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Recent advances in the treatment of lower-risk non-del(5q) myelodysplastic syndromes (MDS)

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ABSTRACT

Patients with lower-risk myelodysplastic syndromes (MDS) are affected primarily by symptoms of chronic anemia and fatigue rather than progression to acute myeloid leukemia. Severe thrombocytopenia, although less common in lower-risk MDS, is associated with increased risk of bleeding. For anemic patients, the principal aim of treatment is to improve anemia and decrease red blood cell transfusions. For transfusion-dependent patients with lower-risk MDS without chromosome 5q deletion [non-del(5q) MDS], there are limited effective treatments. Erythropoiesis-stimulating agents (ESAs) are generally first-line therapy, yielding frequent responses with a median duration of 18–24 months. Immunosuppressive therapy or allogeneic stem cell transplantation are restricted to select patients. New strategies for ESA-refractory or relapsed patients include lenalidomide, alone or in combination with ESAs; oral azacitidine; and new molecules such as the activin receptor type II ligand traps luspatercept and sotatercept. In thrombocytopenic patients, thrombopoietin receptor agonists are under evaluation. While trials to evaluate these treatment strategies are underway, efforts are needed to optimize therapies through better patient selection and response prediction as well as integrating molecular and genetic data into clinical practice. We provide an overview of current treatment approaches for lower-risk non-del(5q) MDS and explore promising directions for future research.

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1. Introduction

1.1. The burden of MDS

Myelodysplastic syndromes (MDS) are a group of malignant bone marrow disorders characterized by ineffective hematopoiesis leading to refractory cytopenias, with an increased risk of progression to acute myeloid leukemia (AML) [1]. Development of MDS is a multifactorial process that includes mutations in genes affecting various cellular pathways [2,3]. Outcomes in this group of disorders vary widely, and prognostic scoring systems were developed to stratify patients into lower- and higher-risk groups based on laboratory features [4,5]. The widely used International Prognostic Scoring System (IPSS) stratifies patients into 4 risk groups (Low, Intermediate-1, Intermediate-2, and High) based upon the percentage of blasts in the bone marrow, karyotype, and number of cytopenias present [4]. Further refinements to risk-group definitions were made in the revised IPSS (IPSS-R) by assigning greater weight to the cytogenetic risk categories and the severity of cytopenias, and by refining bone marrow blast percentage thresholds [5]. Current studies are integrating data on somatic gene mutations into prognostic indices to further refine risk stratification [6–8].

MDS represents one of the most common hematologic malignancies in Western countries whose incidence markedly increases with age [9]. In patients aged ≥ 70 years in Western countries, the incidence of MDS is conservatively estimated at 30–40 cases per 100,000 population per year [10,11]. With an aging population, an escalation in the number of cases of MDS is expected in the coming years. Notwithstanding the reduced rate of leukemic transformation of lower-risk patients, most patients are affected by anemia and anemia-related symptoms with profound effects on patient-reported outcomes. In addition, patients may have an increased risk of hemorrhagic complications due to thrombocytopenia and platelet dysfunction. In a study of patients with lower-risk MDS, hemoglobin level was the most important independent predictor of health-related quality of life (HRQoL) [12]. In addition, anemia is associated with greater cardiovascular complications and an increased risk of falls [13]. According to data from the European LeukemiaNet MDS (EUMDS) registry, 51% (508 of 1000) of patients with lower-risk MDS received red blood cell (RBC) transfusions within 2 years of diagnosis, of whom 20% (197 of 1000 patients) had received transfusions prior to the diagnosis of MDS [14]. Chronic transfusions may have a profound impact on patients' everyday lives. In a survey of transfusion-dependent (TD) MDS patients, 34% reported that they felt they were burdening their family, and 65% said they would consider treatment that temporarily made them feel worse if it stopped or reduced the need for transfusions [13]. Moreover, previous research has shown that TD MDS patients typically have significantly lower overall survival (OS) than those who do not require regular transfusions [15–17].

