EBMT ALWP recommendations for transplantation in patients with FLT3-ITD AML

 **Alexander Maurer**  **Ali Bazarbachi** | May 1, 2020

Patients with *FLT3*-mutated AML represent 25–30% of all newly diagnosed AML cases, and their overall prognosis is poor due to the aggressive course of the disease and the risk of early relapse. While there is general agreement on the incorporation of FLT3 inhibitors in frontline treatment and the use of measurable residual disease (MRD) assays, the strategy for allogeneic hematopoietic stem cell transplantation (allo-HSCT) differs between centers.

Globally, hematologists agree on quick treatment initiation followed by allo-HSCT once patients have achieved their first complete remission (CR1). However, clinical protocols vary regarding indication for allo-HSCT according to risk profiles, modalities of allo-HSCT, and post-transplant maintenance. Therefore, the Acute Leukaemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) recently published in *Haematologica* their position statement on allo-HSCT for patients with *FLT3* internal tandem duplication (*FLT3*-ITD) AML.[1]

A panel of 32 members mostly from the EBMT was selected by the chairs, Professor Ali Bazarbachi and Professor Mohamed Mohty, based on their expertise in research and clinical practice in AML and allo-HSCT. Using the Delphi technique, three panelists provided statements addressing key questions to the remaining panel members who scored their agreement with those statements and suggested rephrasing where necessary. Available evidence from public databases was used to rate the strength of recommendations and evidence level.

Indication for allo-HSCT in *FLT3*-mutated AML

As a rule, allo-HSCT in CR1 should be performed in patients with *FLT3*-ITD AML when feasible. Nevertheless, many additional variables can influence the indication for allo-HSCT in this subgroup of patients, such as allelic ratio, concomitant mutations, or MRD status post-induction. The authors state that at the moment, there is insufficient data to provide a rigorous recommendation taking into consideration every possible combination of these variables.

However, the need for transplantation in CR1 is debatable for the small subgroup of patients with *FLT3*-ITD^{low} (allelic ratio < 0.5) AML and co-existing *NPM1* mutations, who achieved MRD-negativity after induction therapy. Given the favorable risk profile of this group, many European cooperative groups recommend withholding allo-HSCT for later stages of the disease, while the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) still recommend allo-HSCT in CR1 for these patients. Overall, changes in the allelic ratio during the evolution of the disease, along with the variability in assessment techniques and the lack of a precise cut-off level, make it difficult to draw any firm conclusions from the published data.

Stem cell transplantation and predictive factors for outcome

Patients with *FLT3*-ITD mutated AML tend to benefit from allo-HSCT performed in CR1, leading to a 2-year leukemia-free survival (LFS) of 50-60%, but the authors advocate for the need to identify predictive factors which can help to better determine the outcome of transplantation. For instance, the presence of *NPM1* mutation and the *in vivo* T cell depletion with anti-thymocyte globulin (ATG) have a positive impact on the outcome. On the other hand, conditioning intensity and the type of donor do not correlate with the outcome and should be selected based on the patient's age, donor type, and disease status.

When selecting a stem cell donor, it is advised to follow the EBMT general guidelines,[2] which may include the use of cord blood or a haploidentical donor if a matched sibling donor cannot be identified.

The authors highlight a recent large EBMT registry study published by Bazarbachi *et al.*[3] where data from 462 patients with *FLT3*-mutated AML were analyzed. The results suggest that the use of ATG after transplant decreased the rate of chronic graft-*versus*-host disease (GvHD) and significantly improved LFS, overall survival (OS), and GvHD-free relapse-free survival (GRFS), without increasing the risk of relapse. Therefore, this procedure can now be considered a safe and effective option for these patients.

Post-transplant maintenance in *FLT3* mutated AML

There are limited treatment options for patients with *FLT3*-ITD AML who relapse, as standard chemotherapy and FLT3 inhibitors, also combined with donor lymphocyte infusions, show little efficacy in this setting. A second allo-HSCT is a hazardous option and only feasible in a minority of patients.

Therefore, the aim of adding FLT3 inhibitors as maintenance therapy is to delay relapse after the first allo-HSCT. After reviewing the available published data, the panel recommends the addition of post-transplant maintenance therapy with an FLT3 inhibitor (in the absence of a clinical trial) for all patients, except for those with active acute GvHD. Pending the results and approval of other FLT3 inhibitors, at the moment, sorafenib is the preferred option. The initiation of the maintenance therapy should be done as soon as possible after allo-HSCT and hematologic reconstitution.

Even in this high-risk setting, sorafenib seems to be safe and effective in improving progression-free survival (PFS) and OS, with manageable toxicities, as reported in different studies such as the SORMAIN trial. The recommended dose is 400 mg/day administered in two divided doses for a minimum of two years. Patients presenting with MRD-positive disease can also be initially treated with a higher dose (800 mg/day). The dose should be adapted gradually, according to tolerance. In the case of GvHD requiring corticosteroids, sorafenib should be discontinued and may be cautiously resumed when GvHD is in remission.

You can find more information about maintenance therapies being investigated for patients with AML in the monthly editorial theme published recently on the AML Hub.

Conclusion

The main limitation of these recommendations is the lack of data in the subgroup of patients with *FLT3*-ITD AML. Therefore, the panel was only able to review results from retrospective cohort studies and several phase II trials.

Regardless, the authors firmly recommend that allo-HSCT at CR1 should generally be offered to all patients with *FLT3*-ITD AML. However, there are some controversies about whether patients with *FLT3*-ITD^{low} and *NPM1* mutations who achieved MRD-negativity should proceed to transplantation, or save it for later stages of the disease where there are less therapeutic options available. More work is required to identify standards for assessing the *FLT3*-ITD allelic ratio and cut-off level.

Although maintenance therapy with FLT3 inhibitors is recommended in patients with *FLT3*-ITD AML after transplantation, many questions remain to be answered. There are still uncertainties around, for example, the duration of the maintenance (a minimum of two years is recommended but not established), the effect on immune reconstitution, the use of pre-emptive *versus* prophylactic donor lymphocyte infusion, possible combinations with other drugs, or the safest time for immunosuppression withdrawal.

Large prospective randomized trials are currently on-going that may shed light and provide additional evidence to support the optimal treatment of patients with *FLT3*-ITD AML.

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