



Guidelines

Part 3: Myelodysplastic syndromes—Treatment of low-risk patients without the 5q deletion



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PICO system

Using the PICO system, the P corresponds to patients with low-risk myelodysplastic syndrome without the 5q deletion, I to the indication of treatments, and the O to the outcome (prognosis).

Thus, 31 studies were found and selected to answer the clinical question ([Appendix I](#)).

Objective: The objective of these guidelines is to evaluate existing treatments for low-risk myelodysplastic syndromes with no 5q deletion.

What treatments exist for low-risk myelodysplastic syndromes without the 5q deletion?

Erythropoietin-stimulating agents

Anemia is one of the main clinical problems for patients with low-risk myelodysplastic syndromes (LR-MDS). The evolution of the disease results in transfusion dependence and iron

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overload. The addition of erythropoietin (EPO) to the *in vitro* culture of erythroid colonies leads to an increased formation of colonies, particularly when it is associated with other hematopoietic factors. Recombinant human erythropoietin (rHEPO, epoetin alfa) and darbepoetin alfa, both prescribed alone or in combination with granulocytic colony stimulating factor (G-CSF), have been extensively shown to improve erythropoiesis and reduce transfusion requirements in patients with anemia and MDS. The Scandinavian group validated a predictive response scheme for erythropoietic agents in which serum EPO (sEPO) levels and transfusion requirements predict response to these drugs^{1,2} (B).

Recombinant human erythropoietin (epoetin alfa)

A retrospective study evaluated MDS patients who were submitted to red blood cell (RBC) transfusions [hemoglobin (Hb) <8.5 g/dL]. Of 192 patients, 83 patients received rHEPO treatment for at least 12 weeks, and of these 24 patients (28.9%) achieved an erythroid response according to the International Working Group (IWG) 2006 criteria. The response to rHEPO was significantly associated with lower levels of endogenous EPO, lower percentage of blasts in bone marrow and less transfusion requirements. The median duration of response was 17 months. There was no difference between treated and untreated patients in terms of progression to acute myeloid leukemia (AML) and other causes of death (infections, bleeding, secondary tumors, cardiovascular and thromboembolic events) and no death could be attributed to rHEPO. No difference was found in the median overall survival (OS) between patients who received and those who did not receive treatment (36 vs. 38 months, respectively). However, a longer OS was found in responders as compared to non-responders (mean 42 vs. 31 months, respectively; *p*-value <0.009) and the response to rHEPO remained an independent prognostic value for OS in the multivariate analysis³ (B).

In a prospective study to evaluate the efficacy of fixed doses of epoetin alfa, 55 patients with a median age of 78 years, low or intermediate-1 International Prognostic Scoring System (IPSS) risk and Hb <10 g/dL received subcutaneous rHEPO (40 000 IU) once weekly for at least 3 months. After a 12-week period, 65.5% of patients achieved an erythroid response (IWG 2006 criteria). Considering the transfusion requirement, rHEPO led to improvements in anemia in 27 of the 33 patients without prior transfusions and in nine of the 22 patients with prior transfusions. Serum EPO levels <200 mU/mL were associated with a better response rate to rHEPO treatment. There was a trend toward a higher response rate in patients with lower risk (by IPSS and the World Health Organization Classification-Based Prognostic Scoring System). Treatment was well tolerated with minor side effects being observed in 7.2% of patients; discontinuation of treatment was required in only one patient due to intractable pruritus⁴ (B).

In a biosimilar study of epoetin alfa, 24 over 65-year-old patients with LR-MDS were treated with 40 000 IU once a week for 12 weeks. No major side effects were observed. Sixteen patients (66.6%) achieved erythroid response and all of them except for one became transfusion-independent for at least 3 months. Responders had significantly higher levels of Hb and less transfusion requirements than non-responders. There

was also a positive correlation between the Hb levels and the quality of life (QoL) of these patients [Functional Assessment of Cancer Therapy-Anemia score (FACT-An): *p*-value <0.003; Mini Mental State Examination (MMSE) evaluation: *p*-value <0.01]⁵ (B).

