EUROPEAN HEMATOLOGY ASSOCIATION

Myelodysplastic syndromes - Section 3

Indications for transplantation in myelodysplastic syndromes

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Take-home messages

- Selection of MDS patients candidate to allogeneic transplantation should be based on both disease and patient-related factors
- Revised IPSS (IPSS-R) is expected to improve the choice of optimal timing of transplantation in early disease stages
- The use of hypomethylating agents is of increasing interest as part of a comprehensive strategy to prevent relapse after transplantation in high risk patients
- Somatic mutations may provide more accurate risk stratification of individual patients and further refine transplantation decision-making in MDS

Introduction

Despite improved understanding of the molecular pathogenesis of myelodysplastic syndromes (MDS) currently available therapies lead to prolongation of life and no cure.[1] Therefore, allogeneic hematopoietic stem cell transplantation (HSCT) is increasingly used as a curative treatment option. This increase in HSCT activity can be attributed largely to the introduction of reduced-intensity regimens that have extended the indication for HSCT to older patients with comorbidities or reduced fitness.[2] Despite its curative potential, because of the inherent complications of the transplantation leading to treatment-related mortality and the risk of relapse, a careful calculation of the benefit for each patient is mandatory, taking into account disease status, comorbidities and effective non-transplant therapies.[1,3]

Current status of the art

Which tools are available for transplantation decision making?

Since MDS range from indolent conditions to subtypes analogous to acute myeloid leukemia (AML) a risk-adapted treatment strategy is mandatory. Prognostic factors may be subdivided into those related to the patient's general health condition and those related to the characteristics of the MDS clone.[1] The definition of disease-related risk in MDS is based on the use of International Prognostic Scoring System (IPSS).[4] A number of studies have shown that advanced disease risk at transplantation is associated with inferior survival, and cytogenetic abnormalities (i.e., complex/monosomal karyotype) have been found to be predictive of high risk of disease relapse.[2] Recently a revised version of IPSS (IPSS-R) was proposed, including five cytogenetic risk groups together with refined categories for marrow blasts and cytopenias.[5] In patients receiving HSCT, IPSS-R score significantly improves the prediction of patient prognosis with respect to IPSS.[6] The implementation of IPSS-R is expected to result in a more effective selection of candidates to HSCT among patients with early disease stage.

Different patient-related factors may affect clinical outcome and decision-making in MDS. The majority of trials in patients treated with HSCT consider a patient's age as a major prognostic factor for non-relapse mortality (NRM). However, these results were obtained mainly after standard myeloablative conditioning. Two recent large studies address the specific issue of elderly MDS receiving reduced intensity conditioning regimens (RIC).[7,8] There was only a trend for a higher incidence of relapse and NRM in the group >60 vs. <60 years of age, which was not statistically significant. Because patient's age per se is not a major risk factor, other factors, such as comorbidities are taken into account. Sorror et al. found that comorbidity predicts posttransplantation outcome in MDS, and they developed the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) to estimate the individual risk of NRM after HSCT.[9] Accounting for both disease- and patient-related factors considerably improves risk stratification than considering IPSS alone.

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What is the optimal timing of transplantation?

Although transplantation early after diagnosis is associated with the most favourable post-transplantation outcome,[2] it remains unclear whether early transplantation leads to maximal life expectancy for patients with early stage MDS that may experience a long period of stable disease after diagnosis. A previous decision analysis by the IBMTR concluded that life expectancy of patients with low or intermediate-1 IPSS risk was higher when transplantation was delayed but performed before the progression of AML. Conversely, for high-risk MDS transplantation soon after diagnosis conferred the best prognosis.[10] This study has substantially influenced clinical practice. Preliminary data suggest that the clinical implementation of IPSS-R may improve transplant decision making process.[11] Using IPSS-R, the estimated life expectancy was maximized when transplantation was delayed until progression from the very low/low to the intermediate risk, and then decreased (Figure 1). Within the low and intermediate-1 IPSS risk, IPSS-R identified a subgroup of patients (30%) who may benefit from early transplantation. Overall, there was a 2-year gain in life expectancy using the IPSS-R vs. IPSS-based transplant policy.[11]

Should cytoreductive treatment be performed before transplantation in high risk patients?