Here, we discuss current approaches to the management of lower-risk MDS without chromosome 5q deletion [non-del(5q) MDS], highlighting the potential benefit of therapies currently under development. A detailed evaluation of the current literature, which was carried out in preparation for this review, is provided in the Supporting information.

2. Current treatment approaches for lower-risk non-del(5q) MDS

2.1. MDS treatment guidelines

Improving anemia and anemia-related symptoms while reducing transfusion burden are the therapeutic goals in patients with TD lower-risk MDS. Current guidelines developed by the National Comprehensive Cancer Network [18], European LeukemiaNet (ELN) [19], and European Society for Medical Oncology (ESMO) [20] are generally consistent with regard to the management of patients with lower-risk non-del(5q) MDS. Pre-emptive treatment of asymptomatic patients is not recommended, and treatment should be reserved for those with symptomatic cytopenias, in particular anemia. Initial treatment decisions are based on serum erythropoietin (EPO) level and RBC transfusion requirement. For younger patients, the likelihood of response to immunosuppressive therapy (IST) is also considered [18,19].

3. Treatment of anemia

3.1. RBC transfusion

RBC transfusion remains a key component of supportive care and symptom management for all MDS patients. Approaches vary between countries and individual treatment centres; however, in general, RBC transfusions are recommended for patients with severe anemia (hemoglobin < 8 g/dl) or symptomatic anemia (regardless of hemoglobin level) [18,19].

Although RBC transfusions are essential for short-term symptom management, RBC transfusion dependence (RBC-TD) and its intensity may be a marker of more aggressive disease and define a group of patients with poor prognosis [19]. In fact, RBC-TD is associated with various complications in lower-risk MDS patients, including increased hospitalizations, iron overload, and higher morbidity, due to fluctuations in hemoglobin levels, which may result in shorter OS. Data from a retrospective analysis of 467 MDS patients showed that RBC-TD was associated with both inferior OS ($P < 0.001$) and shorter leukemia-free survival ($P < 0.001$) [15]. In a similar study of 381 untreated patients with lower-risk MDS and del(5q), RBC-TD patients had significantly shorter OS (44 months) compared with transfusion-independent (TI) patients (97 months; $P < 0.0001$) [17]. Although the economic impact of RBC transfusions is not comparable with that of active treatment, it is not negligible

and should be taken into account when evaluating the costs and health benefits of treatment [21].

3.2. Erythropoiesis-stimulating agents (ESAs)

ESAs are generally accepted as the first-line treatment for symptomatic anemia for most patients with lower-risk non-del(5q) MDS. The benefits of recombinant human EPO (rhEPO) have been evaluated in several studies [22–28]. Treatment with rhEPO should be considered for lower-risk patients with low transfusion burden (<2 packed RBC units per month) or low baseline serum EPO levels (<500 mU/ml) [19] as these factors have consistently been shown to predict response to ESAs [22,24,29,30]. Increased access to medical care and increased awareness of the disease have led to earlier diagnosis of lower-risk MDS patients [30]. Consequently, the majority of newly diagnosed lower-risk MDS patients with symptomatic anemia have baseline serum EPO levels <500 mU/ml and either no or a relatively low RBC transfusion requirement and, therefore, would be eligible for a therapeutic trial with ESAs [31].

Other parameters predictive of response to ESAs in MDS patients include normal cytogenetics, low blast percentage (<10%) in the bone marrow, and World Health Organization (WHO) subtypes RA (refractory anemia) and RARS (RA with ring sideroblasts) [32]. In a recent retrospective analysis of IPSS lower-risk patients previously selected for treatment with ESAs on the basis of the above reported criteria (i.e., low serum EPO and transfusion requirement), those who were classified as High and Very High risk according to the IPSS-R had lower response rates to ESAs [33]. In multivariate analysis, IPSS-R score, serum EPO, and serum ferritin level were significantly associated with erythroid response (from 85% response in IPSS-R Very Low-risk patients to 31% in Very High-risk patients). A model based on IPSS-R score, serum EPO, and serum ferritin level may provide additional value in predicting the response to ESAs [33]. In a recent study by Kosmider et al., there was an inverse correlation between the number of somatic gene mutations and response to ESAs [34]. These data suggested that early initiation of ESA therapy may increase the likelihood of a long-term response [34].