Darbepoetin alfa

Sixty-two patients, mostly with low and intermediate-1 IPSS risk MDS and endogenous EPO levels <500 mU/mL, received darbepoetin 300 mg subcutaneously once weekly (considered equivalent of 20 000 U of recombinant epoetin alfa three times per week). Forty-four patients (71%) presented erythroid response. There was no response in the platelet or neutrophil lineages. The median time from the onset of treatment to response was 4 weeks. In 11 patients, the treatment had to be discontinued temporarily due to Hb levels above 14 g/dL. Eight of the 13 patients who had been unsuccessfully treated with recombinant EPO alfa or beta responded to darbepoetin. Ten of the patients who did not respond to darbepoetin alone received G-CSF for 12 weeks with only two responding. The overall response rate was 74%⁶ (B).

Thirty-seven patients (23 transfusion-dependent) with low IPSS risk and anemia received darbepoetin (150 µg) subcutaneously once a week. Erythroid responses were detected in 40.5% patients with a stable Hb level >9.5 g/dL being seen in most after 7–22 months of treatment. Serum EPO levels <100 mU/mL, no excess of blasts in the bone marrow, low or no RBC transfusion requirements and hypoplastic bone marrow were confirmed as predictors of erythroid response in multivariate analyses. No significant side effects were reported during the study⁷ (B).

Ten studies (647 patients) were included in a recently published meta-analysis to evaluate the efficacy and safety of darbepoetin. The erythroid response rate varied from 38 to 72%; the response duration was from 12 to more than 51 months. Better responses were observed in patients with sEPO <100 mU/mL and in patients not previously treated with erythropoiesis-stimulating agents. Higher hemoglobin levels, higher doses, transfusion independence and lower risk disease were associated with better response rates⁸ (A).

Erythropoietin vs. darbepoetin

A meta-analysis involving rHEPO-treated MDS patients (22 studies; 925 patients) or patients who received darbepoetin alfa (8 studies; 389 patients) evaluated erythroid response using the IWG criteria (rHEPO: 584 patients; Darbepoetin: 389 patients). Univariate analysis showed a better erythroid response for patients with refractory anemia or refractory anemia with ring sideroblasts (RA/RARS; *p*-value <0.001), low sEPO levels and the use of a fixed-dose regimen as opposed to a weight-based regimen. There was no difference in erythroid response rates between rHEPO and darbepoetin (57.6 vs. 59.4%, respectively; *p*-value = 0.828)⁹ (A).

rHEPO vs. rHEPO plus filgrastim (G-CSF)

Anemic patients with LR-MDS were randomized to receive rHEPO (30 000 IU weekly; *n* = 15) or the same dosage of rHEPO

plus G-CSF (300 µg twice weekly; $n = 15$) for at least 8 weeks. An erythroid response was observed in 40% of patients treated with r-HEPO alone compared to 73.3% of patients receiving the combined regimen, but there was no statistical difference between the groups. Taking into consideration the need for transfusions, rHEPO was effective in improving anemia in 55.5% of previously non-transfused patients and in 16.6% of previously transfused patients, whereas the combined treatment induced a favorable response in 80 and 60% non-transfused and previously transfused patients, respectively. No relevant side effects were reported in the two groups. After 4 months of treatment, the response rate was 33% for rHEPO and 62.5% for rHEPO plus G-CSF (p -value = 0.032). QoL was assessed using the FACT-An questionnaire at the beginning of treatment and after 8 and 16 weeks. There was an apparent correlation between erythroid response and QoL¹⁰ (B).

