How we treat lower risk Myelodysplastic syndromes

Pierre Fenaux and Lionel Adès
Hôpital Avicenne – Service d’hématologie clinique -Paris 13 university - France

Correspondance: Pierre Fenaux, MD, PhD
Groupe Francophone des Myelodysplasies, France
Hôpital Avicenne – Service d’hématologie clinique -Paris 13 university
Assistance Publique-Hopitaux de Paris (AP-HP)
125 rue de Stalingrad
93009 Bobigny – France

e-mail: pierre.fenaux@avc.aphp.fr
Abstract

Lower risk MDS are defined as having low or intermediate 1 risk by the IPSS, and are mainly characterized by anemia in most cases. Supportive care, mainly red blood cell transfusions, remains an important component of their treatment, but expose patients to insufficient correction of anemia, alloimmunization, and organ iron overload (for which the role of iron chelation remains debated). Treatment aimed at preventing anemia recurrence should therefore be used whenever possible. ESAs remain the first line treatment of anemia in most lower risk MDS without del(5q), while anemia of low risk MDS with del 5q responds to Lenalidomide in two thirds of the cases, but this drug should be used cautiously because profound cytopenias may occur initially. Treatment after failure of those first line therapies are overall disappointing, many patients eventually requiring long-term transfusions, but encouraging results have been reported with hypomethylating agents and lenalidomide. Selected patients respond to antithymocyte globulins, while thrombopoietin receptor agonists are under investigation in lower risk MDS with thrombocytopenia. Some patients, while remaining « lower risk » MDS, have severe cytopenias and/or poor prognostic factors using newer prognostic parameters, and/or resistance to treatment, making them rapidly candidates for more intensive approaches, including allogeneic stem cell transplantation (SCT).
Myelodysplastic syndromes (MDS) are clonal stem cell disorders characterized by ineffective hematopoiesis leading to blood cytopenias and by a high incidence of progression to acute myeloid leukemia (AML)\(^1\). The pathophysiology of MDS is a multistep process involving genetic changes detectable by conventional cytogenetic techniques or smaller anomalies detectable only by more sophisticated methods like SNP array technology\(^2,3,4\) or sequencing techniques. Somatic mutations, now detected in most MDS cases\(^5\), can involve genes encoding signaling molecules (NRAS, KRAS, CBL, JAK2, FLT3)\(^5,6\), epigenetic regulators (TET2, ASXL1, EZH2, UTX, IDH1, IDH2, DNMT3A, SETBP1)\(^5,7-11,12\), splicing factors (SF3B1, SRSF2, ZRSF2, U2AF1)\(^13,14,15,16\) and transcription regulators (RUNX1, NPM1 and TP53)\(^5,17-19\). Widespread gene hypermethylation, on the other hand, is a major finding during progression of MDS\(^20,21\).

Main prognostic factors in MDS include the number and importance of cytopenias, marrow blasts percentage and marrow cytogenetic abnormalities, combined in a “classical” International Prognostic Scoring System (IPSS), very recently revised (“revised” IPSS or IPSS-R), that distinguishes between various subgroups with significantly different risk of progression to AML and survival\(^22,23\). Other prognostic factors include the presence of grade >=2 marrow fibrosis\(^24\), of certain somatic gene mutations\(^5\) and possibly of some flow cytometry parameters\(^25\), but the last 2 tests are currently not routinely performed in most laboratories.

Although the division is schematic, it is customary since publication of the classical IPSS to separate MDS in “higher risk” MDS (corresponding to IPSS High or intermediate-2) and “lower risk” (corresponding to IPSS Low or intermediate-1)\(^22\). Higher risk MDS carry a major risk of progression to AML and short survival, and treatment in those patients should aim, whenever possible, at modifying the natural disease course. Treatments used in higher risk MDS therefore include allogeneic stem cell transplantation (SCT), the hypomethylating agents (HMA) azacitidine\(^26\) and decitabine\(^27\) and, although now less often, chemotherapy (mainly intensive anthracycline-AraC combinations)\(^28\). In lower risk MDS, the risk of AML progression is smaller and survival longer, about one half of those elderly patients dying from cause other than the consequences of MDS or AML\(^29\). In those patients, the main priority is generally the treatment of cytopenias, mainly of anemia (usually the predominant cytopenia), and the improvement in quality of life. Still, some of those patients may be identified, either rapidly by their revised IPSS score\(^23\) or by other biological characteristics\(^30\), or subsequently by their resistance to first line treatment as carrying poorer prognosis, and may benefit from treatments generally applied to higher risk MDS.
I) How do we treat cytopenias in lower risk MDS?