ESAs and granulocyte colony-stimulating factor (G-CSF) are believed to act synergistically to promote production of erythrocytes and inhibit apoptosis. Several studies have suggested that patients with ring sideroblasts are more likely to respond to the combination of ESAs and G-CSF than to ESAs alone [35,36]; these data, however, are disputed by others [37]. There are no data from randomized prospective studies to confirm this [38]. With the introduction of higher-dose ESA therapy, including long-acting forms, G-CSF combination therapy may offer less benefit over what can be achieved by ESAs alone (unpublished data from French MDS study group; [39]).

Data from both retrospective and prospective studies indicate that response to growth factors is associated with improved quality of life [26,28,30,40–44]. These studies further suggest that response to ESAs does not increase the risk of AML progression, but instead confers a possible survival benefit [41,42]. This may be due to improved hemoglobin levels, fewer cardiovascular complications, and/or reductions in iron overload in responding patients compared with those who require regular transfusions, as well as more favorable disease biology as reflected by the higher probability of response in those with the lowest IPSS-R score.

The cumulative data strongly support ESAs as effective first-line strategy for a majority of lower-risk MDS patients who have symptomatic anemia and baseline serum EPO <500 mU/ml. Although there is insufficient evidence to conclude that ESAs may improve OS, these data highlight effectiveness of this therapy in reducing or delaying onset of RBC-TD.

3.3. Iron chelation therapy (ICT)

An important side effect of chronic RBC transfusions is systemic iron overload. Among patients with MDS, those with lower-risk disease are more likely to receive transfusions over an extended period of time and, therefore, have a higher risk of iron overload, with up to 60% of these patients reported to develop iron overload [45]. Sustained administration of ICT to these patients continues to be a challenge. Both the ELN and NCCN guidelines recommend ICT for patients receiving chronic RBC transfusions to minimize the consequences of iron overload. Although the guidelines lack uniform recommendations, most recommend initiating ICT in patients with RBC-TD MDS when serum ferritin levels reach 1000–2500 ng/ml [18,19].

The benefits of ICT in patients with thalassemia are well established; however, randomized trials supporting the effectiveness of ICT on clinical outcomes in MDS patients are lacking [46–48]. In a retrospective study, use of ICT was an independent covariate associated with improved OS in patients with lower-risk MDS receiving regular transfusions [49]. Given the difficulties in adequate parenteral chelation with desferrioxamine in the elderly population, 4 prospective Phase 2 studies evaluated the effect of the oral iron chelator deferasirox in RBC-TD patients with lower-risk MDS. The EPIC study included 341 patients with MDS and showed a significant reduction in serum ferritin levels with deferasirox treatment [47,50]. Similarly, in a US multicenter study involving 176 TD lower-risk MDS patients, median serum ferritin levels decreased by 23.2% in patients who completed 12 months of deferasirox treatment, 36.7% in patients who completed 2 years, and 36.5% in patients who completed 3 years despite continued transfusion requirements. This reduction in ferritin levels was accompanied by normalization of non-transferrin-bound serum iron [51]. Deferasirox significantly reduced liver iron concentrations in a study of 47 MDS patients by Porter et al. [46]. Among 159 patients with lower-risk MDS and signs of iron overload, ICT was shown to reduce serum ferritin level [48].

