellular      |
|                       | Chemotherapy  |
|                       | Growth-factor |
|                       | Hypomethylating |
|                       | Targeted*     |
|                       | Thalidomide analogues |
| Included diseases     | Only MDS      |
|                       | MDS and other diseases |
| Risk category         | Lower-risk MDS |
|                       | IPSS low–intermediate-1 |
|                       | IPSS-R very low–intermediate |
|                       | Without excess of blasts |
| Higher-risk MDS       | IPSS intermediate–2–high |
|                       | IPSS-R intermediate–very high |
|                       | With excess of blasts |
|                       | Refractory to hypomethylating agents |
|                       | Prior or upcoming stem cell transplantation |
| Not specified         | Including (almost) all risk categories |
|                       | Risk category not specified |
| Trial end-points      | Primary end-points |
|                       | General end-points: survival and QoL |

IPSS, International Prognostic Scoring System; IPSS-R, revised IPSS; MDS, myelodysplastic syndromes; QoL, quality of life.

*We defined targeted therapies as agents that specifically target MDS-associated cellular processes or surface markers.
Twenty-eight of the 44 agents investigated in phase III trials failed to meet the primary end-point or are unpublished. Nine are ongoing and seven showed a clinical benefit compared to the control arm. Agents in phase III trials had a success rate of 20%, success rates were 33% for LR-MDS and 18% for HR-MDS. Currently, four agents are approved by the FDA [luspatercept, lenalidomide, azacytidine (intravenous and oral administration), decitabine] and five by the EMA (luspatercept, lenalidomide, erythropoietin, azacytidine, decitabine).

Clinical benefit of approved agents

We then objectively assessed the resulting clinical benefit of approved MDS agents using the ESMO-MCBS V1.1, which takes into account the produced survival benefit or response rates as well as QoL and side effects of the therapy evaluated. Based on these scores, azacitidine and decitabine both yield a substantial benefit based on superior response rates and a survival benefit compared to placebo, based on studies before FDA approval was obtained. Lenalidomide, erythropoietin and luspatercept yielded only a minor clinical benefit: both showed increased haematological response rates compared to placebo, but no survival benefit or improved HRQoL. Post approval, erythropoietin, lenalidomide, azacitidine, and decitabine showed an increase in QoL compared to placebo.\(^7\)\(\text{–}\)\(11\) QoL results for luspatercept have yet to be published.\(^12\)

Discussion

Here, we observed that the number of initiated MDS trials (\(n = 904\)) and investigated agents (\(n = 384\)) is relatively low compared to recent reports on AML, for which 397 phase II and 64 phase III trials were conducted between 2000 and 2020 to investigate targeted agents alone.\(^5\) The number of trials in LR-MDS is particularly low, while LR-MDS is nearly twice more frequent than HR-MDS.

Although the number of initiated phase I trials and investigated targeted agents for HR-MDS increased over the years, we observe no clear increase at all in trials initiated for LR-MDS. In phase II, the number of initiated trials even decreased over the past ten years. This implies that the preclinical efforts made in the last 20 years have not (yet) resulted in an increase in investigated agents for LR-MDS. The low number of trials for LR-MDS compared with HR-MDS may be partially explained by: (i) the lower clinical incentive to initiate LR-MDS trials since survival and QoL are less affected in this MDS subcategory and (ii) the need of larger sample sizes and longer follow-up than HR-MDS trials. This makes LR-MDS trials particularly expensive and perhaps unattractive for industry to facilitate. Furthermore, we observed that compared with trials in general, continuation rates of agents in all trial phases are low in MDS.\(^13\) However, specifically comparing oncology trials with MDS trials, continuation rates in phase I and II trials in MDS are similar, while in phase III continuation rates to approval or a positive clinical trial are low (20% in MDS vs 36% in other malignancies).\(^13\) This might reflect the relatively small number of agents being developed specifically for MDS: most phase I trials include both MDS and other diseases and many agents were not investigated in a phase I trial including MDS patients prior to the phase II trial. Drug repurposing from one malignancy to another in basket-like trials may lead to the unexpected identification of patients (subgroups) benefitting from a particular intervention.\(^14\) Our data indicate that this strategy is less successful for MDS patients. A separate issue that may arise due to the lack of MDS-specific phase I trials is the lack of data needed to establish the therapeutic index in MDS, i.e. a quantitative measurement of relative safety of the drug for MDS patients. This may lead to
suboptimal dosing of a drug, potentially increasing failure rates due to suboptimal efficacy or increased toxicity. 15

