

HSCT FOR MYELOYDYSPLASTIC SYNDROMES (MDS)

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MYELOYDYSPLASTIC SYNDROMES (MDS)

INTRODUCTION

Myelodysplastic syndrome (MDS) is a clonal disorder that is characterized by cytopenias, dysplasia in one or more cell lines, ineffective hematopoiesis and, depending on its subtype, may have presence of blasts, being frequently associated with genetic alterations. In approximately 30% of cases it can progress to acute myeloid leukemia.

CLASSIFICATION AND PROGNOSTIC STRATIFICATION

Detailing in the classification is very important, as it is decisive in defining the initial conduct and in the prognosis of the disease. Currently, we use the WHO classification 2016.^[10-14,34] A very relevant aspect are the situations in which we have cytopenias, sometimes severe, with transfusion dependence or even complex karyotypes with large numbers of mutations, and even so the diagnosis of MDS cannot be concluded, being defined as Clonal Cytopenia of Undetermined Meaning (CCUS) NCCN Guidelines version 2.2020^[35], where there is already a discussion of HSCT, in selected cases.

Risk stratification in MDS can be performed using different scores, such as R-IPSS, IPSS, WPSS and MD Anderson Score.^[15-17] This first is the most used and is divided into five prognostic groups (Very Good, Good, Intermediate, Poor and Very poor), in which cytogenetics is crucial for classification. Despite being revised and being more refined in cytogenetic changes, it still does not fully cover the complexity of stratification of this pathology, as it does not consider marrow fibrosis and the presence of prognostic mutations, among the most relevant we have TP53, RUNX1, ASXL1, EZH2, ETV6, TET2 and DNMT3.^[18-21]

We know that some patients classified as low risk (LR) could have a poor evolution, due to severe neutropenia, recurrent infections and a high transfusion need^[22], which, if not resolved, can lead to lethal outcome.

TREATMENT

The rationale for treatment is based on the risk stratification of the patient at low risk (LR) or high risk (HR). In patients classified as LR in the R-IPSS, who are not transfusion dependent, management should be conservative. Clinical treatment, if necessary, is the best option, based on the use of erythropoietin and oral iron chelators in case of ferritin > 1000 ng / mL or more than 20 transfusions.^[35]

INDICATION OF ALLOGENEIC HSCT IN MDS

Allogeneic HSCT is still the only curative procedure, but some questions are imposed in the face of this statement: who and when?. Since most of these patients are elderly and have comorbidities, many are ineligible for HSCT. We can use the HCT-CI comorbidity index^[24-26] and prognostic stratification to assist in this difficult decision. Cutler et al. through Markov's analysis, it was determined that patients classified as high risk should be considered eligible for early allogeneic HSCT if the IPSS was used as a prognostic instrument.^[26]

Comprehensive geriatric evaluation (CGA) is currently considered a fundamental criterion for defining eligibility and type of conditioning.

With the use of R-IPSS, some patients previously considered LR by IPSS, were reclassified as HR. This modification, added to the presence of factors of bad prognosis, such as marrow fibrosis, CD34 positivity in immunohistochemistry or presence of mutations

of poor prognosis, can be considered, at the moment of clinical decision, for the implementation of a more aggressive therapy such as use of hypomethylating agents and allogeneic HSCT.^[36]

Myeloablative allogeneic HSCT should be considered for patients under 60 years of age who have an identical HLA related donor. In elderly patients over the age of 60 years, allogeneic HSCT with reduced intensity conditioning (RIC) becomes an alternative, as studies show that age alone should not be considered a contraindication. Some European groups have proposed the 55-year limit for defining the type of conditioning, but this conduct is not a consensus. We believe that the individual characteristics, associated with HCT-I and CGA, can be reliable parameters in defining the type of conditioning. With the possibility of RIC and the inability to cure with chemotherapy drugs despite increased survival,^[27] more and more, we are faced with the dilemma of the indication of allogeneic HSCT in the elderly. The growth of haploidentical transplantation, made the chance of an alternative family donor and the intensity was more reduced.

