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MAINTENANCE TREATMENT POST-TRANSPLANT

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Disease recurrence is the most common cause of HCT failure in patients with AML, ALL and SMD and factors such as the presence of measurable residual disease before and after transplantation, stage of the disease before transplantation and the cytogenetic and molecular risk profile are factors associated with increased risk of recurrence.

The development of treatments with less toxicity for acute leukemias and high-risk MDS has resulted in the emergence of several agents potentially useful in this context. This issue has a greater relevance in patients who receive reduced intensity conditioning (CIR), due to the high and early recurrence rates observed in these patients¹. The emergence of maintenance treatment options has raised several issues in addition to their effectiveness, including the duration and time of initiation of treatment, their interactions with the clinical sequelae of graft versus host disease (GVHD), grafting, hematopoietic toxicity and potential impacts on the effects of the donor graft. Nowadays, HCT is performed early in the course of the disease and improvements in supportive care, the use of conditioning regimes with less toxicity make patients more able to receive post-transplant treatments and several anti-neoplastic agents are available for the preemptive prevention treatment or treatment (in those patients who already have positive DRM) of relapses, including tyrosine kinase inhibitors, epigenetic modifiers, checkpoint inhibitors, bcl-2 inhibitors, drug-monoclonal antibody conjugates, monoclonal antibodies specific products, in addition to cellular engineering products.

The choice of agents for maintenance treatment must take into account the toxicity of the same (mainly myelotoxicity), their interaction with the patient's post-transplant medications, as well as their interference with the development of GVHD and the graft response against leukemia.

If a mutation is present, it may be tempting to use approved agents for the treatment of active disease, such as BCR-ABL inhibitors, FLT3, IDH1 and IDH2. Registry studies have shown that AML patients with

FLT3 ITD mutations have a higher risk of relapse after allogeneic HCT than patients who do not have the mutation².

Several FLT3 inhibitors have been studied in the post-TCH maintenance scenario with superior results reported with sorafenib when compared with historical controls³⁻⁶. A small prospective randomized study (total of 83 patients) reported superior developments in patients in complete hematological remission receiving sorafenib, when compared to placebo⁶, however the lack of information provided on the frequency of FLT3 alleles at diagnosis, pre-HCT DRM and persistence or recurrence of DRM in post-HCT did not clarify which subpopulation of these patients may benefit from this treatment.

Midostaurin was the first FLT3 inhibitor drug approved to treat AML patients with the gene mutation. The approval was based on a randomized study that demonstrated a better overall survival rate (OS) in patients who received midostaurine in combination with induction and consolidation chemotherapy⁷. Patients recruited in this study discontinued the drug before HCT because it was not intended to assess the role of midostaurin in post-transplant maintenance, but a continued benefit in OS in the post HCT period was observed in those patients who received the drug before transplantation. The RADIUS study randomized 60 patients to receive midostaurine after HCT or standard treatment⁸. There were no significant differences in relapse-free survival (RFS) rates between the two arms of the study; the estimated two-year RFS and OS was 85% for midostaurine and 76% for standard treatment. There was a 40% reduction in the risk of recurrence and 42% in the risk of death in the midostaurine arm. Both studies excluded patients who had received previous treatment with FLT3 inhibitors and those who had morphological evidence of post-HCT relapses.

Other preliminary studies have evaluated the use of FLT3 inhibitors to prevent recurrences after HCT^{4,6}. More recently, two randomized phase 2 studies have been completed in patients with AML and mutated

FLT3. The SORMAIN study randomized 83 patients to receive sorafenib (n = 43) or placebo (n = 40)⁹. There was a significant improvement in the RFS rate but without a significant improvement in the OS rate.

Nevertheless, this and other single-arm studies are the basis for some groups to indicate the use of other FLT3 inhibitors only partially studied, after allogeneic HCT. A randomized phase 3 maintenance study with gliteritinib is ongoing and includes the determination of DRM by PCR of the FLT3-ITD mutation and should result in important information to identify which patients could have benefit.

Azacitidine can induce remissions in patients who relapse after HCT¹⁰. A series of small studies using azacitidine preemptively or prophylactically in patients with decreased CD 34 + cell chimerism suggested a delay in these patients' relapse, by inducing an anti-leukemic cellular response by CD 8 + ^{11,12}T lymphocytes. In another study, azacitidine was combined with donor¹³ lymphocyte infusion. Although at the expense of a higher incidence of acute and chronic GVHD, recurrence rates were low and that of SG promising. These are uncontrolled studies, given the difficulties of conducting a study of controlled cases in this scenario. In a recent prospective, randomized study of azacitidine (N = 93) versus observation (N = 94) after allogeneic HCT, there were no differences in disease recurrence: the recurrence-free survival curves were virtually overlapping¹⁴. The development of oral azacitidine formulations has shown benefit in a randomized study as maintenance after induction chemotherapy in AML, therefore maintenance studies after HCT should be reviewed with these new agents^{15,16}.