The lack of agents specifically developed for MDS (especially in LR-MDS), may be explained by the limited availability of preclinical models to evaluate therapeutic agents. Few MDS cell lines are available, and virtually all are derived from HR-MDS patients. Moreover, the use of xenotransplant models is particularly challenging as samples of
LR-MDS patients engraft poorly and erythropoiesis in mice is distinct from that in humans. An additional factor presumably hampering agent development is that biology underlying MDS remains poorly understood.16,17 MDS comprise multiple myeloid malignancies that harbour similarities to AML, myeloproliferative neoplasms, aplastic anaemia and inflammatory diseases.3 In recent years, a plethora of mechanisms have been shown to contribute to MDS pathology, including a highly inflammatory environment,18 short telomere length19 and genetic abnormalities.20 However, we are likely barely scratching the surface, and we have a long way to go before MDS is understood on a similar level as cancers such as melanoma, lung cancer and colon cancer. The high number of phase II trials with agents evaluated in MDS that are not preceded by phase I studies including MDS patients — and their low continuation rates — illustrates that agents are perhaps being repurposed without solid underlying evidence for a potential benefit. Further exploration of preclinical models and MDS disease pathology is essential to increase the number of available agents.

Identifying patients most likely to benefit from therapeutic intervention is a crucial aspect of clinical trial design. Trialists in MDS often include patients with MDS and other diseases, making it difficult to define a clear-cut, pre-defined patient population in advance. As HR-MDS is often considered similar to AML, trials in HR-MDS frequently include AML patients. Unfortunately, of the agents that have been recently approved for AML, none are currently available for HR-MDS, although gemtuzumab ozogamycin, glasdegib, enasidenib and ivosidenib were evaluated in pivotal trials also including HR-MDS patients. These unsatisfactory outcomes warrant rethinking trial design or approval requirements for agents evaluated in HR-MDS. Although clearly interpretable cut-off points — such as 20% blasts for MDS and AML — enable clinicians to differentiate patients, clinicians have to be careful not to lose valuable information in our preference for ‘dichotomania’. Less rigid cut-offs likely reflect biology more accurately and would increase therapeutic options for MDS patients that border on AML.21

In general, clinical trials including patients based on biomarkers report higher success rates compared with trials that do not make use of biomarkers (11% vs 1%).22 In MDS, selecting subgroups for inclusion is challenging. The International Prognostic Scoring System Revised (IPSS-R) and WHO classification provide tools to stratify MDS patients. However, within most identified subgroups substantial heterogeneity remains. Recent efforts aimed to further dissect MDS in more homogenous subgroups based on genetic lesions and immunophenotyping.23 This may expedite agent development by targeted discovery. Collaborative initiatives such as HARMONY [https://www.harmony-
that integrate large molecular datasets with trial data, in tandem with adaptive trial designs may facilitate the identification of subgroups of MDS patients benefitting from a specific therapy. We observed that trials in MDS take longer to complete compared to trials in other haematology or oncology studies. Especially the completion time of phase I (41 months in MDS vs 19 months in other diseases) and phase II (43 months in MDS vs 35 months in other diseases) is markedly longer compared with trials in other fields of oncology. Low accrual hampers timely study completion: patients suffering from MDS are in general over 70 years old and suffer from comorbidities, which may reduce willingness to participate in clinical trials. Minimizing the burden of trial participation by reducing the number of hospital visits may provide a solution. This could be achieved by introducing wearable technologies for data collection, participation of local doctors (e.g. general practitioners, local hospitals) in data acquisition, remote delivery of trial medication, and at-home infusion of medicine. Besides increasing willingness of patients to participate in clinical trials, increasing the scope of clinical trials to a continental or global level will facilitate inclusion rates as well. As an additional benefit, results of clinical trials — which are based on results from a highly selected patient population — may become more generalizable, and will predict real-world outcome more accurately.

Finally, we observed a heterogeneous use of endpoints, while the most important end-points — OS and QoL — are not always included in MDS trials. In HR-MDS, all phase III studies evaluated some survival parameter as primary endpoint, of which approximately half of the studies use overall survival as end-point and the remainder surrogate survival endpoints. Surrogate survival end-points have not yet been proven reliable in HR-MDS, and should be avoided if possible. QoL was measured in less than half of all HR-MDS studies. This is problematic, especially since none of the available therapies is curative or significantly increases survival. Since the majority of MDS patients are frequently frail and senior (median age 75 year), we urge QoL to be included in all phase III and possibly phase II MDS trials.