Anemia, the predominant cytopenia in most cases of lower risk MDS, generally focuses most of the attention. It often requires repeated RBC transfusions, leading to potential iron overload.

A) Treatment of anemia

1. RBC transfusions or drugs?

Chronic RBC transfusions could be considered as sole treatment of anemia of lower risk MDS, as very few drugs are approved in this situation and none has clearly demonstrated that it could improve survival. However, chronic RBC transfusion are associated, not so much to risks of viral infection or of alloimmunization which are now very low, but to chronic anemia, with average hemoglobin levels below 10 g/dl, leading to excess morbidity, especially due to cardiac failure and falls, fatigue, and also to lower quality of life. Transfusions are also time consuming for the patient, induce their “dependence” towards the medical system, and require hospital beds while their cost (including patient transportation, serum testing, iron chelation, etc...) is important, although generally lower than that of erythropoiesis stimulating agents (ESA). Although this remains disputed (see below), iron overload due to RBC transfusions may also be deleterious to various organs. Finally, we and others also recently found that in lower risk MDS with anemia, receiving ESAs had no impact on progression to AML but was an independent favorable prognostic factor for survival, although it was unclear whether this was due to ESA treatment itself and/or to maintaining hemoglobin level higher than 10g/l and/or avoiding iron overload.

2. What is our first line treatment of anemia in lower risk MDS?

   a. Patients without del(5q): Erythropoiesis stimulating agents (ESAs)

ESAs, ie recombinant EPO or darbepoetin (DAR), remain the first choice treatment of anemia in most lower risk MDS without del(5q). Indeed, major favorable prognostic factors for response to ESAs are low or no RBC transfusion requirement (less than 2 units/per month) and baseline serum EPO level below 500U/l. Most lower risk MDS are now considered for anemia treatment when no or limited RBC transfusions are required, and in our experience their EPO level was below 200 UI in 62% of the cases. Weekly doses of 40 000 units of EPO alpha (Procrit* or Eprex*), 30 000 units of EPO beta (Recomron*), or 150 to 300 mg of DAR (Aranesp*), yield about 60% of erythroid responses, according to IWG 2006 response criteria, when the baseline EPO level is low and transfusion requirement absent or limited, and response rates appear to be somewhat higher using 60000 versus
30000 units/week of EPO, and 300 ug versus 150ug /week of DAR. The efficacy of ESAs can be further improved by the addition of G-CSF, although to a lesser extent when high doses of ESAs (60000 U/week of EPO, or 300 ug/week of DAR) are used. Contrary to previous findings, we did not find in 2 large patient series that RARS or RCMD (+/- RS) responded less favorably to an ESA alone than RA. Finally, there are no data showing that one ESA could be superior to another.

Most responses to ESA occur within 8 weeks of treatment, although some patients respond only after 12 weeks. During initial treatment, close monitoring of Hemoglobin level is required in order to avoid increases to >12 g/dl, associated with a potential risk of systemic hypertension and thrombosis when ESAs are used for renal failure (although they have not been documented in MDS). Supplemental iron (oral or intravenous) is advocated mainly in case of relapse of anemia after initial response to ESAs, as prolonged ESA may lead to iron deficiency.

Median duration of response to ESA is about 2 years, and responses longer in patients with major response according to IWG 2000 criteria, IPSS low or intermediate-1, marrow blasts < 5%, and no multilineage dysplasia. Interestingly, about 70% of the relapses of anemia after initial response to ESAs are not associated to progression to higher risk MDS but simply to loss of sensitivity of erythroid progenitors to ESAs, and “second line” treatments in those patients may be different from those required in patients showing concomitant progression to higher risk MDS.