Darbepoetin plus filgrastim (G-CSF)

In a study conducted by the French group, 95 patients with LR-MDS received darbepoetin alfa (500 µg) subcutaneously every 2 weeks. For non-responders at 12 weeks, filgrastim was added to the treatment (300 µg twice weekly; this dose was subsequently adjusted to maintain white cell count between 5.0 and $10.0 \times 10^9 L^{-1}$) and maintained for an extra 12 weeks. Erythroid response according to the IWG criteria at 12 weeks was achieved in 48% of patients. The addition of filgrastim in non-responders increased the overall response rate to 56% at 24 weeks. Improvement in the QoL assessed by FACT-An was seen in responders, but no difference was detected in physical performance. With a mean follow-up of 52 months, mean response duration was not reached and the 3-year cumulative incidence of AML and OS were 14.5 and 70%, respectively. The sEPO level was the only independent predictor of response at 12 weeks with the most discriminant cutoff value being 100 mU/mL¹¹ (B).

Recommendations

A better response to erythropoiesis-stimulating agents is associated with a lower serum EPO level, lower RBC transfusion requirements and a lower percentage of blasts in the bone marrow. Responders tend to have better OS and improved QoL. Side effects are minimal, and no increased risk for leukemic transformation has been documented. Erythropoietin and darbepoetin alfa, associated with filgrastim (G-CSF) or not, prove to be effective.

Immunosuppressant agents

Immunosuppressive therapy, which includes antithymocyte globulin, cyclosporin A and alemtuzumab, has been used based on an observation of abnormal T-cell function in patients with LR-MDS, increased levels of proinflammatory cytokines and apoptosis of bone marrow cells. The National Comprehensive Cancer Network (NCCN) guidelines list five characteristics that may indicate the possibility of response to immunosuppressants: IPSS score <1, age <60 years,

hypocellular bone marrow, presence of the paroxysmal nocturnal hemoglobinuria (PNH) clone and expression of HLA-DR15.

In a retrospective study, 29 patients with LR-MDS were treated with cyclosporin A alone (2–6 mg/kg/day to maintain blood concentration at 150–250 ng/mL) or associated with antithymocyte globulin ($n = 5$). Eight patients (27.6%) had complete remission and nine (31.0%) achieved some hematological improvement resulting in an overall response rate of 58.6%. The median OS was 8.6 years with OS at 5 and 10 years of 74.5 and 48.3%, respectively. OS rate of responders at 5 and 10 years was 100 and 72.7%, respectively, was better than in non-responders (41.7 and 15.6%, respectively; p -value <0.001)¹² (B).

Seventy-one patients with LR-MDS received either antithymocyte globulin therapy for 4 days (dose 4 mg/kg/day) followed by cyclosporin A (3–5 mg/kg/day) for 3 months or cyclosporin A alone. The total hematological response rate according to the IWG 2006 criteria was 77.5% (55/71 cases) with 11 complete responses. Of the responders, 77% had an erythroid response with the median increase in Hb being 3.6 g/dL. Of the 71 cases, 60 (84.5%) were alive at the end of the 24-month follow-up period. During this follow-up, 69 patients remained without increased blast cell counts or leukemic transformation¹³ (B).

Recommendations

In selected patients with LR-MDS, the use of immunosuppressants (cyclosporin A alone or in combination with antithymocyte globulin) leads to a high rate of long-lasting erythroid response.

Thrombomimetic drugs

Thrombocytopenia occurs in 37–65% of individuals with MDS and can result in hemorrhagic complications, including mortality in around 24% of cases. In addition, many of the agents used to treat MDS can cause or exacerbate thrombocytopenia. Romiplostim is an agent that binds and activates thrombopoietin receptors, stimulating platelet formation through a mechanism similar to that of endogenous thrombopoietin.

Twenty-nine patients with MDS receiving decitabine were randomized to receive either romiplostim (750 µg; $n = 15$) or placebo ($n = 15$). The group receiving romiplostim did not present a reduction in major bleeding events compared to the Placebo Group but presented a reduction in the need for transfusions and in the number of transfused units. The drug was well tolerated and only one patient in each group progressed to AML¹⁴ (A).

