Clinical practice recommendation on hematopoietic stem cell transplantation for acute myeloid leukemia patients with *FLT3*-internal tandem duplication: a position statement from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

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Ferrata Storti Foundation

Haematologica 2020
Volume 105(6):1507-1516

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Received: November 19, 2019.

Accepted: March 19, 2020.

Pre-published: April 2, 2020

doi:10.3324/haematol.2019.243410

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/105/6/1507

ABSTRACT

The *FMS-like tyrosine kinase 3* (*FLT3*) gene is mutated in 25-30% of patients with acute myeloid leukemia (AML). Because of the poor prognosis associated with *FLT3*-internal tandem duplication mutated AML, allogeneic hematopoietic stem-cell transplantation (SCT) was commonly performed in first complete remission. Remarkable progress

has been made in frontline treatments with the incorporation of FLT3 inhibitors and the development of highly sensitive minimal/measurable residual disease assays. Similarly, recent progress in allogeneic hematopoietic SCT includes improvement of transplant techniques, the use of haplo-identical donors in patients lacking an HLA matched donor, and the introduction of FLT3 inhibitors as post-transplant maintenance therapy. Nevertheless, current transplant strategies vary between centers and differ in terms of transplant indications based on the internal tandem duplication allelic ratio and concomitant nucleophosmin-1 mutation, as well as in terms of post-transplant maintenance/consolidation. This review generated by international leukemia or transplant experts, mostly from the European Society for Blood and Marrow Transplantation, attempts to develop a position statement on best approaches for allogeneic hematopoietic SCT for AML with *FLT3*-internal tandem duplication including indications for and modalities of such transplants and on the potential optimization of post-transplant maintenance with FLT inhibitors.

Introduction

FMS-like tyrosine kinase 3 (FLT3) is a transmembrane ligand-activated receptor tyrosine kinase that is normally expressed by hematopoietic stem cells and early myeloid and lymphoid progenitor cells, and is involved in the proliferation, differentiation and apoptosis of hematopoietic cells[1] through various signaling pathways, including phosphatidylinositol 3-kinase (PI3K) and rat sarcoma (RAS) signal-transduction cascades.[2-7] *FLT3* is mutated in about 25-30% of newly diagnosed cases of acute myeloid leukemia (AML),[8-10] either by internal tandem duplications (*FLT3*-ITD) of the juxtamembrane domain (19-25%), and/or by a point mutation, usually involving the tyrosine kinase domain (TKD) at D835 or I836 in the activating loop (7-10%).[11-13] Both mutations are more frequent in cytogenetically normal AML and both constitutively activate *FLT3* causing dimerization in a ligand-independent manner, resulting in proliferation and survival of leukemia cells.[14,15]

FLT3-ITD mutations in newly diagnosed AML are associated with a greater disease burden, manifesting as an elevated white blood cell count and a high percentage of blasts at the time of diagnosis as well as a tendency to early relapse and a poor overall prognosis.[8,10-12,16,17] Both European LeukemiaNet (ELN) recommendations and National Comprehensive Cancer Network (NCCN) guidelines incorporate *FLT3*-ITD mutations in risk-stratifying patients based on allelic burden and nucleophosmin-1 (*NPM1*) co-mutation.[18,19] In cytogenetically normal patients, *FLT3*-ITD mutations in the presence of a concomitant *NPM1* mutation, mainly when the *FLT3*-ITD allele ratio is low (<0.5), fare better than those with wild-type *NPM1*.[8,10,16,17,20-22] Despite the great effort to harmonize and cross-validate the FLT3 assays within clinical trials,[23] there is still no consensus on the *FLT3*-ITD allele ratio threshold and there is considerable variability between centers in the assessment of the *FLT3*-ITD ratio according to the technique used, if one is available. Furthermore, in addition to *NPM1* mutations, a significant overlap with other mutations (*WT1*, *IDH1*, *DNMT3A*) as well as *NUP98/NSD1* fusions modify outcome as well as response to therapy. Although patients with *FLT3*-ITD AML respond to conventional induction chemotherapy with remission rates similar to those seen in other subtypes of AML, they are much more likely to relapse and to relapse quickly.[11,12,24-28] The prognostic impact of *FLT3*-TKD is less clear,[29-32] but it, too, is influenced substantially by *NPM1* co-mutation which confers a better prognosis.[33-35]

