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TITLE: Review on treatment modalities for patient with myelodysplastic syndrome (MDS)

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Executive summary

- Myelodysplastic syndrome (MDS) is a group of medical conditions derived from progressive bone marrow failure that result in ineffective production of blood cells. Ineffective haematopoiesis leads to blood cytopenias and by an overall high risk of progression to acute myeloid leukaemia (AML). About 30% of patients with MDS progress to AML. Although it is rarely curative, the treatment options available for MDS greatly improved over the last 2 decades.
- MDS is predominant in the elderly and is complicated by severe anaemia, but it can also affect younger people. The incidence of MDS in Europe is about 4 cases per 100,000 persons per year. However, there is a paucity of local prevalence data of MDS.
- In lower-risk MDS patients, therapeutic options include watchful waiting strategy, supportive care (symptom management, blood transfusions, treatment of iron overload), and allogeneic haematopoietic stem cell transplantation which has curative potential for MDS.
- Red blood cell transfusion is the most widely used active therapy for anaemia in lower risk MDS patients. Recent studies have shown that it is very important to start erythropoiesis-stimulating agent (ESA) treatment before the onset of a permanent transfusion need.

1. Introduction

Myelodysplastic syndromes (MDS) are a group of cancers in blood in which bone marrow fails to produce healthy blood cells. It is comparatively rare and complex disease predominantly occurring in elderly people but can also affect younger people. As the bone marrow fails to produce healthy blood cells, it affects all types of blood cells – red blood cells (erythrocytes), white blood cells (leukocytes) and blood platelets (thrombocytes), causing a range of symptoms [1]. People diagnosed with MDS tend to develop anaemia, neutropenia, thrombocytopenia or a combination of all three. Anaemia is the most frequently experienced cytopenia, leading to symptoms of fatigue and shortness of breath. Other symptoms include infections, spontaneous bleeding and bruising. The diagnosis of MDS is usually made with the help of blood and bone marrow examination, bone marrow examination being golden standard.

The current World Health Organisation 2016 classification of tumours [9] categorises MDS into six broad types:

1. Refractory cytopenia with unilineage dysplasia (RCUD)
2. Refractory anaemia with ring sideroblasts (RARS)
3. Refractory cytopenia with multilineage dysplasia (RCMD)
4. Refractory anaemia with excess blasts (RAEB)
5. Myelodysplastic syndrome unclassified (MDS-U)

MDS associated with isolated del(5q)

The disease classification or risk scoring system is used to determine the severity of the disease, prognosis and the course of the treatment. The conventional risk scoring system – International Prognostic Scoring System (IPSS) – has been used to classify the patients based on the percentage of marrow blasts, number and extent of blood cytopenias and marrow cell karyotype. Based on IPSS risk score patients are classified into lower-risk MDS (low/intermediate-1, LR-MDS) and higher-risk MDS (intermediate-2/high, HR-MDS) [2]. The revised version of IPSS (IPSS-R) classified patients into five risk groups: very low-risk, low-risk, intermediate-risk, high-risk and very-high risk MDS [3]. Around 30% of patients with a diagnosis of MDS progress to acute myeloid leukaemia (AML), a cancer of the white blood cells [4]. MDS has significant impact on health-related quality of life (HRQoL. Generally, treatment for MDS has improved over the last two decades; in lower-risk states mainly because of better supportive care and treatment for anaemia, in higher-risk cases because more patients can be successfully cured by allogeneic stem cell transplantation [1].

This review builds on a recent review of the literature on the management of (adult) patients with a diagnosis of MDS [5], as well as the work conducted as part of the MDS-RIGHT (H2020) [6] that provided a more general overview on the management options for MDS. The aim of this report is to summarise the current treatment options including different combination, personalised treatments and observed treatment pathways for LR-MDS patients.

2. Prognostic tools to determine risk-based therapeutic options

Diagnosis of MDS is usually done with a morphological assessment of blood and bone marrow, standard metaphase bone marrow cytogenetics and, in some cases, analysis of acquired mutations in marrow cells [7]. MDS constitute an extremely heterogeneous group of bone marrow malignancies. As a result, prognostication can be difficult in the individual case. The prognosis of MDS patient depends on many factors including those not related to MDS such as age and general fitness.

IPSS-R is the most commonly used scoring system. The risk score is calculated from blood count results, the number of blasts (abnormal immature cells) in bone marrow, and chromosome test results from bone marrow at diagnosis. The final score is categorised into five IPSS-R risk groups which describe the expected survival and expected risk of developing AML (Table 1).