Most phase III studies in LR-MDS reported transfusion independence or haematological improvement as a primary endpoint, and included QoL evaluation. Survival parameters, however, were mostly absent as a primary end-point, although life expectancy is reduced in LR-MDS. Remarkably, lenalidomide and luspatercept were both approved before improvement of QoL was reported, while impact on duration of life was absent and both agents induce side effects. We question whether solely a reduction in transfusion frequency should be sufficient for approval of novel agents, especially if the agent is more costly than supportive care. In recent years, clear definitions of required trial end-points have been developed and QoL assessment has been validated in MDS. We anticipate this will aid in trial development and will hopefully result in new therapeutic agents that benefit MDS patients.

Limitations

We analysed publicly available clinical trial data as objectively as possible. For classification, we were forced to make a few choices that may have impacted our results.

First, we classified drugs as ‘failed’ when no subsequent phase II or III trial started within one year of finalization of a preceding trial with the same compound and when no other ongoing trials of the same drug could be identified. Clearly, extending this time frame leads to identification of fewer drug failures. However, phase III trials are often already initiated before finalization of phase II, and therefore, our one-year timeframe is rather conservative and should sufficiently allow drug developers to proceed to a next phase.

Second, we classified individual compounds into drug classes to give insight in trends over time. Definition of drug classes is not straightforward and can depend on their indication. In this study, we defined targeted therapies as drugs that were developed for disease-specific targets or targets that have more or less specific expression in or on malignant bone marrow cells. Chemotherapy and hypomethylating agents were classified separately. As thalidomide analogues are considered immunomodulatory in most conditions, but act as targeted in del5q MDS, we classified these drugs separately as thalidomide analogues.

Last, we included data from clinicaltrials.gov and EudraCT, two major trial registries. We expect that we have thereby collected data from the majority of MDS trials performed over the past two decades. However, by excluding several other smaller registries, the number of trials reported here is not complete. We expect that the observed trends remain similar when other additional trial registries (such as ISRCTN) would be included.

Conclusions

The low number of initiated clinical trials and their long completion time combined with the lack of drugs specifically developed for MDS underlies the paucity of available effective treatments for these patients. Future research should aim to further to dissect the molecular and microenvironment-related basis of MDS, and trials should be optimized to facilitate timely accrual and efficient identification of patients benefitting from a particular intervention. Only through collaborative efforts and emerging insights in MDS pathobiology, can significant progress be made for patients with MDS.

Author contributions

CD, DGJC, TBP and GJO designed the research. CD, DGJC and TBP collected and analysed data. All authors interpreted the data. CD and DGJC wrote the first draft of the paper. TBP, JJWM, GJO, EHE and AAvdL critically reviewed the manuscript and provided corrections.
Conflicts of interest
The authors have no competing interests.

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Supporting Information
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Complete list of unique agents identified in clinical trials including MDS patients from 2000 to 2020.