There is increasing evidence to suggest that ICT can improve hematopoiesis and lead to a reduction of RBC transfusion requirements in MDS [52,53]. The exact mechanism by which this occurs is not completely understood. Data from preclinical studies suggest that buildup of reactive oxygen species generated by excess iron may compromise the clonogenic and differentiation potential of hematopoietic stem and progenitor cells [54,55]. Iron overload-induced oxidative stress may also negatively affect hematopoiesis by altering the supportive bone marrow stroma environment [56]. Deferasirox induced erythroid and platelet responses in 11% and 15% of patients, respectively; the 12-month cumulative incidence of RBC transfusion independence (TI) adjusted for death and disease progression was 15.5% [48].

The long-term benefits of ICT in MDS have yet to be demonstrated prospectively in a randomized trial. Data from the ongoing prospective TELESTO trial (ClinicalTrials.gov Identifier: NCT00940602) will hopefully provide insight into the long-term potential of ICT therapy in MDS.

There is accumulating evidence to suggest that iron overload is associated with increased treatment-related mortality after allogeneic stem cell transplantation (allo-SCT) in MDS [57]. In addition, progressive iron overload in the heart can result in cardiac complications. Magnetic resonance imaging (MRI) T2-weighted (T2*) assessment can provide an estimate of cardiac iron deposition, allowing initiation of ICT before cardiac symptoms develop. Low cardiac T2* MRI values (<20 ms) predicted a high risk of developing heart failure in a study of 75 regularly transfused MDS patients [58]. Based on these findings, both lower-risk patients who may be

considered for allo-SCT and those with low heart T2* values may be candidates for ICT.

4. Other treatment options for lower-risk non-del(5q) MDS

4.1. Immunosuppressive therapy (IST)

IST is a treatment option for a select group of lower-risk non-del(5q) patients. Those most likely to respond are aged <60 years with <5% blasts, or those with hypocellular bone marrow, human leukocyte antigen DR15 class II phenotype, presence of a paroxysmal nocturnal hemoglobinuria clone, trisomy 8, or STAT-3-mutant cytotoxic T-cell clones [18,19]. Studies of antithymocyte globulin (ATG), cyclosporin A (CSA), or a combination have reported hematologic improvement in approximately 20–60% of selected patients with MDS [59–65], although patient selection criteria varied considerably between studies, particularly in terms of the MDS subtype and the cytogenetic profile of patients. Results of a multicenter, randomized Phase 3 study confirmed the potential benefits of IST seen in single-arm studies for patients with MDS [64]. In this study, patients were randomized to a combination of horse ATG and CSA versus best supportive care. At 6 months, the proportion of patients who achieved a hematologic response was significantly higher in the ATG plus CSA treatment group (29%) than in the best supportive care group (9%; $p = 0.0156$). Responses to ATG were durable in the majority of patients (median: 16.4 months). Despite higher response rates, no significant effect on transformation-free survival was observed. Adverse events, including hematologic toxicity and associated severe adverse events, such as hemorrhage and infections, have been reported with IST. The monoclonal antibody alemtuzumab, which targets CD52 on lymphocytes, has also produced response rates of up to 68% in relatively small studies of highly selected patients with lower-risk MDS [66–68]. While clinical trials are ongoing in the USA, alemtuzumab is no longer available for use in lower-risk MDS in Europe.

4.2. Hypomethylating agents (HMAs)

HMAs are a well-established treatment option for higher-risk MDS and AML [69–72]. Azacitidine has been shown to prolong survival and improve quality of life in higher-risk MDS patients [73]. HMAs may be an option for lower-risk non-del(5q) patients who are unresponsive or refractory to ESAs and have a low probability of responding to IST [18]. HMAs are approved in the USA and Japan for treatment of lower-risk MDS, but are currently not an approved treatment in the EU. Data suggest that the HMAs azacitidine and decitabine are effective in lower-risk non-del(5q) patients, producing RBC-TI rates of 10–60% and hematologic improvement in 25–55% of patients [74–78]. However, response data are very heterogeneous, and prospective data are limited. In the only prospective study to date, 20% of ESA-refractory patients achieved RBC-TI, although for the majority of these (4 of 6), the duration of response was less than 6 months [79].

