First-line Therapeutic Strategies for Myelodysplastic Syndromes

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Abstract

The precise diagnostic tests and subsequent prognostic stratification for patients with myelodysplastic syndrome (MDS) are often cumbersome, yet they are the basis of successful therapy. Diverse treatment options are available for these patients; however, the decisions in real-life are often not grounded on the available evidence. Although the International Prognostic Scoring System and revised International Prognostic Scoring System are still driving the medical approach to MDS patients, additional variables must be considered when therapeutic intervention is needed. A rational scheme for first-line therapy is described that allows for the possibility of selecting the optimal individual therapy for MDS patients.

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Introduction

Myelodysplastic syndrome (MDS) refers to a heterogeneous group of diseases, and it is quite difficult at present to continue to refer to them as a unique nosologic entity. The diagnosis is difficult and requires expertise in morphology, cytogenetics, and, increasingly, molecular techniques. The prognosis is dominated by the disease characteristics; however, individual patient-related variables such as age, frailty, comorbidities, and personal wishes and compliance could also be determinants in the choice of therapy. Regardless, it is clear that the first step to establishing a good treatment strategy is to properly evaluate each suspect case of MDS and, once the diagnosis has been confirmed, provide an accurate prognostication. The International Prognostic Scoring System (IPSS)[1] and the revised IPSS (IPSS-R)[2] are tools widely used in first evaluations. Both scoring systems have taught us to consider MDS patients in terms of having a low or a high risk of progression to acute leukemia and to consider the therapies accordingly. Nevertheless, the depth of cytopenia in "low-risk" patients could constitute an obstacle to maintaining a decent quality of life and could result in death, in the absence of any disease progression. In contrast, patients with "high-risk" MDS could experience prolonged survival with disease stabilization and an acceptable quality of life. At present, it is fundamental to determine the correct strategy to manage MDS, because, although several therapeutic options are possible, their sequence and, in particular, the first-line choice can be critical to the disease course.

First, the inception of therapy should be determined exclusively by the symptoms to actively alleviate them and on the possibility of delaying the progression to leukemia and eradicating the disease.

First-line Treatment of Lower Risk MDS

The management of lower risk MDS (ie, very low, low, and intermediate IPSS-R risk), as indicated by the most recent guidelines (National Comprehensive Cancer Network),[3] has recently been revisited.[4] The presented algorithm was created from quite articulated evidence, and each drug option was determined from several individual- and disease-related parameters. The recommendations include first and subsequent lines of treatment. The focus of the present report was the choice of first-line therapy (Figure 1).

Symptomatic anemia is the most frequent trigger for therapeutic intervention. As much as possible, transfusions should be used only in emergency situations. Whenever possible, transfusion should not be considered as standard continuous treatment without testing alternative approaches, both to maintain the best quality of life and to avoid cardiac and systemic complications.[4]

When red blood cell (RBC) transfusions are necessary, and they can be for most MDS patients at some stage of the disease, they should be given using a hemoglobin threshold derived from individual symptoms, not from the routine use of transfusions in other

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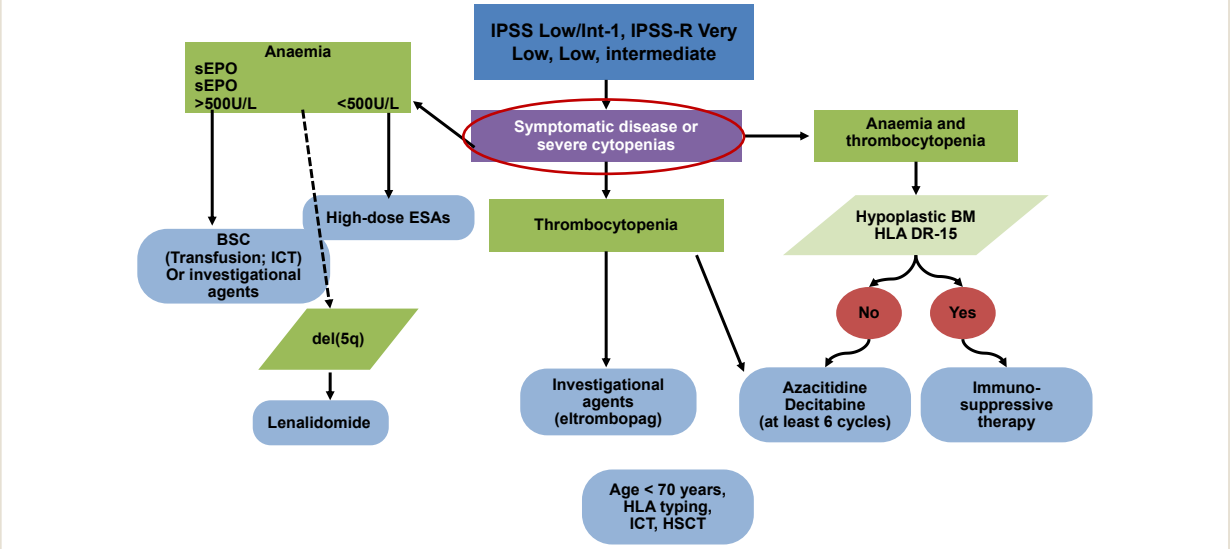
Figure 1 First-line Therapeutic Algorithm for Lower Risk Myelodysplastic Syndrome (MDS)