In patients with advanced disease, disease relapse represents the leading cause of transplant failure. The issue of performing cytoreductive treatment before HSCT to reduce the risk of relapse is a matter of debate. Concerns about AML-like chemotherapy mainly include risk of long-lasting myelosuppression and organ toxicities.[1,3] It should be considered in addition that there is no definitive evidence of a survival benefit associated with administering chemotherapy before HSCT

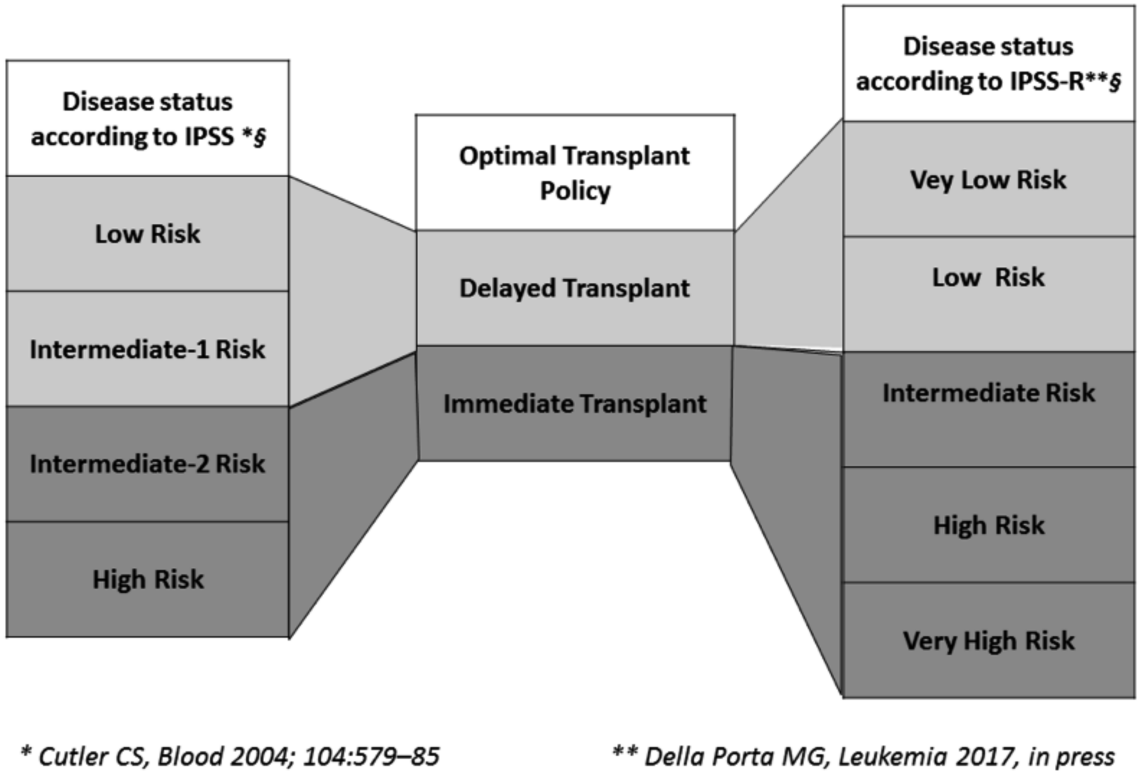

Figure 1. Decision analysis of allogeneic hematopoietic stem cell transplantation for patients with myelodysplastic syndrome stratified according to currently available prognostic scores.

in MDS.[12]

The availability of hypomethylating agents (HMA) has changed the landscape of MDS treatment. Importantly, HMA were found to be effective even in MDS who had unfavourable cytogenetics and/or TP53 mutations, in which chemotherapy is clearly ineffective.[13,14] Although azacitidine and decitabine can induce hematological and cytogenetic responses, these therapies do not appear to eradicate MDS clones, and recent data suggest that even in high risk patients aged >60 years, transplantation (RIC) offers survival benefit with respect to non-transplant procedures.[15] Several studies have evaluated the role of HMA given before transplantation, though very few were conducted prospectively. Overall, these investigations showed similar post-transplantation outcome for patients receiving HMA vs. chemotherapy. Moreover, in some cases an improved survival of patients transplanted in complete remission vs. active disease at the time of HSCT was reported.[16] In the absence of data from prospective trials, the decision to perform a cytoreductive treatment should be made accounting for clinical considerations with respect to each specific patient.

Future perspectives

Mutations in several genes have been reported to influence survival and risk of disease progression in MDS.[17] MDS associated with SF3B1 mutations form a distinct entity with a favourable prognosis, while SRSF2, RUNX1, U2AF1, ASXL1 and TP53 mutations are associated with increased risk of leukemic evolution.[18] The integration of somatic mutations into prognostic scoring systems may provide more accurate risk stratification of individual patients and further refine clinical decision-making in MDS. A recent study in 401 patients who received HSCT for MDS or MDS/AML showed that somatic mutations in ASXL1, RUNX1, or TP53 were associated with unfavorable outcomes and shorter survival.[19] A larger CIBMTR study reported relevant new findings. RAS pathway mutations and JAK2 mutations were associated with a poor outcome after HSCT, independently of TP53 mutations in patients >40 years.[20] Possible interventions in patients with high risk of disease relapse according to genotype may include the anticipation of the transplant procedure in early disease phase, the use of innovative conditioning regimens to increase the probability to eradicate MDS clone, and prophylaxis of disease recurrence after transplantation. These results serve as a proof of concept that the integration of somatic mutations significantly increase the capability to capture prognostic information in MDS patients receiving HSCT, and may provide a basis for improving transplantation decision-making.