The availability of active FLT3 inhibitors that are able to disrupt the oncogenic signaling initiated by FLT3 has improved the overall survival (OS) of patients with *FLT3*-mutated AML.[36] Midostaurin, a multikinase inhibitor, was granted Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for the treatment of patients with newly diagnosed *FLT3*-mutated AML, in combination with intensive chemotherapy, and by the EMA in addition as maintenance treatment after conventional consolidation therapy. This approval was based on the results of the RATIFY trial, which demonstrated that the combination of midostaurin with standard induction therapy resulted in significantly prolonged OS (not censored for transplant) for AML with either *FLT3*-ITD or *FLT3*-TKD mutations.[37] The benefit was particularly remarkable in patients who went on to receive allogeneic hematopoietic stem cell transplantation (allo-SCT) in first complete remission (CR1). Following the results of the ADMIRAL trial, gilteritinib, a second-generation FLT3 inhibitor, was recently approved for relapsed/refractory *FLT3*-mutated AML with *FLT3*-ITD and *FLT3*-TKD mutations.[38] Promising data were also reported for quizartinib and crenolanib.[39,40] Finally, because of its long-time availability, sorafenib has been tested, alone or in combination, in various settings in *FLT3*-ITD AML, such as first-line therapy[41,42] or for the treatment of disease relapse,[43-45] including after failure of allo-SCT.[45-57] However, recent data appear to support incorporating sorafenib into the treatment of patients with *FLT3*-mutated AML, possibly with induction therapy[41,58,59] as well as maintenance therapy after allo-SCT.[43,60-65]

Because of the diversity in *FLT3*-mutated AML, which depends on the type of *FLT3* mutation, *FLT3*-ITD allelic burden, insertion site and co-occurring mutations, the decision regarding whether to perform allo-SCT in CR1 is becoming more challenging.[66-75] With the use of more effective therapies, especially with the incorporation of FLT3 inhibitors, deeper responses are being achieved. The assessment of minimal/measurable residual disease (MRD) at the time of response has enabled prediction of outcomes in AML, and tailoring of post-remission therapeutic strategies accordingly.[76-78] Additionally, substantial progress has been made in allo-SCT in recent years, including improvement of transplant techniques, the use of haplo-identical donors in patients lacking an HLA-matched donor,[79-81] and post-transplant preventive strategies, such as prophylactic or preemptive use of FLT3 inhibitors.[63,82-85] Nevertheless, current transplant strategies

vary between centers and differ in terms of indications for the transplants and treatments following them. This review provides a consensus from European Society for Blood and Marrow Transplantation (EBMT) experts on best approaches to allo-SCT in AML with *FLT3*-ITD including the indications for and modalities of allo-SCT and on potential optimization of post-transplant maintenance therapy with FLT3 inhibitors.

The consensus process

Two chairpersons (AB and MM) appointed a panel of 32 physicians (hereafter referred to as the Panel) selected mostly from the EBMT) for their expertise in research and clinical practice in AML and allo-SCT. A physician with expertise in clinical epidemiology (ML) ensured the methodological correctness of the process. The objective of the Panel was to identify practical issues pertinent to all physicians involved in the therapeutic management of patients undergoing allo-SCT for AML with *FLT3* mutations and to generate best practice recommendations on indications for and modalities of allo-SCT and on potential optimization of post-transplant maintenance with FLT3 inhibitors. This was done through a number of questions according to the Delphi technique.[86] A search for relevant literature in English was performed in the MEDLINE, EMBASE and PubMed databases (up to August 2019). Most of the studies used for these recommendations are retrospective cohort studies or phase II trials, with only a few prospective randomized trials. Three panelists drafted statements that addressed the key questions identified, and the remaining panelists scored their agreement with those statements and provided suggestions for rephrasing them.

The evaluation of evidence and the subsequent recommendations were graded according to the system used by Couriel.[87] The strength of the recommendations (*Online Supplementary Table S1*) and evidence levels (*Online Supplementary Table S2*) were rated by all participants of the consensus process.

Overview of prognosis and current indications for allogeneic stem-cell transplantation in *FLT3*-mutated acute myeloid leukemia

The indication for allo-SCT in *FLT3*-ITD AML depends largely on *FLT3* variables (allelic burden, insertion site and co-occurring mutations), on disease status (including MRD), and on the use of FLT3 inhibitors during induction/consolidation treatment, in addition to other patient-, donor- and graft-related factors. Unfortunately, there are no prospective randomized trials evaluating the best post-remission therapeutic strategy in *FLT3*-mutated AML, taking in consideration all the diverse combinations.