Several studies at an early stage suggest that the use of hypomethylating agents (HMA) can prevent the occurrence of recurrence^{10,17} by inducing an anti-leukemic cellular response by CD 8 + T lymphocytes and treating early recurrences after TCH¹¹. In another study, azacitidine was combined with donor lymphocyte infusion¹². Although at the expense of a higher incidence of acute and chronic GVHD, recurrence rates were low and that of OS promising. These are uncontrolled studies, given the difficulties of conducting a controlled case study in this scenario. The combination of these results with the low toxicity of HMA and its potential role in improving the effect of the graft against leukemia in the post HCT¹³ resulted in the development of post-HCT maintenance protocols with HMA. A randomized study from the MD Anderson Cancer Center compared azacitidine (n = 93) to standard treatment (n = 94) in patients with MDS and AML¹⁸. There was no significant difference

in RFS at 1 year, which was 2.07 years (azacitidine) versus 1.28 years (standard treatment). The dose of azacitidine was 32 mg / m² daily for five consecutive days, and although the planned duration of maintenance treatment was one year, only 29% of patients completed treatment. Among the causes of discontinuation of treatment with azacitidine are: relapse (47%), toxicity (18%), patient preference (15%) and infection (11%). There was a trend towards better RFS in patients who received at least nine post-HCT maintenance cycles. The oral formulation of azacitidine can improve its effectiveness, treatment adherence and tolerability, with better outcomes^{14,18}.

There is currently interest in studying hypomethylating agents combined with a variety of other agents such as venetoclax, checkpoint inhibitors and monoclonal antibodies, although the evidence for these strategies has not yet been established.

Probably the greatest risk for AML recurrences after HCT is the presence of a mutation of the p53 gene¹⁵. APR-246 is being developed specifically for patients with myeloid neoplasms and mutated p53. The results of the initial studies seem promising, with a complete remission rate (CR) of around 80% in patients with AML and SMD15. There is an ongoing phase 2 study evaluating the combination of azacitidine combined with APR-246 in the post-HCT period for patients with AML and MDS with a p53 mutation. The primary endpoint of the study is SLR at 1 year.

Ivosidenib and enasidenib are recently approved agents that target IDH 1 and IDH 2, respectively^{16,19}. They are well tolerated and could, theoretically, be used as a maintenance treatment after allogeneic HCT in patients with AML with these mutations. Studies with these agents are underway and will allow us to first understand the relevance of these mutations in the dynamics of post-HCT relapses and to assess their tolerance in this scenario. There is currently no evidence to support the use of these agents in maintenance.

An ideal maintenance treatment should not only reduce the risk of relapse but also the incidence of GVHD. Donor lymphocyte infusions (DLI) have been used for several years in this scenario. A multicenter study suggested that donor lymphocyte administrations in patients with post-HCT AML were able to convert mixed chimerisms into complete²⁰. In another study, DLI after the first month after HCT in a total of three administrations in patients with AML and SMD resulted in high rates, lower incidence of relapses and high rates of chimerism conversion, but at the expense of a higher incidence of GVHD²¹. Subse-

quent studies found higher survival rates in patients with myeloid neoplasms who received prophylactic or preemptively DLI²²⁻²⁴. A study conducted by EBMT (n = 343) demonstrated that the use of DLI is associated with a reduction in the rate of relapse (28%) in five years when administered preemptively to reverse mixed chimerism or when used prophylactically in patients with high-risk diseases. However, the cohort of patients with positive MRD who received preemptive DLI had a recurrence rate of 43%²⁵.

In conclusion, due to the complexity of the HCT, the risks of GVHD and infections, the high costs involved and the patients' own adherence to maintenance treatments, studies in this area are difficult to carry out. In myeloid neoplasms, we will have more and more treatment "targets" that can be studied in this

scenario. It should also be noted that any maintenance treatment after HCT must be started early, since a significant rate of recurrence occurs in the first 3 to 6 months after HCT, as well as the duration of treatment must take into account that the greatest risks of relapse occur in the first and second years after HCT. The decision to initiate maintenance treatment after HCT will depend on the judgment of the transplant team and the assessment of parameters such as risk factors for the disease, the patient's "performance status", genetic and molecular profile of the disease and the accessibility and cost of the chosen agent. So far, maintenance treatment for AML is considered experimental and should preferably be carried out in a clinical study context.

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