Oral administration of azacitidine may allow for extended dosing schedules. Phase 1 studies with oral azacitidine (CC-486) have shown biological activity and tolerability in patients with MDS and AML. In a recent Phase 1/2 trial in which lower-risk patients received oral azacitidine 300 mg once daily in extended treatment schedules, overall response (i.e., complete or partial remission, RBC or platelet TI, or hematologic improvement [International Working Group (IWG) 2006 response criteria]) was attained by 36% of patients receiving 14-day dosing and 41% receiving 21-day dosing [80]. Extended dosing schedules of oral azacitidine are currently under investigation as first-line therapy in patients with lower-risk MDS and thrombocytopenia (ClinicalTrials.gov Identifier: NCT01566695).

4.3. Allogeneic stem cell transplantation (allo-SCT)

Allo-SCT is typically reserved for medically fit higher-risk MDS patients [18]. It may be considered an option for selected lower-risk patients, such as those aged <60–70 years with IPSS Intermediate-1-risk MDS, poor-risk cytogenetics, or persistent blast elevation, if alternative therapeutic options, including growth factors, IST, and HMAs, are ineffective [19,81]. In a decision analysis, Cutler et al. [82] found that delaying allo-SCT maximized OS in lower-risk patients, especially in those aged <40 years. Outcomes were also improved when allo-SCT was done before progression to AML. Using a continuous-time multistate Markov model, Alessandrino et al. [83] recently compared allo-SCT with best supportive care in patients aged ≤65 years. In this analysis, estimated life expectancy increased when transplantation was delayed from the initial stages of MDS until progression to IPSS Intermediate-1 risk, and decreased in higher-risk patients [83]. These data suggest that an optimal therapeutic window for allo-SCT exists between worsening of the disease and leukemic transformation [81–83].

5. Recent advances

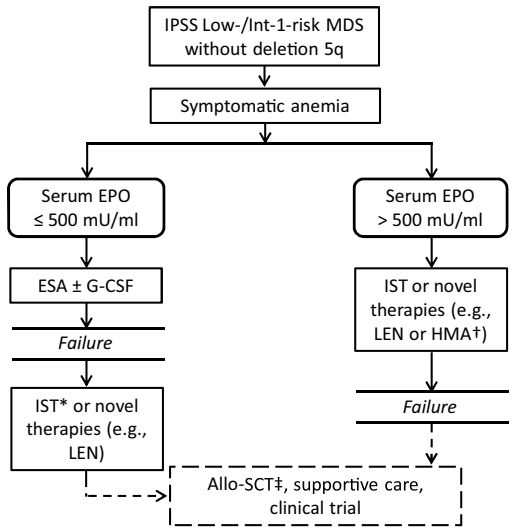
5.1. Treatment of anemia in lower-risk MDS

There is an unmet therapeutic need in lower-risk non-del(5q) MDS patients who are ineligible for or unresponsive to ESAs. Several therapeutic approaches are currently being explored in an effort to reduce RBC-TD in this setting.

5.2. Lenalidomide

Lenalidomide is approved by the US Food and Drug Administration (FDA) for the treatment of patients who have TD anemia due to IPSS lower-risk MDS with del(5q) with or without additional cytogenetic abnormalities [84]; in the EU, its use is restricted to RBC-TD IPSS Low- or Intermediate-1-risk MDS with isolated del(5q) [85]. In non-del(5q) MDS, lenalidomide has been shown to induce durable RBC-TI in 26% of patients [86]. Use of lenalidomide in non-del(5q) patients with anemia who are ineligible for or refractory to ESAs was recently assessed in a Phase 3 placebo-controlled study [87]. Overall, 27% of patients treated with lenalidomide achieved RBC-TI ≥ 8 weeks compared with 2.5% of patients treated with placebo ($P < 0.001$). The median duration of RBC-TI with lenalidomide was 30.9 weeks (95% confidence interval, 20.7–59.1). Low baseline serum EPO level predicted response to lenalidomide [88], and response to lenalidomide was associated with improved HRQoL [89]. The adverse event profile of lenalidomide in non-del(5q) patients was consistent with data in del(5q) MDS patients [84,87], with the principal adverse events being grade 3–4 neutropenia and thrombocytopenia, while the frequency of these events was lower in non-del(5q) patients (49.3% vs. 73.7% for neutropenia and 37.3% vs. 64.2% for thrombocytopenia) [90].