In HR patients, hypomethylating therapy should be considered in the first approach, with azacitidine being the drug of choice with level of evidence 1A according to the NCCN Guidelines version 2.2020.^[35] This drug can be used in pre-HSCT while looking for a compatible donor. The need for compulsory cytoreduction prior to HSCT has been questioned, since retrospective studies of the German (Schoederer, BMT)^[39] and Latin American (Duarte, BBMT)^[40] groups have not shown significant differences in the results of transplants. Perhaps the reduction of the time between donor preparation and the time of transplantation, is more relevant.

In patients with no doubt in the indication of allogeneic HSCT and the absence of a related donor, we must start the search for unrelated donors. According to retrospective data from the CIBMTR,^[28,29] corroborated by the EBMT data,^[30] this procedure should not be disregarded, since the analysis of 4-year survival is similar to that of patients undergoing HSCT with a related donor.

The possibility of using umbilical cord cells should be considered mainly in pediatric patients. In addition to disease recurrence, the high rate of graft failure should be considered, and more recently an early monitoring of chimerism has been proposed as a way to better monitor this complication.^[31]

STRATEGIES AFTER ALLOGENEIC HSCT

The relapse of MDS after allogeneic HSCT is a concern, especially in patients undergoing HSCT with

RIC. It has been associated with reduced survival in two years, with prognostic factors being the presence of acute GVHD and relapse in the first six months after HSCT. Donor lymphocyte infusion and a second allogeneic HSCT are options in this context, when possible.^[32]

Azacitidine started to play an important role in post-HSCT^[32] due to its immunomodulatory action and the ability to raise T-reg Lymphocytes,^[33] in order to maintain remission. Some studies propose that when there is evidence of loss of chimerism, azacitidine can be started early, being able to prevent disease relapse. The use of azacitidine after HSCT can be an alternative to increase the action of the graft versus leukemia, without increasing GVHD.^[33-38] However, in a prospective and randomized study (Oran B et al),^[41] the role of isolated maintenance with azacitidine was questioned, with no significant survival difference between the groups using or not using azacitidine. Numerous studies with new drugs have been conducted, among them, the associations of venetoclax, check point inhibitors and APR-246 associated with the hypomethylating agent, showing at first an improvement in maintenance results, but still without randomized studies. The role of the association of DLI (donor lymphocyte infusion) cannot be forgotten.

CONCLUSION

The chronic course of some patients with MDS and transplant-related mortality (TRM) lead to a reluctance to offer such a procedure earlier, but this delay can compromise the chances of success. We must surround ourselves with criteria for this decision, remembering the use of the specific comorbidity index for HSCT, CGA and risk stratification. The possibility of using reduced intensity conditioning decreased the TRM, allowing one to envision this procedure for patients previously considered ineligible. The IPSS and the R-IPSS are useful parameters to guide the clinical decision to decide the allogeneic HSCT, especially in patients with a HLA compatible donor. According to data from the NCCN, survival in HR patients is better if the transplant is performed early.

Already classified as LR, we must surround ourselves with the greatest possible prognostic refinement to

make this decision. The valuation of mutations, especially p53, TET2, DNMT3, ASXL1, has been increasingly relevant as a prognostic factor for treatment, indication for transplantation and sometimes follow-up of minimal residual disease. The p53 mutation specifically confers an independent prognostic factor, is associated with a complex karyotype and when present together with the 5q deletion, it has been related to the loss of response to lenalidomide and confers a poor prognosis even with transplantation.

With the knowledge we have today, allogeneic HSCT for MDS is an option, which can be performed in elderly patients, with acceptable levels of mortality and morbidity related to transplantation. The decision of when to perform the HSCT should be based on the patient's comorbidities and on the predictive factors of the disease, always evaluating the benefit-risk between the transplant and the other treatment options.

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