Several recent reports have suggested that allele burden might affect prognosis of *FLT3*-ITD AML treated with standard induction chemotherapy.[17,22,88,89] Indeed, the presence of a high allelic burden of *FLT3*-ITD mutations (≥0.5) confers a poor prognosis.[12,27,90,91] Several studies have demonstrated that allo-SCT significantly improves survival outcomes in this category[69, 92-95] and that the negative impact of high allele burden might be overcome when patients undergo allo-SCT in CR1.[17] Therefore, all patients with *FLT3*-ITD^{high} should be considered for allo-SCT in CR1.[66,69,92-96] These patients still face higher rates of early relapse and poor responses to further therapy and eventually poor long-term survival.[92,97] The worst prognosis is observed in patients who relapse after allo-SCT, who have predicted 1-year OS rates below 20%.[98] However, a subcategory of patients with *FLT3*-ITD^{high}/*NPM1* mutation of the ELN intermediate-risk group treated with FLT3 inhibitors, and who achieve MRD negativity, may be offered the possibility of post-remission consolidation with longitudinal MRD monitoring of *NPM1*.[91] This approach should be undertaken with caution, and preferably within a clinical trial, since recent data suggest the possible extinction of the *NPM1* clone after chemotherapy while the *FLT3*-ITD clone persists.

Additional mutations may, however, influence the prognosis of AML with *FLT3*-ITD. For example, the co-existence of *NPM1* mutation with *FLT3*-ITD is associated with improved outcomes, particularly in patients with a low *FLT3* allelic ratio (<0.5).[8,10,16,20] According to the 2017 ELN recommendations, this subcategory is stratified as favorable risk, advocating against the need for allo-SCT.[91] Nonetheless, the good prognosis of a low allelic ratio is not universally recognized, with data suggesting better outcome for allografted patients regardless of *NPM1* mutation status.[99] A threshold for *FLT3* allelic burden is also controversial and differs according to studies. It was mainly based on the median of the mutant-to-wildtype ratio found in different retrospective studies. For example, in one study evaluating the prognostic factors of newly diagnosed AML, a *FLT3* ratio above 0.78 was associated with worse survival, whereas in another study the threshold was 0.51.[11,17] Therefore, the allelic burden has a continuous effect on survival outcomes and a ratio of 0.5 is a chosen threshold based on maximum clinical prognostic data. With the advent of FLT3 inhibitors in the frontline treatment of *FLT3*-mutated AML, the OS has improved regardless of the allelic burden and the use of allo-SCT. Whether *NPM1*-mutant *FLT3*-ITD^{low} AML warrants post-remission allo-SCT in CR1 or not is still debatable. Although some studies analyzing the effect of allo-SCT in patients with *NPM1*-mutant *FLT3*-ITD^{low} found no improvement in OS or relapse risk, we must take into consideration the retrospective nature of the analysis and the small number of patients with a non-statistically significant improvement in OS and relapse risk.[17,22] Interestingly, patients with newly diagnosed AML with *NPM1*-mutant *FLT3*-ITD^{low} treated with frontline midostaurin and intensive chemotherapy, had a 3-year OS rate of around 75%. In a retrospective subgroup analysis, the benefit of allo-SCT was only seen in the adverse ELN subgroup [hazard ratio (HR)=0.39; *P*=0.003], but not in the favorable (HR=0.78; *P*=0.62) and intermediate risk subgroups (HR=0.81; *P*=0.53).[91] These findings should, however, be interpreted with caution as the RATIFY trial was not powered to demonstrate a difference of benefit of allo-SCT among diverse *FLT3-ITD/NPM1* genotypes. For example, the total number of patients in the favorable ELN subgroup was 85 and these patients were divided into four small groups according to whether they did or did not receive midostaurin and/or allo-SCT in CR1.[91]

The deleterious effect of *FLT3*-ITD was most clinically relevant in patients with concomitant *NPM1* and *DNMT3A* mutations, suggesting that AML patients with *NPM1*, *FLT3*-ITD and *DNMT3A* mutations (triple-positive AML) should be transplanted regardless of the *FLT3*-ITD allelic ratio.[8] A recent study conducted on 147 patients

found that *NPM1*-positive AML with low allelic *FLT3*-ITD still had an unfavorable outcome, with an OS rate of only 41%, but with significant improvements in both relapse-free survival (RFS) and OS for those allografted in CR1.[99] This challenges the notion of withholding transplant for patients with supposedly favorable outcomes. In that sense, a recent study from the MD Anderson Cancer Center showed that allo-SCT improved leukemia-free survival (LFS) and OS independently of the *FLT3*-ITD allelic ratio and *NPM1* mutation status.[100] This fits with recent NCCN guidelines still offering allo-SCT for all patients with *FLT3*-ITD mutations regardless of allelic ratio or NPM1 mutation status.[18]

On the other hand, patients with a low allelic ITD ratio lacking an *NPM1* mutation (and lacking other adverse risk mutations) are currently considered intermediate risk, hence in a gray prognostic area with no proper consensus on optimal treatment strategy. There is conflict regarding the current practice between proceeding to allo-SCT for these patients or limiting allo-SCT only to those who do not achieve MRD negativity by multiparametric flow cytometry. Indeed, technical limitations prevent the use of *FLT3* mutation for assessment of MRD which must therefore rely on multiparametric flow cytometry.[101] Finally, Versluis *et al*. reported that in patients with wildtype *NPM1* AML without *FLT3*-ITD or with a low allelic ratio of *FLT3*-ITD, reduced intensity conditioning allo-SCT resulted in better OS and RFS rates as compared with chemotherapy or autologous SCT.[89]