The results of the first phase of a blinded, randomized, controlled phase II study on the use of eltrombopag vs. placebo for LR-MDS patients with thrombocytopenia were recently published. Ninety patients were analyzed with 59 being allocated to the Eltrombopag Group. The median follow-up to evaluate the platelet response was 11 weeks with platelet response being reported in 47% of the Eltrombopag Group vs. 3% in the Placebo Group (p -value = 0.0017). There were more bleeding events in the Placebo Group (42 vs. 14%; p -value = 0.0025).

Progression to AML or disease progression occurred in 12% of the Eltrombopag Group vs. 15% of the Placebo Group (p -value = 0.81)¹⁵ (B).

Recommendations

Romiplostim does not lead to a decrease in major thrombocytopenic events but leads to a reduction in the need for transfusions and in the quantity of transfused units with a good tolerance profile. Eltrombopag leads to increases in platelets and decreases in bleeding events without raising the risk of leukemic transformation.

Immunomodulatory agents

Lenalidomide

Forty-three patients with MDS (88% low or intermediate-1 IPSS risk) without response to erythropoietin (77%) or thalidomide (30%) and transfusion-dependent or with symptomatic anemia received lenalidomide at a dose of 25 or 10 mg/day for 21 days in 28-day cycles; the results were evaluated after 16 weeks. Neutropenia (65% of patients) and thrombocytopenia (74% of patients) were the most common side effects. The response rate was 57% for patients with normal karyotypes, 83% for those with karyotypes with del(5q) and 12% for other karyotypes (p -value = 0.007)¹⁶ (B).

A dose of 10 mg/day of lenalidomide was used in 28-day cycles in a study of 214 transfusion-dependent patients with low or intermediate-1 IPSS risk MDS, without del(5q) and with a platelet count above $50.0 \times 10^9 \text{ L}^{-1}$. A 43% erythroid response was observed with 26% of transfusion independence and 18–27% hematological toxicity¹⁷ (B).

In a randomized, double-blind, placebo-controlled (2:1) phase III study of patients with LR-MDS without del(5q) and ineligible for or refractory to erythropoiesis stimulating agents, an improvement in transfusion independence was observed in a group (n = 160) treated with lenalidomide (26.9 vs. 2.5%) with a median response of 30.9 months [95% confidence interval (95% CI): 20.7–59.1 months]. The presence of transfusion independence at 8 weeks was associated to an improvement in QoL (p -value = 0.01). The most important side effects included neutropenia and thrombocytopenia¹⁸ (B).

Efficacy and safety of lenalidomide in the treatment of LR-MDS with or without del(5q) was evaluated in a meta-analysis considering 17 studies with 2160 patients, 607 of whom were without del(5q). Patients with the del(5q) had a higher erythroid response (79%; 95% CI: 71–87%) than those without the del(5q) (31%; 95% CI: 24–37%; p -value = 0.002). In both del(5q) and non-del(5q) patients, transfusion burden ≤ 4 units/8 weeks was associated with a higher rate of RBC transfusion independence¹⁹ (A).

The efficacy of the combination of lenalidomide- and erythropoiesis-stimulating agents was evaluated in a phase III study with 131 LR-MDS patients without del(5q) but with transfusion dependency after failure of erythropoiesis-stimulating agents. Patients received lenalidomide alone (10 mg/day) for 21 days every 28 days or associated with EPO (60 000 U/week). Erythroid response (IWG 2006 criteria)

was observed in 23.1% of the cases with lenalidomide alone and 39.4% in the association (p -value = 0.044); transfusion independence was achieved in 13.8 and 24.2%, respectively (p -value = 0.13). The median response duration was similar in both groups (p -value = 0.47) as was the incidence of side effects. The basal level of sEPO and the G polymorphism of the CRBN gene were predictive of erythroid response²⁰ (B).

Thalidomide

Sixty patients with MDS were treated with thalidomide (100 mg/day initially with progressive increases to up to 400 mg/day) for 12 weeks. Seventeen (28%) of the 60 patients achieved hematological responses. Four (9.5%) patients attained complete or partial remission. The most common side effects were constipation (85%), leukopenia (50%) and dizziness (41.7%)²¹ (C).