Abbreviations: ATG = antithymocyte globulin; BM = bone marrow; BSC = best supportive care; ESA = erythropoietic-stimulating agent; HLA = human leukocyte antigen; HSCT = hemopoietic stem cell transplantation; ICT = iron chelation therapy; sEPO = serum erythropoietin.

settings, which have a threshold of 8 g/dL. Nilsson-Ehle et al[5] reported that good correction of anemia with transfusions is possible and that their efficacy in maintaining high hemoglobin levels correlated with quality of life in an equivalent manner to that of erythropoietic-stimulating agents (ESAs). However, the chronic RBC transfusions typically needed for patients with MDS cannot resolve chronic anemia. Although life-saving, such transfusions will not correct the morbidity and poor quality of life, because the transfusions will not usually normalize the hemoglobin levels. In addition, the transfusions expose the patients to fluctuating hemoglobin levels. Also, iron overload due to RBC transfusions can be deleterious to organs such as the liver and heart and to hemopoiesis itself. Thus, iron chelation therapy is recommended as a part of best supportive care, when $\geq$ 20 U of RBCs have been transfused.[6]

ESAs can be effective in resolving the anemia of MDS and should be as first-line treatment. When feasible, ESAs should be used before transfusions (as defined by the International Working Group criteria[7]) and, certainly, before the transfusion burden has become too great. Ideally, ESAs should be prescribed as soon as the hemoglobin levels significantly affect the patient's physical function. ESAs will achieve the best results in terms of erythroid response when used in IPSS lower risk MDS patients, with serum erythropoietin levels $<$ 500 U/L, without transfusion dependence, and with a normal karyotype and the absence of blasts in the bone marrow.[8] The presence of pure erythroid dysplasia, low serum ferritin, very low and low IPSS risk,[9] the presence of $<$ 2 somatic mutations,[10] and the timely start of therapy, within 6 months of the diagnosis, will ensure the greatest rate of response.[11] For such patients, the response has been $>$ 70%.[9] The optimal doses have been established as 30,000 to 80,000 U of erythropoietin (EPO; Epoetin alfa)[12] and 150 to 300 μg of darbepoetin alfa in subcutaneous injections weekly.[13] Whether standard or higher doses of ESAs are preferable is still a matter of investigation. The preliminary results reported for 2 randomized registered trials comparing the safety and efficacy of EPO and darbepoetin alfa with placebo have further demonstrated the activity of ESAs in MDS, although at rates inferior to those published reported (EPO, 31.8% vs. placebo, 4.4%; darbepoetin alfa, 14.7% vs. placebo, 0%).[14,15] The lower rates mainly resulted from the interruption of ESA treatment in accordance with the study scheme, such that when the hemoglobin levels increased and approached 12 g/dL ESA treatment was discontinued. However, the effect of ESAs on dysplastic erythropoiesis is temporary and disappears with interruption of ESAs.

A survival advantage has been suggested for patients receiving ESAs,[16] although a recent comparison with an untreated matched population by our group indicated that this advantage is substantial only for a subgroup of MDS patients (Messa et al, manuscript submitted).

ESAs have no major contraindications for use in patients with MDS. No increase in thrombotic events and no hint of any increase in disease progression have been observed compared with non–ESA-treated patients,[17] in contrast to reports of solid neoplasms. To maintain the response, the serum iron, vitamin B_{12}, and folate levels should be controlled. The most relevant difference with other hematologic and nonhematologic neoplasias is that the anemia of MDS is, by itself, "the" disease and is chronic and, therefore, requires continuous treatment. The response to ESAs is not immediate in MDS, although it is generally observed within 12 weeks. Thus, evaluations of the response before 12 weeks should not result in stopping the treatment and crossover to an alternative therapy.[4]

The addition of granulocyte colony-stimulating factor to ESAs has been reported to increase the rate of response.[16] The use of