**b. Lower risk MDS with del 5q: Lenalidomide (LEN).**

Anemia of lower risk MDS with del 5q, compared to that of other lower risk MDS, showed lower response rates to ESA (39% versus 52% in our experience) and significantly shorter responses to ESA (median one year versus 2 years). However, it dramatically responds to Lenalidomide, approved by FDA in this indication if anemia is transfusion-dependent (TD), based on 2 large studies (MDS 003 and 004 trials). In those trials, lenalidomide (5 to 10 mg/d) yielded RBC Transfusion-independence (RBC-TI) in 55 to 65% of the subjects, with a median duration of RBC-TI of 2 to 2.5 years.

Cytogenetic response was achieved in 50 to 73% of subjects (including 30 to 45 % complete responses). Combining results of those 2 studies showed higher RBC-TI and cytogenetic responses with a daily dose of 10mg (compared to 5mg), less RBC-TI in patients with cytogenetic abnormalities in addition to del 5q and with high RBC-TD. TP53 gene mutations, found in about 20% of lower risk MDS with del 5q, seem to confer resistance to lenalidomide and a higher risk of AML progression, and their presence may require more aggressive treatment.
Grade 3 or 4 neutropenia and thrombocytopenia, seen in about 60% of the patients during the first weeks of treatment, constitute the most common adverse events of LEN. Close monitoring of blood counts is therefore required during this period, and drug discontinuation made if ANC lower to less than 0.5G/L or platelets below 25 G/L, and the drug restarted at half dose upon correction of cytopenias. Addition of G-CSF can however be recommended if ANC<1G/L, to avoid neutropenia and further dose reductions of LEN, as higher LEN doses may be associated to better erythroid and cytogenetic responses, as seen above. The TPO receptor agonist Romiplostim may reduce thrombocytopenia in that context, but it is not available in routine practice.

Other side effects of LEN in low risk MDS with del 5q include deep venous thrombosis (DVT) and/or pulmonary embolism. Although DVT was observed in 8 of the 95 patients treated in the French patient named program, it was reported in only 0.53% of greater than 7500 MDS treated with lenalidomide in a US post marketing experience (but the incidence was higher in patients with concurrent use of EPO). Prophylactic measures of DVT in MDS treated with lenalidomide are not codified, except in patients with a history of DVT, where prophylactic anticoagulation is probably justified.

Rash is frequent with lenalidomide in MDS, although generally transient, while diarrhea can be long lasting, with limited efficacy of symptomatic treatment.

In responders, the optimal duration of LEN treatment is unknown. Because stem-cell with del (5q) persist in responders, prolonged treatment may be required to avoid rapid relapse. On the other hand, drug discontinuation in patients who have achieved complete cytogenetic response may be associated with prolonged responses.

While FDA approved lenalidomide in lower risk MDS with del 5q, the European Medicines Agency (EMA) raised concern over a potential risk of lenalidomide to trigger AML progression in some lower risk MDS with del 5q and, asked additional analyses. In the absence of prospective randomized trials, 3 retrospective analyses comparing the long term outcome of lower risk MDS with del 5q treated with and without lenalidomide found no excess risk of AML with lenalidomide. Until new EMA examination, therefore, EU investigators should use LEN as second line treatment, after ESA failure, and preferably in a clinical trial. Because LEN is currently approved only in case of RBC-TD, patients with non TD anemia may also be candidates for ESA. Furthermore, lenalidomide is currently only indicated in case of RBC transfusion dependent anemia, and lower risk MDS with del 5q patients with non transfusion dependent anemia are also candidates for first line treatment with ESAs.
3. What second line treatments for anemia of lower risk MDS?

a. Patients without del 5q.

Treatment after ESA failure (primary resistance or relapse after a response), in patients who remain with IPSS low or int 1 MDS, remains overall disappointing, most patients eventually requiring long term RBC transfusions. In our experience, early ESA failure (no response to ESA, or relapse within 6 months), is a marker of disease severity, associated with frequent subsequent AML progression and a median survival of only 3 years. In such patients, second line treatments with a potential impact on disease course may have to be considered. The second line treatments we currently use include ATG, hypomethylating agents and Lenalidomide.

a.1 ATG

ATG, with or without ciclosporin, can yield an erythroid response (associated to response on other cytopenias, especially thrombocytopenia), in 25 to 40% of the patients treated. Response rates, however, depend largely on the population treated. ATG results are better in relatively young (<65 years) low risk MDS patients with a RBC transfusion history of less than 2 years, with normal karyotype (or possibly trisomy 8), with no excess blasts, HLA DR15 genotype, and possibly in patients with thrombocytopenia in addition to anemia, a small PNH clone or with marrow hypcellularity.