Table 1: IPSS–R prognostic risk category clinical outcomes [3]

Risk category	Risk score	Median survival in years	Median time (years) to 25% AML evolution
Very low	≤1.5	8.8	Not reached
Low	>1.5–3.0	5.3	10.8
Intermediate	>3.0–4.5	3.0	3.2
High	>4.5–6.0	1.6	1.4
Very high	>6.0	0.5	0.73

The current clinical guidelines focus on assessing disease risk at diagnosis by assessing clinical and patient characteristics [8], and use established prognostic scoring system such as IPSS-R to estimate survival and risk of progression to AML. The prognostic risk scoring system helps clinicians to guide therapeutic recommendations.

3. Treatment options for MDS

The primary goal of MDS treatment is to improve cytopenia(s), i.e. increase the number of healthy blood cells in body thereby improving the quality of life (QoL).

The treatment options for MDS depends on the type of MDS and the risk classification and include the following:

- Watchful waiting (when the blood counts are not too low)
- Supportive care (symptom management, transfusion therapy, iron chelation)
- Growth factor treatment for anaemia
- Immunosuppressive therapy (treatment to lower the body's immune response)
- Azacytidine
- Chemotherapy
- Bone marrow transplant (for replacing damaged stem cells in the bone marrow with health ones)

4. Therapeutic options for lower-risk MDS (LR-MDS)

In LR-MDS (IPSS low/intermediate-1, IPSS-R very low, low, intermediate up to 3.5 points) anaemia is the predominating symptom (cytopenias). The main aim of the therapy for LR-MDS is to improve cytopenia(s). Figure 1 shows the treatment options available for patients with LR-MDS.

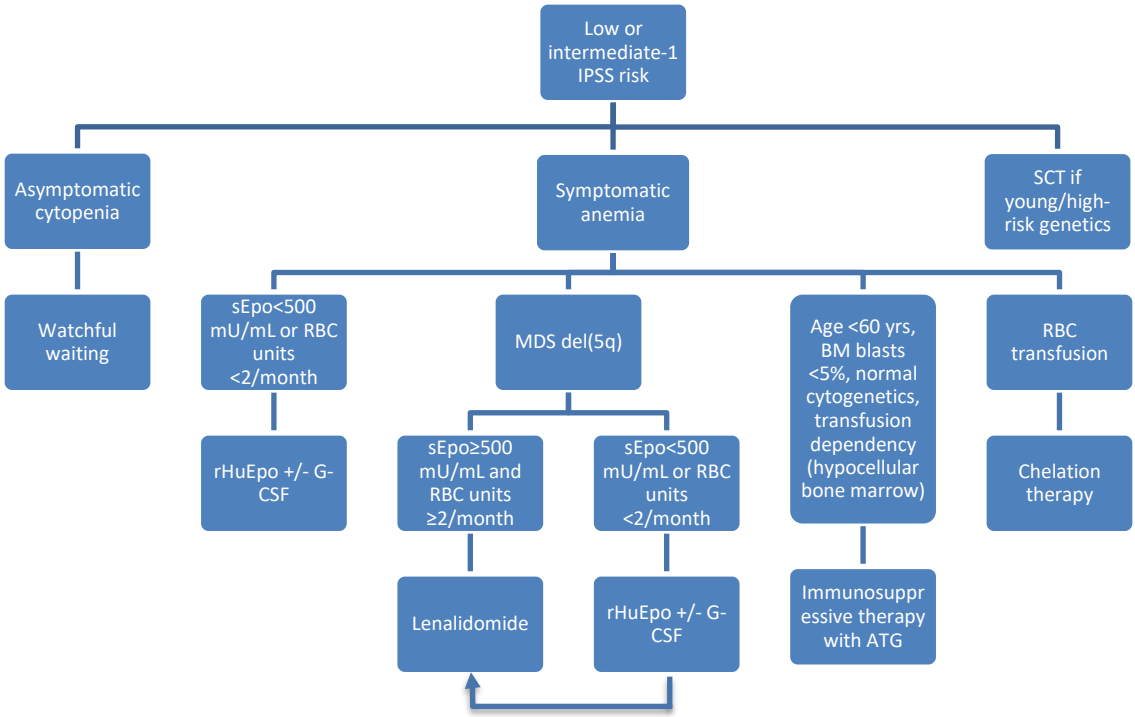

Figure 1: Treatment by international prognostic scoring system risk group (low or intermediate-1) [6]

4.1. Watchful observation

The majority of patients with the LR-MDS do not require the treatment because cytopenias are mild and asymptomatic. As they have asymptomatic cytopenia, no blast excess and no poor-risk cytogenetic abnormalities, they should be followed regularly without specific treatment. The watchful-waiting strategy might change in the future if safe treatment capable of modifying the natural history of disease are developed. In addition, careful surveillance of disease evolution is required, especially if more than one cytopenia is present or in case of a higher risk prognostic profile based on genotype [5]. The safety of this approach dependent upon regular monitoring. The goals of such follow-up include the early recognition of worsening cytopenia, increasing number of circulating or bone marrow blasts, and karyotypic evolution [10].