Recommendations

Lenalidomide can be used in LR-MDS patients who are refractory or non-candidates for erythropoiesis-stimulating agents. LR-MDS patients without del(5q) present an improvement in the erythroid response with a transfusion independence rate of around 25%. EPO can improve the erythroid response rate when combined with lenalidomide. Thalidomide induced a hematological response rate of 28% and complete remission in 9.5% of the patients with important side effects.

Hypomethylating agents

Hypomethylating agents [azacitidine (AZA) or decitabine (DAC)] have a clear role in the treatment of high-risk MDS. These drugs have also been used in patients of lower risk who are transfusion-dependent and refractory to erythropoiesis-stimulating agents. In a retrospective study of the Italian group, 74 patients with LR-MDS, 84% of whom were transfusion dependent, were treated with different AZA regimens giving an overall response rate of 45.9% with hematologic improvement in 20.3%. Responders had a better OS of 94% vs. 54% at 2.5 years (p -value < 0.0014). Grade 3 or 4 adverse events included myelosuppression (21.6%) and infection (6.8%)²² (B).

Three prospective studies have been published on the use of hypomethylating agents in LR-MDS, two with AZA^{23,24} (B) and one with DAC²⁵ (B). The hematological response rates ranged from 10 to 60%. In the Nordic study with 30 patients, 20% became transfusion independent with a short median response and high complication rate²⁴ (B). A randomized phase II study was published as an abstract. The trial compared AZA (75 mg/m²) for 5 days (n = 20) vs. supportive care (n = 20) in patients with LR-MDS who did not have the del(5q) and had no response or were refractory to erythropoiesis-stimulating agents. Using the IWG 2006 criteria, a higher erythroid response rate was observed in patients in the AZA arm (43.7 vs. 5.5%). Moreover, transfusion independence was observed in 31% of cases of the AZA arm with 53% of adverse events (myelotoxicity)²⁶ (B).

Recommendations

A high rate of myelosuppression after the use of AZA is common in patients with LR-MDS, no del(5q) and refractory to erythropoiesis-stimulating agents although erythroid response can be obtained.

Iron chelators

Iron overload in patients with MDS is due to recurrent transfusions, increased iron absorption and ineffective erythropoiesis. Iron overload leads to organ damage, particularly the liver, heart and endocrine glands. Patients with transfusion-dependent MDS have lower OS and leukemia-free survival.

Deferasirox

The use of deferasirox in the clinical practice was investigated in a prospective, multicenter, observational, non-interventional study. Data of 123 patients with MDS who had not received iron chelators were compared with 44 patients who had received iron chelators. A reduction in serum ferritin levels was seen in treatment-naïve patients, but the decrease was not significant in those previously treated with chelators. Side effects were documented in 34.1% of the patients in the treatment-naïve group and in 40.9% of the previously chelated patients. Most of the side effects were diarrhea, nausea, increased serum creatinine levels and rash of low to moderate severity²⁷ (B).

One hundred and seventy-three patients with low- to intermediate-risk MDS who had received at least 20 units of RBC and who had serum ferritin levels >1000 µg/L were selected to receive an initial dose of 20 mg/kg/day of deferasirox with subsequent doses being readjusted to a maximum of 40 mg/kg/day based on the serum ferritin level, patient weight and serum creatinine. Efficiency was assessed by comparing ferritin levels at baseline and at 1, 2 and 3 years. In the first year, mean ferritin fell by 23.2% ($n=91$), by 36.6% at the end of the second year and by 36.5% at the end of the third year. Of the 173 patients, 51 (28%) presented hematological improvements according to the IWG 2006 criteria. During the 3-year course, side effects, death and problems to administer the drug were responsible for a 79.7% rate of discontinued treatment. The main adverse effects were related to gastrointestinal symptoms²⁸ (B).

Patients with LR-MDS ($n=33$) and HR-MDS/AML ($n=27$) and serum iron levels of at least 1000 ng/mL were treated with deferasirox at a dose of 20 mg/kg/day for at least 1 year. An absolute reduction in ferritin levels compared to baseline values was obtained in the patients with LR-MDS. The most common side effects were related to the gastrointestinal tract²⁹ (B).