References

1. Malcovati L, Hellstrom-Lindberg E, Bowen D, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. Blood 2013; 122: 2943-64.
2. Alessandrino EP, Della Porta MG, Bacigalupo A, et al. WHO classification and WPSS predict posttransplantation outcome in patients with myelodysplastic syndrome: a study from the Gruppo Italiano Trapianto di Midollo Osseo (GITMO). Blood 2008, 112:895-902
3. de Witte T, Bowen D, Robin M, I, et al. Use of hematopoietic cell transplantation for patients with myelodysplastic syndrome and chronic myelomonocytic leukemia. Blood. 2017 Jan 17. [Epub ahead of print]
4. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997; 89:2079–88.
5. Greenberg PL, Tuechler H, Schanz J, F et al. Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes. Blood 2012; 120: 2454-65.

*6. Della Porta MG, Alessandrino EP, Bacigalupo A, et al. Predictive factors for the outcome of allogeneic transplantation in patients with MDS stratified according to the revised IPSS-R. Blood 2014; 123:2333-42.

IPSS-R score significantly improves the prediction of MDS patient prognosis receiving HSCT with respect to IPSS.

7. Lim Z, Brand R, Martino R, et al. Allogeneic hematopoietic stem cell transplantation for patients 50 years or older with myelodysplastic syndromes or secondary acute myeloid leukemia. J Clin Oncol. 2010;28:405-11.
8. McClune BL, Weisdorf DJ, Pedersen TL, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. J Clin Oncol 2010;28:1878-87.

*9. Sorror ML, Sandmaier BM, Storer BE, et al. Comorbidity and disease status based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. J Clin Oncol 2007;25:4246-54.

Comorbidity predicts posttransplantation outcome in MDS, and Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) allows to estimate the individual risk of NRM.

10. Cutler CS, Lee SJ, Greenberg P, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: Delayed transplantation for low-risk myelodysplasia is associated with improved outcome. Blood 2004; 104:579–85.
11. Della Porta MG, Jackson CH, Alessandrino EP, et al. Decision analysis of allogeneic hematopoietic stem cell transplantation for patients with myelodysplastic syndrome stratified according to the revised international prognostic scoring system (IPSS-R). Leukemia. 2017 Mar 21. doi: 10.1038/leu.2017.88. [Epub ahead of print]
12. de Witte T, Hermans J, Vossen J, et al. Haematopoietic stem cell transplantation for patients with myelo-dysplastic syndromes and secondary acute myeloid leukaemias: A report on behalf of the Chronic Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Br J Haematol 2000; 10:620–30.

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13. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: A randomised, open-label, phase III study. Lancet Oncol 2009;10:223–32.

*14. Welch JS, Petti AA, Miller CA, et al. TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes. N Engl J Med. 2016;375:2023-36

Hypomethylating agents induce clinical response in MDS who had unfavorable cytogenetics and/or TP53 mutations, in which chemotherapy is clearly ineffective.

15. Koreth J, Pidala J, Perez WS, et al. Role of reduced-intensity conditioning allogeneic hematopoietic stem-cell transplantation in older patients with de novo myelodysplastic syndromes: an international collaborative decision analysis. J Clin Oncol 2013; 31:2662-70.

16. Damaj G, Duhamel A, Robin M, et al. Impact of azacitidine before allogeneic stem-cell transplantation for myelodysplastic syndromes: A study by the Société Française de Greffe de Moelle et de Thérapie-Cellulaire and the Groupe-Francophone des Myélodysplasies. J Clin Oncol 2012; 30:4533–40.

17. Cazzola M, Della Porta MG, Malcovati L. The genetic basis of myelodysplasia and its clinical relevance. Blood 2013;122: 4021-34.

18. Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood 2013;122:3616-27

*19. Della Porta MG, Gallì A, Bacigalupo A, et al. Clinical effects of driver somatic mutations on the outcomes of patients with myelodysplastic syndromes treated with allogeneic hematopoietic stem-cell transplantation. J Clin Oncol 2016 Sep 6. [Epub ahead of print]

In MDS patients, somatic mutations of ASXL1, RUNX1 or TP53 genes are associated with unfavorable outcomes and shorter survival after HSCT.

*20. Lindsley RC, Saber W, Mar BG, et al. Genetic Alterations Predict Outcomes in Patients with Myelodysplastic Syndrome Receiving Allogeneic Hematopoietic Stem Cell Transplantation. N Engl J Med 2017;376:536-547

In MDS patients, mutations of TP53, JAK2 and RAS pathway genes are associated with a poor outcome after HSCT.