In the French registry of MDS, those patients represented only 6.5% of the low risk MDS, suggesting that good ATG candidates may be relatively rare in MDS. ATG may also be considered in patients where thrombocytopenia is the predominant cytopenia.

More recently Alemtuzumab treatment, in 32 lower risk MDS having favorable criteria for ATG response, yielded a 77% response rate, sustained improvement in blood counts and cytogenetic remissions. However, the drug is not widely available in this indication. In addition, this patient series was highly selected, as it included patients with good prognostic factors of response to immunosuppression.

a.2 Hypomethylating agents

Hypomethylating agents have been reported to yield RBC TI in 30 to 40% of the patients, and may also be effective on other cytopenias in lower risk MDS. They are approved in this situation in several countries, including the US. In a phase II trial randomizing AZA and AZA + EPO in RBC transfusion dependent lower risk MDS clearly identified as resistant to ESA, however, we observed only 17% RBC TI, without difference between the 2 treatment arms, possibly suggesting lower efficacy in patients who are clearly ESA resistant.

We use hypomethylating agents as second line treatment particularly in patients with thrombocytopenia in addition to anemia (or isolated thrombocytopenia). Even though they have not demonstrated a survival advantage in low risk MDS, we also use them in patients with early ESA
failure (no response or relapse within 6 months of response), whose progression rate and survival is rather unfavorable \(^{60}\).

\textit{a.3 lenalidomide}

Lenalidomide yields RBC-TI in 25 to 30% of lower risk MDS without del 5q resistant to ESA\(^{72,73}\). Because it induces neutropenia and thrombocytopenia (although to a lesser extent than in patient with del 5q), it is however difficult to use when those cytopenias are present in addition to anemia. Furthermore, it is unclear if LEN, in addition to improving anemia, has any impact on disease progression and survival in those patients. Therefore Lenalidomide, in non-del 5q patients, appears justified only in clinical trials. Preliminary results suggest that the combination of LEN and ESA may yield high RBC-TI rates in patients resistant to an ESA alone, and we are currently trying to confirm those results in a prospective randomized trial\(^{74}\).

\textit{b. Patients with del 5q}

Results of MDS 003 and MDS 004 trials \(^{47,48}\) (described above) also suggest that resistance to LEN in lower risk MDS with del 5q is associated with poor prognosis, even if no immediate progression to high risk MDS is observed. Patients with TP53 gene mutation may have a particularly poor outcome\(^{50}\). Although no prospective data exist, those patients should probably be candidates to approaches having demonstrated a survival benefit in MDS, including hypomethylating agents, and whenever possible allo SCT. Our recent experience with AZA after LEN treatment failure showed a 50% response rate and a median overall survival of 32 months in responding patients\(^{79}\).

3. Long term RBC transfusions and iron chelation therapy

In many patients with lower risk MDS, anemia will eventually become resistant to all available drug treatments, even in the absence of evolution to higher risk MDS, and will require repeated RBC cell transfusions \(^{60}\). For those patients, it is recommended to administer transfusions at sufficiently high hemoglobin threshold, ie at least 8 g/dl, and 9 or even 10g/dl in case of comorbidities worsened by anemia (coronary artery disease, heart failure...) or in case of poor functional tolerance. In addition, a sufficient number of RBC concentrates should be transfused each time, if necessary over 2 or 3 days, to increase the hemoglobin level above 10g/dl and thereby limit effects of chronic anemia.