There is evidence to suggest that the efficacy of lenalidomide may be improved in this setting by combining it with ESAs [91–94]. In a Phase 3 trial evaluating lenalidomide with or without rhEPO in 131 RBC-TD patients with lower-risk non-del(5q) MDS refractory to ESAs, combination therapy induced erythroid response in approximately 40% of patients (vs. 23% with lenalidomide alone; $p = 0.044$) and RBC-TI in 24% of patients (vs. 14% with lenalidomide alone; $p = 0.13$) [93]. The median duration of erythroid response was 18.1 months with lenalidomide and 15.1 months with the combination of lenalidomide and rhEPO. A Phase 3 trial by the ECOG-ACRIN Cancer Research Group evaluating lenalidomide alone



* Good probability to respond to IST [18,19].
† Poor probability to respond to IST; NCCN recommendation only [18].
‡ Select patients only [18,19].

Fig. 1. Proposed therapeutic algorithm for lower-risk non-del(5q) MDS. Allo-SCT, allogeneic stem cell transplantation; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony-stimulating factor; HMA, hypomethylating agent;.
Int, Intermediate; IPSS, International Prognostic Scoring System; IST, immunosuppressive therapy; LEN, lenalidomide; MDS, myelodysplastic syndromes; SCT, stem cell transplantation.

or in combination with EPO in lower-risk MDS patients who are either unresponsive or have a low probability to respond to EPO recently completed accrual.

Lenalidomide and azacitidine are used as single agents in patients with lower-risk non-del(5q) MDS after failure of treatment with ESAs [95]. In a retrospective analysis of non-del(5q) MDS patients failing ESAs, rates of erythroid hematologic improvement were significantly higher in patients who received lenalidomide as first-line therapy compared with those who received lenalidomide as second-line therapy following azacitidine treatment (38% vs. 12%; $p = 0.04$) [95]. Although these data require validation in larger cohorts, this finding suggests that lenalidomide should be considered before azacitidine after ESA treatment failure in lower-risk non-del(5q) MDS patients.

6. Future directions

Efforts to optimize the benefits of therapies currently available to patients with lower-risk non-del(5q) MDS remain a priority (Fig. 1). This includes improved methods for profiling patients, predicting response, and integrating the results of molecular studies into clinical practice [96–98]. Combining available agents with different modes of action (e.g., ESAs and HMAs) may improve outcomes and should continue to be evaluated. Evaluation of novel agents that address biologically relevant targets is also underway.

6.1. Activin receptor type II ligand traps

The activin receptor type II ligand traps, luspatercept and sotatercept, were well tolerated and exhibited promising activity in Phase 2 trials of patients with lower-risk MDS who were ineligible for or refractory or unresponsive to ESAs [99,100]. Encouraging response rates were observed with luspatercept in ring sideroblast-positive/*SF3B1* mutation-positive patients, although the number of non-sideroblastic patients in this study was small [100,101]. An open-label extension study to assess long-term safety and tolerability of luspatercept among patients previously enrolled in this Phase 2 trial is ongoing. Luspatercept is being investigated in a Phase 3 study for treatment of anemia in patients with IPSS-R Very Low-, Low-, or Intermediate-risk MDS and ring sideroblasts who require regular RBC transfusions.

