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Current treatment strategies in low-risk myelodysplastic syndromes

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ATG

Summary Myelodysplastic syndromes (MDS) are categorized into different risk groups according to the International Prognostic Scoring System (IPSS). Patients with low- and intermediate-1-risk disease are usually qualified as low-risk-MDS and treated with common treatment strategies. Recently, a number of new therapies have emerged and proved very promising, both in best supportive care as well as in interventional therapeutic strategies. Given that most patients with early MDS will eventually become transfusion dependent, effective iron chelation is an important part of the therapeutic management. The new iron chelator deferasirox has the advantage of high bioavailability after oral ingestion and leads to effective iron chelation with an acceptable toxicity profile. Other drugs may be used to reduce transfusion-dependence: Lenalidomide has shown astonishing erythroid responses in patients with del(5q) chromosomal abnormality, irrespective of karyotype complexity. Adverse events are manageable, including grade III and IV thrombocytopenia and neutropenia. Erythropoietin ± G-CSF may be used in non-del(5q) patients with low erythropoietin levels and a low pre-therapeutic transfusion dependence. Young patients with low transfusion burden and a HLA-DR15 phenotype may be especially prone to respond to antithymocyte globulin and cyclosporin A treatment. Responders seem to have an improved overall survival compared to non-responding patients. Finally, valproic acid, a histone deacetylase inhibitor, does strengthen the erythroid lineage in a significant part of low-risk IPSS patients and may be used in patients not eligible for other treatment strategies.

Introduction

The *decision-making process* for a distinct therapeutic strategy in myelodysplastic syndromes (MDS) is based on several factors: Apart from the obvious need for patients' informed consent, their prognosis without therapy, their age and

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complicating comorbidities, the availability of treatments, and the experience of the treating physician with the assigned treatment modality are prerequisites for success. Getting true *informed consent* from a patient is not a trivial task. Every doctor is subject to his own convictions that are only partly derived from medical evidence, but may rather be influenced by personal experience, word-of-mouth recommendation, or local policies. Most patients will not question the verbal information presented to them if they accept the physician as an authority in the field. A large proportion of patients may not even read through endless pages of informed consent sheets that tend to confuse or intimidate them more than they help. Therefore, it is the physician's responsibility to thoroughly evaluate the pros and cons of a treatment modality before talking to the patient. A good approach is to ask oneself what one would do if a near relative was affected by the disease. Once the doctor reaches a clear decision for himself, he then needs to focus on the patient's individual motivation, his social and economic situation, religious beliefs, and other factors. The *prognosis* of myelodysplastic syndromes is dependent on a large number of risk factors that have been combined in different prognostic scoring systems. The *International Prognostic Scoring System* (IPSS)[1] is the most widely used, but requires cytogenetic analysis. In countries where access to karyotyping may not be universal, other prognostic scoring systems based on low-budget analyses are available.[2] In this manuscript, we will focus on a decision model on the basis of the IPSS, though. Patients with low- and intermediate-1 risk disease will be grouped together and considered as low-risk MDS. As described above, other important factors for the decision towards a therapy are age and comorbidities. As an example, allogeneic bone marrow transplantation is rarely an option for MDS patients because of their advanced age at diagnosis, and comorbidities including cardiac disease, severe diabetes mellitus, secondary haemochromatosis, and others, may prevent the patient from being assigned to an optimal treatment strategy. Furthermore, a number of drugs including several recently licensed therapies for MDS (azacytidine, decitabine, lenalidomide) are extremely expensive and will not be covered by health insurance in many countries, remaining inaccessible for many patients. Finally, doctors may not provide optimum therapy to their patients if they are uncomfortable with a therapy because of lack of personal experience. Clear guidelines are needed to enable doctors to use different drugs in a responsible way. It is for this purpose that this article is written. However, it is based on the assumption that we live in what Voltaire called the ''best of the world's'', i.e. all therapies are available to all doctors and patients without restrictions.

Best supportive care

Best supportive care aims at reducing complications due to the underlying disease, improving quality of life, and preventing or alleviating adverse events of therapy. In myelodysplastic syndromes, the main fields of supportive care are *blood component therapy*, *iron chelation therapy*, and *infectious prophylaxis*. It should be born in mind that supportive care is still the standard of care in MDS treatment and that all other therapeutic efforts are subject to comparison with this approach. Transfusion of red blood cells (RBC) and platelets are routine procedures for MDS patients, but considerable uncertainty remains as to the exact threshold of transfusion need. Many patients will tolerate haemoglobin levels as low as 8 g/dl, and some even lower. However, a recent analysis in 39 MDS patients showed that the haemoglobin level was strongly correlated with cardiac remodelling and that each unit of haemoglobin reduced the risk by 50%.[3] *Cardiac remodelling* represents an important aspect of heart failure development regardless of the underlying cause. The heart — especially the left heart chamber — increases in size, develops wall hypertrophy, and becomes more spherical. These changes lead to reduced cardiac performance and increase the risk of mitral regurgitation, preceding heart failure resistant to conventional therapy. Oliva et al.[3] calculated a haemoglobin threshold of 10.7 g/dl as a more appropriate level for RBC transfusion, the higher haemoglobin reducing cardiac remodelling development significantly. In terms of iron overload, a higher transfusion threshold is unlikely to increase transfusion requirements, and should not prevent adopting this approach. Given that many low-risk MDS patients will remain transfusion-dependent for a long time; these results may lead physicians to reconsider their transfusion strategy especially in the elderly patient population that has additional risk factors for cardiac disease. Long-term transfusion-dependent patients should be administered *leukocyte-depleted* RBC concentrates. These prevent the risk of alloimmunisation against leukocyte antigens and febrile, non-haemolytic transfusion reactions in patients with acquired alloantibodies. Furthermore, leukocyte-depletion largely eliminates the risk of transfusing cell-bound viruses like CMV, HHV-8, and HTLV-I/II. *Irradiation* of blood component irreversibly damages DNA of transfused lymphocytes and is a cheap method of preventing potentially fatal graft-versus-host disease. In some countries, irradiation of transfused blood cells is mandatory in patients expected to undergo, or during, autologous or allogeneic bone marrow or stem cell transplantation. Platelet transfusions in MDS patients are required to prevent bleeding from severe thrombocytopenia. Transfusions are expensive and may lead to alloimmune antibody formation in the long run. There are no universal guidelines for platelet transfusion therapy in MDS patients; however, it is sensible to use them reluctantly to prevent transfusion refractoriness due to antibody formation. Prophylactic platelet transfusion should be used in the elderly MDS patient when the platelet count falls below 10.000/μl in the absence of other risk factors, or when the platelet count is below 20.000/μl in case of fever, plasmatic coagulation disorders, previous incidents of bleeding at lower platelet levels, or important cutaneous or mucosal haemorrhage without symptoms. In severely thrombocytopenic patients requiring regular platelet transfusions, epsilon aminocaproic acid may result in a reduction of transfusion need and a prevention of severe hemorrhage.[4] Another important part of supportive therapy is *iron chelation therapy*. Given that a transfusion of one unit of red blood cell concentrates contains 200—250 mg of iron[5] and that only 1 mg of iron is excreted per day through urine, faeces, skin and nails,[6] long-term transfusion dependence will inevitably lead to iron overload. In the el-