A large debate exists about the deleterious effect of iron overload in MDS patients, and whether iron chelation may be useful in patients with iron overload. In particular, while heart iron overload is a well-documented cause of heart failure in children with thalassemia\(^{76,77}\), its incidence and clinical consequences are uncertain in transfused MDS patients, especially as many of them already have
other causes of cardiac morbidity. Some authors may therefore consider that in those patients iron overload as just one cause of cardiac failure 78, while others may consider that this additional cause may precipitate a sometimes unstable cardiac situation79,80. Discrepancies are also probably related to the variable median number of RBC units transfused in different published series. Indeed, significant iron overload appears to occur later in the heart than in other organs, especially the liver. However, heart MRI studies show that heart iron overload (reflected by a decrease in MRI heart T2*) is frequent in patients having received at least 70 to 80 RBC concentrates or more, a frequent situation in low risk MDS, and that a heart T2* value below 20 milliseconds is associated with decreased LVEF and a risk of heart failure81.

Thus, very heavily transfused MDS patients develop major iron overload, especially in the heart and liver, that may reduce survival through cardiac failure or liver cirrhosis. It has been suggested in 3 retrospective studies that adequate chelation in highly transfused patients may improve their survival 82,83,84. Prospective randomized studies are underway to confirm those results, but they are difficult to conduct because two chelating agents (desferoxamine and deferasirox) are approved in this indication in MDS.

In the absence of prospective studies, published recommendations for iron chelation therapy only result from expert opinions 85,86. We generally advocate starting chelation in patients with relatively favorable prognosis (ie low or int 1 risk MDS), who have received at least 50 to 60 RBC concentrates, or if serum ferritin raises above 2500 U/l, or if cardiac T2* is significantly reduced. Future candidates to allogeneic SCT are an exception. Indeed, although the underlying mechanisms are unclear, there is a consensus over the fact that even relatively moderate iron overload before allogeneic SCT is associated to increased transplant related mortality 87-90. In addition, intensive chelation treatment prior to transplant may improve survival in those patients, although this was observed only in a retrospective study 91. Thus, in MDS patients that may be, one day, candidates to allogeneic SCT, we start iron chelation after around 20 RBC concentrates or above a serum ferritin level of 1000 UI. The same thresholds have been advocated in low risk MDS as a whole in some recommendations 85,86, but as said above they not based on prospective studies.

Iron chelation is now made easier by the availability of oral iron chelators (especially deferasirox), in addition to the classical parenteral desferoxamine. Deferasirox is however frequently associated with gastrointestinal side effects, and cannot be used in patients with renal failure 92. Deferiprone, another oral iron chelator, is currently not approved for MDS in most countries, and can cause neutropenia in a small percentage of patients, a side effect that is problematic in MDS 93.
B) Treatment of neutropenia and thrombocytopenia

In lower risk MDS, neutropenia and thrombocytopenia are less frequent than anemia, and are infrequently isolated or profound.

1) Neutropenia

WBC are less than 1.500 mm$^3$ in only 7% of lower risk MDS, and neutropenia is rarely associated with life threatening infection if no drugs worsening neutropenia are used. G-CSF and GM-CSF can improve neutropenia in 60 to 75% of those cases, but their prolonged use has not demonstrated impact on survival, while a risk of stimulating progression to higher risk MDS or AML has not been formally excluded. They may be used for transient periods, in patients who experience severe sepsis, but this has never occurred in our clinical practice. One should recommend to neutopenic MDS patients immediate use of broad-spectrum antibiotics in case of fever or other signs of infection. In the absence of previous infection episode with resistant strains, we ask our neutropenic patients to take immediately amoxicillin-clavulanic acid and ciprofloxacin in case of fever and rapidly contact their physicians.

2. Thrombocytopenia

Platelets below 50.000/mm$^3$ are seen in about 30% of low risk MDS, and severe bleeding is relatively rare unless drugs interfering with hemostasis are used. We sometimes use high dose androgens, which can improve thrombocytopenia in about 1/3 of thrombocytopenic lower risk MDS, but response is generally transient. Growth factors non specific of the platelet lineage, including IL3, IL6, and IL11 have been used with some success, but also side effects. In exceptional cases, a peripheral mechanism of platelet destruction may predominate in MDS, as evidenced by platelet lifespan studies, with a possible success of splenectomy in our experience. Because TPO itself is immunogenic, leading to thrombocytopenia, TPO receptor agonists including Romiplostim and Eltrombopag have been designed to treat thrombocytopenias of different origins. Romiplostim at high dose (500 to 1.500 ug/week) yielded 55 % platelet responses in a phase II trial in lower risk MDS with thrombocytopenia. However, in about 15% of the patients, a transient rise in marrow blasts was seen, reversible after drug discontinuation. In a randomized phase II study versus placebo in lower risk MDS with thrombocytopenia, Romiplostim reduced the incidence of severe bleeding and platelet transfusions, but there was a suspected increase in the AML risk, and data are currently under review. Currently, TPO agonist receptors are unavailable for routine practice.