6.2. Small-molecule inhibitors

A number of small-molecule inhibitors of cell signaling have shown promising activity in lower-risk MDS. Rigosertib, a PI3K/PLK pathway inhibitor, has shown clinical efficacy in Phase 1 trials with MDS patients (of whom 62% had IPSS lower-risk MDS); studies are ongoing [102]. SCIO-469, a selective inhibitor of p38-α MAPK, was well tolerated in EPO-refractory lower-risk MDS patients; however, effects were modest, producing an erythroid response in only 18% of patients [103]. Similar results were obtained in an open-label, randomized Phase 1 study of the dual p38 MAPK/Tie2 inhibitor ARRY-614 in lower-risk MDS patients [104].

6.3. Treatment of thrombocytopenia

Profound thrombocytopenia is an uncommon event in lower-risk MDS. Platelet transfusions are the only available treatment option other than azanucleosides, and effective treatment of thrombocytopenia remains an unmet medical need.

Thrombopoietin mimetic agents, such as romiplostim and eltrombopag, are promising in their ability to decrease bleeding events and the need for platelet transfusions [105–109]. The need for dose reductions of some disease-modifying agents that cause thrombocytopenia, such as azacitidine, decitabine, and lenalidomide [105,110], may also be avoided. The benefits of romiplostim and eltrombopag therapy have been evaluated in several studies. The largest study randomized 250 lower-risk MDS patients with thrombocytopenia to receive romiplostim or placebo [108]. Compared with placebo, patients in the romiplostim group showed a reduced incidence of bleeding events (relative risk: 0.92) and platelet transfusions (relative risk: 0.77). Platelet response rates were also higher in the romiplostim treatment group (odds ratio: 15.6). Based on the transient increase in peripheral blast cell counts associated with romiplostim treatment, it has been suggested that romiplostim treatment may confer an increased risk of progression to AML. Although results with romiplostim are not consistent across trials [106,108–110], based on updated results from the only prospective randomized Phase 2 trial, short-term treatment with romiplostim did not appear to increase the risk of AML progression [109].

Similar to romiplostim, eltrombopag is also being evaluated for treatment of thrombocytopenia in patients with MDS. Preliminary results from a randomized Phase 2 study of eltrombopag indicate significant improvements in platelet counts in IPSS lower-risk MDS patients with severe thrombocytopenia [111]. At the time of the interim analysis, 23 of 46 patients (50%) in the eltrombopag group achieved a platelet response compared with 2 of 24 patients (8%) in the placebo group ($p = 0.001$). Although a longer follow-up period is required to evaluate the impact on survival, responding patients exhibited significant improvements in fatigue and showed no sign of an increased risk of leukemic transformation. A recent randomized trial of eltrombopag in combination with azacitidine in higher-risk MDS has been prematurely stopped due to lack of benefit (ClinicalTrials.gov Identifier: NCT02158936).

Extended dosing of oral azacitidine 300 mg/day on days 1–21 of each 28-day cycle is being evaluated for treatment of TD lower-risk MDS patients with thrombocytopenia and anemia.

7. Conclusions

In summary, the current goal of therapy for lower-risk MDS is to reduce RBC transfusion requirement to avoid the negative consequences of long-term, chronic transfusions. Whereas ESAs are the mainstay of treatment for patients without del(5q), few available treatment options have been shown to provide a durable impact on RBC transfusion requirement after ESA failure. Recent insights into the biology of MDS will lead to a better understanding of the heterogeneity that exists among MDS patients and an appreciation of the need for a more individualized approach to therapy. Current research is exploring promising agents and combinations with the aim of identifying the best options to allow a more tailored approach to patient management. The search continues for treatment options that can alter the course of the disease.

Disclosures

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A.A. designed the concept and wrote the manuscript. All authors were involved in analyzing the literature, participated in drafting the article, and approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.leukres.2016.11.008.

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