No study was eligible for inclusion in a systematic review of randomized clinical trials conducted to evaluate the use of deferasirox in patients with MDS³⁰ (A). However, a meta-analysis of eight observational studies with different types of chelators involving 1562 participants (median participants per study: 153; range: 78–534) showed a trend toward longer OS in

patients who took chelators particularly those with LR-MDS. On average, patients who received chelators survived 5 years longer than those who did not use this drug³¹ (B).

Recommendations

LR-MDS patients with ferritin levels >1000 µg/L showed a significant reduction in these levels after 1 year of treatment with deferasirox (initial dose of 20 mg/kg/day and maximum dose of 40 mg/kg/day). There appears to be an improvement in OS in LR-MDS patients with the use of iron chelators.

Appendix A. Appendix I

1. Clinical question

What treatments exist for LR-MDS without the 5q deletion?

2. Structured question (PICO)

Patient patients with low-risk MDS without the 5q deletion
Intervention transfusion of blood components (red blood cells and platelets)

Antibiotic therapy

Iron chelators

Erythropoiesis-stimulating agents (erythropoietin, darbepoetin alfa alone or in combination with G-CSF)

Thalidomide and lenalidomide

Immunosuppressive agents (antithymocyte globulin and cyclosporin A)

Thrombomimetic agents (romiplostim and eltrombopag)

Hypomethylating agents

Outcome prognosis/treatment

3. Initial eligibility criteria for studies

- Components of PICO
- No time limit
- No limit of languages
- Full text availability

4. Search strategies

#1: (Myelodysplastic syndrome OR myelodysplastic syndromes OR dysmyelopoietic syndromes OR dysmyelopoietic syndrome OR hematopoietic myelodysplasia OR hematopoietic myelodysplasias) = 23 074 studies

5. Selection of articles

Initially selected by the title, sequentially by the abstract and finally by the full text, the latter being subjected to critical evaluation and extraction of outcomes related to the outcomes.

6. Critical evaluation and strength of evidence

The strength of the evidence of the studies was defined taking into account the study design and the corresponding risks of bias, the results of the analysis (magnitude and precision) and relevance and applicability (Oxford/GRADE).^{32,33}