4.2. Treatment of anaemia

Anaemia is generally asymptomatic for haemoglobin levels >100 g/L and is the leading symptom in LR-MDS which is associated with fatigue, higher risk of cardiovascular complications, increased risk of falls, and poor QoL in elderly patients [5]. The best practice currently individualises Hb thresholds based on a combination of patient comorbidities, symptoms at a given Hb concentration, observed symptomatic benefits from previous transfusion episodes and patient preference. Red blood cell (RBC) transfusion has traditionally been the most widely used active therapy for MDS patients. RBC transfusions lead to transient relief of anaemia but is associated with established risks (e.g. infection, transfusion reactions, iron toxicity). Symptomatic anaemia leads a decrement in QoL [11].

4.2.1. RBC transfusion therapy

Red cell transfusion is the most widely used active therapy for MDS patients (>50% of the patients receive transfusions). Transfusions are administered repeatedly and frequently in MDS patients with recurrent exposure to multiple donors. Red cell transfusion for severe anaemia is usually symptomatically beneficial but is associated with established risks. Adverse effects of red cell transfusion include simple transfusion reactions, circulatory overload, transfusion-associated lung injury and transfusion of incompatible red cell units. Likewise, red cell alloimmunisation and transfusional iron toxicity are associated adverse effects of recurrent red cell transfusion.

There is paucity of high-quality evidence to determine optimal Hb concentration thresholds for red cell transfusion. The current best practice individualises Hb thresholds based on a combination of patient comorbidities, patient symptoms at a given Hb concentration, observed symptomatic benefit from previous transfusion episodes and patient preference.

4.2.2. Erythropoiesis stimulating agents (ESA)

Recent guidelines advised to use erythropoiesis stimulating agents (ESAs) as a first line drugs for the anaemia of LR-MDS [12]. ESAs include erythropoietin alpha or beta (EPO), generic epoetins, and darbepoetin. ESAs have been used to treat LR-MDS anaemia as first line treatment. Treatment with ESAs may lead to improvements in Hb levels and reduce the need for transfusion in LR-MDS, however ESAs do not induce erythroid response in all LR-MDS patients. Recent studies from the EU MDS Registry have shown that it is very important to start ESA treatment before the onset of a permanent transfusion need, which is now introduced in the European guidelines [12]. The median response duration to ESAs is 2-3 years.

Although ESAs are used widely, prospective clinical trials were recently conducted. A recent prospective trial confirmed the superior efficacy of epoetins alpha compared to placebo (45.9 vs 4.4%), leading to the approval of EPO-alfa in the European Union in patients with serum EPO <200 u/l [13]. However, the response rate varies depending on patient selection, ranging between 23–75%. Side effects of ESAs are limited if one avoids too rapid increase in Hb level by close monitoring of Hb levels and dose reduction if required. Most responses to ESAs occurred within 3 months of treatment onset, and the median duration of response in this trial was 18-24 months [5].

In ESA refractory patients, i.e. patients with no or loss of response to single-agent ESA, addition of Granulocyte-CSF (G-CSF) can induce responses up to 20% of the cases [14]. Retrospective studies showed a survival benefit for patients treated with EPO±G-CSF compared to untreated patients, with no impact on progression to AML.

4.2.3. Treatment of anaemia of LR-MDS with del(5q)

In deletion 5q [del(5q)] MDS patients who failed ESAs or are ineligible for ESA, lenalidomide is the treatment of choice. Lenalidomide responders had longer AML-free survival than non-responders with a median response duration of 2.3 years [15]. However, patients not responding to lenalidomide have a very poor prognosis. The common side effects that may occur during the first week of treatment include severe neutropenia and/or thrombocytopenia. This requires close blood count monitoring and, in case of severe neutropenia, the addition of G-CSF is recommended. Higher proportion of LR-MDS patients receiving Lenalidomide achieve RBC transfusion independence (56%) and cytogenetic response (50–75%) than in the placebo group.

TP53 mutation is present in 20% of MDS patients at diagnosis and is associated with lower haematological response, lower cytogenetic response rates, shorter response duration to Lenalidomide and a higher rate of progression to HR-MDS or AML [5]. Thus, TP53 mutation should be regularly assessed in LR-MDS patients with del(5q). Assessing other genetic mutations in LR-MDS with del(5q) is also important.

4.2.4. Immunosuppressive treatment (IST)

In some patients with LR-MDS, there seems to be a component of immunological dysregulation. These include a greater than expected incidence of autoimmune abnormalities, augmented cytotoxic T-cell activity and dysregulation of regulatory cells. There is an overlap between LR-MDS and aplastic anaemia, which provides the rationale for immunosuppressive agents. Treatment with immunosuppressive agents are now an established and effective treatment for a small subgroup of patients.