References
1. Cazzola M. Myelodysplastic syndromes. N Engl J Med. 2020;383(14):1358–74.
2. Platzbecker U. Treatment of MDS. Blood. 2019;133(10):1096–107.
3. Tanaka TN, Bejar R. MDS overlap disorders and diagnostic boundaries. Blood. 2019;133(10):1086–95.
4. Cucligher DG, Polak TB, Osenkoppele GJ, Uyl-De Groot CA, Cloos J, Zweegman S, et al. Two decades of targeted therapies in acute myeloid leukemia. Leukemia. 2021;35(3):651–60.
5. Kiesewetter B, Cherny NI, Boissel N, Cerisoli F, Dafni U, de Vries EGE, et al. EHA evaluation of the ESMO-magnitude of clinical benefit scale version 1.1 (ESMO-MCBS v1.1) for haematological malignancies. ESMO Open. 2020;5(1):e000611.
6. Santini V. Treatment of low-risk myelodysplastic syndromes. Hematol Am Soc Hematol Educ Program. 2016;2016(1):462–9.
7. 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(2):136–44 e7.
8. Kantarjian H, Issa J-P, 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. 2008;110(8):1794–803.
9. Lübbert M, Suciu S, Bala I, Rüther BH, Platzbecker U, Giagounidis A, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukaemia Group and the German MDS Study Group. J Clin Oncol. 2011;29(15):1987–96.
10. Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, Ochimaru-Reissig R, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol. 2002;20(10):1049–40.
11. Casadevall N, Durie P, Dubois S, Hennery F, Lepage E, Quarré 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(2):321–7.
12. Fenaux P, Platzbecker U, Mufti GJ, Garcia-Manero G, Buckstein R, Santini V, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. N Engl J Med. 2020;382(2):140–51.
13. Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. Biostatistics. 2019;20(2):273–86.
14. Park JH, Siden E, Zoratti MJ, Dron L, Harari O, Singer J, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. Trials. 2019;20(1):572.
15. Salman B, Al-Khabori M. Applications and challenges in therapeutic drug monitoring of cancer treatment: a review. J Oncol Pharm Pract. 2020;27(3):693–701.
16. Stanchina M, Chauldhry S, Karr M, Taylor J. Current state and challenges in development of targeted therapies in Myelodysplastic Syndromes (MDS). Hemato. 2021;2(2):217–36.
17. Rouault-Pierre K, Mian SA, Goulard M, Abarretagi A, Di Tulio A, Smith AE, et al. Preclinical modeling of myelodysplastic syndromes. Leukemia. 2017;31(12):2702–8.
18. Saltman DA, List A. The central role of inflammatory signaling in the pathogenesis of myelodysplastic syndromes. Blood. 2019;138(10):1039–48.
19. Myllymäki M, Redd R, Reilly CR, Saber W, Spellman SR, Gibson CJ, et al. Short telomere length predicts nonrelapse mortality after stem cell transplantation for myelodysplastic syndrome. Blood. 2020;146(26):3070–81.
20. Ogawa S. Genetics of MDS. Blood. 2019;138(10):1049–59.
21. Estey EH, Hasserjian RP, Döhner H. Distinguishing AML from MDS: a fixed blast percentage may no longer be optimal. Blood. 2021. https://doi.org/10.1182/blood.2021011304 [Epub ahead of print].
22. Spreafico A, Hansen AR, Abdul Razak AR, Bedard PL, Sui LL. The future of clinical trial design in oncology. Cancer Discov. 2021;11(4):822.
23. Duetz C, Westers TM, In’t Hout FEM, Cremers EMP, Alhan C, Vennikker-Punt B, et al. Distinct bone marrow immunophenotypic features define the splicing factor 3B mutant myelodysplastic syndromes subtype. Br J Haematol. 2021;199(4):798–803.
24. Brierley CK, Zabor EC, Komoroski RS, DeZern AE, Roboz GJ, Brunner AM, et al. Low participation rates and disparities in participation in interventional clinical trials for myelodysplastic syndromes. Cancer. 2020;126(21):4735–43.
25. Tannock IF, Amir E, Booth CM, Nízsaula S, Ocana A, Seruga B, et al. Relevance of randomised controlled trials in oncology. Lancet Oncol. 2016;17(12):e560–e567.
26. Zeidan AM, Wang R, Gross CP, Gore SD, Huntington SF, Prebet T, et al. Modest improvement in survival of patients with refractory anaemia with excess blasts in the hypomethylating agents era in the United States. Leuk Lymphoma. 2017;58(4):982–5.
27. Bernal T, Martinez-Cambler P, Sánchez-García J, de Paz R, Luizo E, Nomdedeu B, et al. Effectiveness of azacitidine in unselected high-risk myelodysplastic syndromes: results from the Spanish registry. Leukemia. 2015;29(9):1875–81.
28. Sekeres MA, Steensma DP. Rethinking clinical trial endpoints in myelodysplastic syndromes. Leukemia. 2019;33(5):570–5.
29. Visser O, Trama A, Maynadie M, Stiller C, Marcos-Giraga R, De Angelis R, et al. Incidence, survival and prevalence of myeloid malignancies in Europe. Eur J Cancer. 2012;48(17):3257–66.
30. De Witte T, Malcovati L, Fenaux P, Brown D, Symeonidis A, Mittelmann M, et al. Novel dynamic outcome indicators and clinical endpoints in myelodysplastic syndrome; the European LeukemiaNet MDS Registry and MDS-RIGHT project perspective. Haematologica. 2020;105(11):2516–23.
31. Seruga B, Ocana A, Amir E, Tannock IF. Failures in phase III: causes and consequences. Clin Cancer Res. 2015;21(20):4552–60.
32. Fink EC, Ebert BL. The novel mechanism of lenalidomide activity. Blood. 2015;126(21):2366–9.

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