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Hellström-Lindberg E, Negrin R, Stein R, Krantz S, Lindberg G, Vardiman J, et al. Erythroid response to treatment with G-CSF plus erythropoietin for the anaemia of patients with myelodysplastic syndromes: proposal for a predictive model. *Br J Haematol.* 1997;99(2):344-51.
2. Hellström-Lindberg E, Gulbrandsen N, Lindberg G, Ahlgren T, Dahl IM, Dybedal I, et al., Scandinavian MDS Group. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. *Br J Haematol.* 2003;120(6):1037-46.
3. Musto P, Villani O, Martorelli MC, Pietrantonio G, Guariglia R, Mansueto G, et al. Response to recombinant erythropoietin alpha, without the adjunct of granulocyte-colony stimulating factor, is associated with a longer survival in patients with transfusion-dependent myelodysplastic syndromes. *Leuk Res.* 2010;34(8):981-5.
4. Balleari E, Clavio M, Arboscello E, Bellodi A, Bruzzone A, Del Corso L, et al. Weekly standard doses of rh-EPO are highly effective for the treatment of anemic patients with low-intermediate 1 risk myelodysplastic syndromes. *Leuk Res.* 2011;35(11):1472-6.
5. Castelli R, Deliliers GL, Colombo R, Moreo G, Gallipoli P, Pantaleo G. Biosimilar epoetin in elderly patients with low-risk myelodysplastic syndromes improves anemia, quality of life, and brain function. *Ann Hematol.* 2014;93(9):1523-9.
6. Mannone L, Gardin C, Quarre MC, Bernard JF, Vassilief J, Ades L, et al., Groupe Francaise des Myelodysplasies. High-dose darbepoetin alpha in the treatment of anaemia of lower risk myelodysplastic syndrome results of a phase II study. *Br J Haematol.* 2006;133(5):513-9.
7. Musto P, Lanza F, Balleari E, Grossi A, Falcone A, Sanpaolo G, et al. Darbepoetin alpha for the treatment of anaemia in low-intermediate risk myelodysplastic syndromes. *Br J Haematol.* 2005;128(2):204-9.
8. Park S, Fenaux P, Greenberg P, Mehta B, Callaghan F, Kim C, et al. Efficacy and safety of darbepoetin alpha in patients with myelodysplastic syndromes: a systematic review and meta-analysis. *Br J Haematol.* 2016;174(5):730-47.
9. Moyo V, Lefebvre P, Duh MS, Yektashenas B, Mundle S. Erythropoiesis-stimulating agents in the treatment of anemia in myelodysplastic syndromes: a meta-analysis. *Ann Hematol.* 2008;87(7):527-36.
10. Balleari E, Rossi E, Clavio M, Congiu A, Gobbi M, Grosso M, et al. Erythropoietin plus granulocyte colony-stimulating factors better than erythropoietin alone to treat anemia in low-risk myelodysplastic syndromes: results from a randomized single-centre study. *Ann Hematol.* 2006;85(3):174-80.
11. Kelaidi C, Beyne-Rauzy O, Braun T, Sapena R, Cougoul P, Adès L, et al. High response rate and improved exercise capacity and quality of life with a new regimen of darbepoetin alfa with or without filgrastim in lower-risk myelodysplastic syndromes: a phase II study by the GFM. *Ann Hematol.* 2013;92(5):621-31.
12. Hata T, Tsushima H, Baba M, Imaizumi Y, Taguchi J, Imanishi D, et al. Long-term outcome of immunosuppressive therapy for Japanese patients with lower-risk myelodysplastic syndromes. *Int J Hematol.* 2013;98(6):687-93.
13. Xiao L, Qi Z, Qiusheng C, Li X, Luxi S, Lingyun W. The use of selective immunosuppressive therapy on myelodysplastic syndromes in targeted populations results in good response rates and avoids treatment-related disease progression. *Am J Hematol.* 2012;87(1):26-31.
14. Greenberg PL, Garcia-Manero G, Moore M, Damon L, Roboz G, Hu K, et al. A randomized controlled trial of romiplostim in patients with low- or intermediate-risk myelodysplastic syndrome receiving decitabine. *Leuk Lymphoma.* 2013;54(2):321-8.
15. Oliva EN, Alati C, Santini V, Poloni A, Molteni A, Niscola P, et al. Eltrombopag versus placebo for low-risk myelodysplastic syndromes with thrombocytopenia (EQoL-MDS): phase 1 results of a single-blind, randomised, controlled, phase 2 superiority trial. *Lancet Haematol.* 2017;4(3):e127-36.
16. List A, Kurtin S, Roe DJ, Buresh A, Mahadevan D, Fuchs D, et al. Efficacy of lenalidomide in myelodysplastic syndromes. *N Engl J Med.* 2005;352(6):549-57.
17. Raza A, Reeves JA, Feldman EJ, Dewald GW, Bennett JM, Deeg HJ, et al. Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1 risk myelodysplastic syndromes with karyotypes other than deletion 5q. *Blood.* 2008;111(1):86-93.
18. Santini V, Almeida A, Giagounidis A, Gröppler S, Janasova 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(25):2988-93.
19. Lian XY, Zhang ZH, Deng ZQ, He PF, Yao DM, Xu ZJ, et al. Efficacy and safety of lenalidomide for treatment of low-/intermediate-1-risk myelodysplastic syndromes with or without 5q deletion: a systematic review and meta-analysis. *PLoS ONE.* 2016;11(11):e0165948.
20. Toma A, Kosmider O, Chevret S, Delaunay J, Stamatoullas A, Rose C, et al. Lenalidomide with or without erythropoietin in transfusion-dependent erythropoiesis-stimulating agent-refractory lower-risk MDS without 5q deletion. *Leukemia.* 2016;30(4):897-905.
21. Chung CY, Lin SF, Chen PM, Chang MC, Kao WY, Chao TY, et al. Thalidomide for the treatment of myelodysplastic syndrome in Taiwan: results of a phase II trial. *Anticancer Res.* 2012;32(8):3415-9.
22. Musto P, Maurillo L, Spagnoli A, Gozzini A, Rivellini F, Lunghi M, et al., Ad Hoc Italian Cooperative Study Group on Azacitidine in Myelodysplastic Syndromes Acute Leukemias. Azacitidine for the treatment of lower risk myelodysplastic syndromes: a retrospective study of 74 patients enrolled in an Italian named patient program. *Cancer.* 2010;116(6):1485-94.
23. Fili C, Malagola M, Follo MY, Finelli C, Iacobucci I, Martinelli G, et al. Prospective phase II study on 5-days azacitidine for treatment of symptomatic and/or erythropoietin unresponsive patients with low/INT-1-risk myelodysplastic syndromes. *Clin Cancer Res.* 2013;19(12):3297-308.
24. Tobiasson M, Dybedahl I, Holm MS, Karimi M, Brandefors L, Garelus H, et al. Limited clinical efficacy of azacitidine in transfusion-dependent, growth factor-resistant, low- and Int-1-risk MDS: Results from the nordic NMDSG08A phase II trial. *Blood Cancer J.* 2014;4:e189.
25. Garcia-Manero G, Jabbour E, Borthakur G, Faderl S, Estrov Z, Yang H, et al. Randomized open-label phase II study of decitabine in patients with low- or intermediate-risk myelodysplastic syndromes. *J Clin Oncol.* 2013;31(20):2548-53.
26. Sanchez-Garcia J, Falantes J, Medina A, Hernandez-Mohedo F, Torres-Sabariego A, Bailen A, et al. Final results of phase II randomized trial of azacitidine versus support treatment in patients with low-risk myelodysplastic syndrome without the 5q deletion. *Leuk Res.* 2015;39(1):S59.
27. Gattermann N, Jarisch A, Schlag R, Blumenstengel K, Goebeler M, Groschek M, et al. Deferasirox treatment of iron-overloaded chelation-naïve and prechelated patients