ATG and hypomethylating agents appears to give platelet response in 35 to 40 % of the cases of lower risk MDS, in addition to erythroid responses, and we sometimes use them in this context.
II) Identifying lower risk MDS with poorer outcome

While management of cytopenias, mainly anemia, is generally the major clinical objective in lower risk MDS, some patients may have, at diagnosis or during evolution, features associated with a risk of progression to high risk MDS/AML or life threatening cytopenias that may justify treatment strategies aimed at modifying the disease course, especially with hypomethylating agents and, in some younger patients even lead to consider allogeneic SCT.

1) Identifying lower risk MDS patients with poorer outcome

a) at presentation

The “classical” IPSS, defining lower risk MDS as low and int-1 risk IPSS, appears insufficient, especially as it does not incorporate marrow multilineage dysplasia, RBC transfusion dependence, associated to poorer prognosis, and severity of thrombocytopenia, and as some cytogenetic abnormalities like those involving 3q21-26 are considered of intermediate prognosis.

Some of those caveats are addressed by the WPSS, and more importantly by the revised IPSS that appear to better discriminate prognosis in classical IPSS low and int-1. For example, in IPSS Low and Intermediate-1 patients, 27% were shifted to higher risk IPSS-R categories, mainly intermediate.

Presence of grade 2 or greater myelofibrosis in lower risk MDS is also associated in some series with a higher risk of AML progression and poorer survival, although this parameter lacked prognostic significance in the revised IPSS cohort.

A MD Anderson scoring system for IPSS low and int-1 patients, based on specific thresholds for platelets, hemoglobin, age, marrow blasts and cytogenetics was also capable to better discriminate the prognosis of IPSS lower risk MDS, while presence of somatic mutations, especially of EZH2 gene, added independent poor prognostic value to this score.

b) During follow up

Lower risk MDS patients (according to IPSS) who remain with lower risk, but experience early resistance to ESAs (non del 5q patients), resistance to LEN (del 5q patients), who develop a cytogenetic abnormality or a life threatening cytopenia (mainly thrombocytopenia) also have relatively poor survival.

2) How we manage those patients

Although prospective studies are lacking, we increasingly use hypomethylating agents (HMA) (based on their known effect on survival in high risk MDS) treatment in those classical IPSS “lower risk” patients.
We also consider allogeneic SCT in patients aged less than 60-65 with an HLA identical donor and no contraindication to the procedure, in case of life threatening thrombocytopenia, karyotype considered as unfavorable by R-IPSS (including 3q26 rearrangements), TP 53, EZH2 or ASXL1 mutation and in the absence of major response to HMA (or subsequent relapse).

In conclusion, chronic anemia remains the most frequent clinical problem in lower risk MDS, which alters quality of life in those elderly patients. ESA generally constitute the first line treatment of anemia except in patients with 5q deletion, where results of lenalidomide are superior, but responses to both treatments are generally transient. Second line treatments of anemia (including hypomethylating agents, lenalidomide in the absence of 5q deletion, antithymocyte globulin) are less satisfactory, yielding at best one third of responses, so that many patients eventually require repeated RBC transfusions, a situation where indications for iron overload prophylaxis are still somewhat disputed. In a minority of lower risk MDS, thrombocytopenia is the predominating cytopenia, and TPO agonist receptors are currently being tested in this situation, while hypomethylating agents or antithymocyte globulin may be useful. Some patients with lower risk MDS according to IPSS may however, at diagnosis or during evolution, have features associated with poorer prognosis, based on new prognostic scoring systems (revised IPSS, MD Anderson score...), presence of gene somatic mutations, or resistance to first line treatment, that may consider them for more intensive treatment, including in some cases allogeneic SCT.
Authorship

Contributions: PF and LA wrote the manuscript.

Conflict of interest

The authors declare no conflict of interest.
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