Treatment with immunosuppressive agents (IST) such as anti-thymocyte globulin (ATG) and ciclosporin (CSA) may improve cytopenias and abrogate transfusion need in LR-MDS with hypoplastic to normocellular BM. The treatment response for IST with ATG, with or without addition of CSA vary from single-lineage recovery to complete trilineage response. Various predictors of better response include MDS with single lineage dysplasia, absence of ring sideroblasts, a hypoplastic bone marrow, HLA-DR15, age <60 years, female gender, normal karyotype or trisomy 8, presence of a paroxysmal nocturnal haemoglobinuria clone, and short duration of transfusion dependence [16]. Immunosuppressive agents such as ATG and/or CSA are highly specialised treatment with significant adverse events.

4.2.5. Chelation therapy

Transfusion dependency can result in iron toxicity after 20-25 units [17]. Deferasirox, an oral drug, is the most used iron-chelating drug [18]. Deferoxamine has the longest safety and efficacy evidence but in older patients, tolerance and practical administration difficulties may limit usage of this parenteral drug compared to the oral compounds. Deferasirox is licenced for patients whom deferoxamine is contraindicated or inadequate. The threshold of iron overload triggering

the onset of chelation in most LR-MDS who are RBC-TD is however disputed [5]. Deferiprone may be considered if neither deferoxamine nor deferasirox are tolerated and ANC>1.5 × 10^9/L.

4.2.6. New treatments for anaemia in LR-MDS

Luspatercept (ACE-536), a specific activin receptor fusion protein acting as a ligand trap to neutralise negative regulators of late-state erythropoiesis was evaluated for its ability to reduce transfusion requirements in LR-MDS with ring sideroblasts. The results showed high response rates, 63% patients showing erythroid responses and 38% of patients remained transfusion-free for at least 8 weeks [19]. Other drugs currently being tested in clinical trials have shown some efficacy on anaemia of LR-MDS refractory to ESA [5].

4.3. Allogeneic stem cell transplantation (allo-SCT)

Although allogeneic stem cell transplantation is typically used in higher-risk MDS, its indications also exist in LR-MDS patients. Allo-SCT is recommended in LR-MDS patients when nontransplant strategies (ESAs, and lenalidomide have failed. Nontransplant strategies may include more than one line of nontransplant interventions, e.g. treatment with ESAs followed by lenalidomide. However, benefit of allo-SCT in LR-MDS patients has not been demonstrated in prospective studies [5]. It is usually recommended in LR-MDS patients with poor prognosis features and no response to first line treatment. Patient characteristics such as patient age, fitness, comorbidities, wish of the patients and transfusion burden/intensity are taken into consideration while weighing in the benefits and risks of transplant-related mortality. Cytogenetic characteristics and disease stage determine risk of replace after allo-SCT.

4.4. Treatment of neutropenia and thrombocytopenia

In LR-MDS, neutropenia and thrombocytopenia are less frequent than anaemia, and are rarely profound.

Neutropenia

Neutropenia occurs nearly 50% of newly diagnosed patients with MDS, including 15-20% of LR-MDS and 70-80% HR-MDS patients. It is part of a more general process of bone marrow failure combining impaired differentiation, apoptosis resistance and leukemic proliferation [20]. Neutropenia is rarely associated with life-threatening infection if drugs that worsen neutropenia are not used [5]. G-CSF may be used for transient period in patients who experience severe sepsis.

Thrombocytopenia

Thrombocytopenia is commonly seen in MDS patients and bleeding complications are a cause of morbidity and mortality. Thrombocytopenia occurs in about half of patients with LR-MDS and is associated with shortened survival and increased risk of transformation to AML. Severe bleeding is relatively rare in LR-MDS unless drugs that are interfering with haemostatis are used or if platelet function defects are seen [5]. High dose androgens can improve thrombocytopenia

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in about one-third of thrombocytopenic LR-MDS patients, but the response is generally transient.

Beyond disease-modifying therapies, non-pharmacologic management of thrombocytopenic LR-MDS patients include platelet transfusions [21]. ATG and HMAs appear to produce a platelet response in 30-40% of the LR-MDS patients, in addition to erythroid responses.

5. Summary

Myelodysplastic syndromes refer to chronic bone marrow malignancies, leading to low blood cell counts (cytopenias). It is comparatively rare and complex disease, and usually diagnosed with the help of bone marrow examination. Treatment options for patients with low or intermediate-1 IPSS risk mainly aims at improving cypotenia(s), using ESA or in the case of patients with LR-MDS and deletion 5q, lenalidomide, thereby improving the quality of life (QoL). Patients receiving regular blood transfusions invariably develop secondary iron overload needing iron chelation therapy.

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