- with myelodysplastic syndromes in medical practice: results from the observational studies eXtend and eXjange. *Eur J Haematol.* 2012;88(3):260–8.
28. List AF, Baer MR, Steensma DP, Raza A, Esposito J, Martinez-Lopez N, et al. Deferasirox reduces serum ferritin and labile plasma iron in RBC transfusion-dependent patients with myelodysplastic syndrome. *J Clin Oncol.* 2012;30(17):2134–9.
 29. Kim IH, Moon JH, Lim SN, Sohn SK, Kim HG, Lee GW, et al. Efficacy and safety of deferasirox estimated by serum ferritin and labile plasma iron levels in patients with aplastic anemia, myelodysplastic syndrome, or acute myeloid leukemia with transfusional iron overload. *Transfusion.* 2015;55(7):1613–20.
 30. Meerpohl JJ, Schell LK, Rucker G, Fleeman N, Motschall E, Niemeyer CM, et al. Deferasirox for managing iron overload in people with myelodysplastic syndrome. *Cochrane Database Syst Rev.* 2014;(10):CD007461.
 31. Mainous AG 3rd, Tanner RJ, Hulihan MM, Amaya M, Coates TD. The impact of chelation therapy on survival in transfusional iron overload: a meta-analysis of myelodysplastic syndrome. *Br J Haematol.* 2014;167(5):720–3.
 32. Goldet G, Howick J. Understanding GRADE: an introduction. *J Evid Based Med.* 2013;6(1):50–4.
 33. Levels of Evidence and Grades of Recommendations, Oxford Centre for Evidence Based Medicine. Available at: http://cebm.jr2.ox.ac.uk/docs/old_levels.htm