Overall, limitations to the universal incorporation of *FLT3*-ITD allelic ratio into routine clinical practice and the treatment algorithm include the lack of a clear cut-off (0.5 in the ELN recommendations, 0.7 in the RATIFY study) and the potential variability of the allelic ratio over time. A global effort is needed to standardize the technique for determining the *FLT3*-ITD allelic ratio, making it universal with calibration of all laboratories, reminiscent of the global exercise the world did for *BCR/ABL1*. Similarly, the definition of high and low allelic ratio should also be standardized with a clear consensus on a cut-off level. Until these technical challenges are addressed, the transplant indication remains controversial in patients with *FLT3*-ITD who belong to the ELN favorable risk group (low allelic ratio <0.5 with concomitant *NPM1* mutation) and who achieve MRD negativity. Many European cooperative groups follow the ELN algorithm, deferring allo-SCT in patients with *NPM1*-mutant *FLT3*-ITD^{low}, unless there is molecular persistence of *NPM1*. Thus, performing MRD assessment regularly to decide on allo-SCT timing is crucial when selecting this approach. Conversely, the NCCN guidelines are still advocating allo-SCT in CR1 in this setting.

Finally, data on the prognosis of *FLT3*-TKD AML remain conflicting, with some studies suggesting a negative impact of TKD mutations on LFS and OS,[11,25,30] while others suggesting no prognostic effect, or even a benefit when a *NPM1* mutation is present.[29,32,34,35]

Hematopoietic stem cell transplantation and factors predictive of outcome

As stated above, because of the poor prognosis associated with *FLT3*-ITD mutated AML, allo-SCT was most frequently performed in patients in CR1[66-74,102] including fit patients ≥60 years of age.[103] In most studies, the LFS rate at 2 years ranges between 50 to 60% in that setting,[66,92,97,104] although a wide variation from 20%[70,105] to 70%[69] has been reported. There are knowledge gaps about the factors that can predict outcome after allo-SCT.

A previous EBMT study[97] reported that patients with *FLT3*-ITD mutated AML with concomitant mutated *NPM1* had better post-transplant outcomes compared to those with wildtype *NPM1*. Similarly, other studies reported that the presence of active disease or MRD before allo-SCT results in poor post-transplant outcomes.[106,107]

A recent, large EBMT registry study assessed outcomes in 462 allografted *FLT3*-mutated AML patients with a median follow-up of 39 months for alive patients.[63] Forty percent received allo-SCT from matched related donors, 49% from matched unrelated donors and 11% from haploidentical donors. Two-year cumulative incidence of relapse (CIR) and non-relapse mortality rates were 34% and 15%, respectively, whereas LFS, OS and graft-*versus*-host disease (GvHD)-free. relapse-free survival (GRFS) rates were 51%, 59% and 38%, respectively. On multivariable analysis, the need for more than one induction treatment negatively affected outcome, while prescribing an allo-SCT in CR1 resulted in improved CIR, LFS and OS. Presence of an *NPM1* mutation was also associated with better outcomes, including better CIR, LFS, OS and GRFS. Post-transplant maintenance therapy with sorafenib significantly reduced the CIR and improved LFS, OS and GFRS. Outcomes were not affected by the type of donor or conditioning intensity. An important finding from this study was that *in vivo* T-cell depletion with antithymocyte globulin decreased chronic GvHD and significantly improved LFS, OS and GRFS, without an apparent increase in the risk of relapse. This indicates that, even in the setting of *FLT3*-mutated AML, *in vivo* T-cell depletion does not appear to abrogate the graft-*versus*-leukemia effect. Finally, the use of haplo-identical donors was associated with improved GRFS compared to that achieved with other types of donors. Given the high risk of rapid relapse of patients with *FLT3*-mutated AML in CR1 and the poor outcome of allo-SCT in CR2 or beyond,[11,12,108] these results and those of a recent EBMT study suggest that, in the absence of a matched sibling donor, performing haplo-identical transplants in CR1 may be considered.[109] Furthermore, in another large EBMT study on more than 6,500 adult AML patients allografted in CR1, multivariate analysis confirmed the lack of a statistically significant difference in OS following transplants from matched related donors or 10/10 matched unrelated donors, or haplo-SCT.[110] Finally, the results of a CIBMTR, EUROCORD and EBMT collaborative analysis demonstrated that outcomes after umbilical cord blood transplantation are similar to those after allo-SCT from sibling donors for patients with *FLT3*-ITD AML.[110]

Post-transplant maintenance in *FLT3*-mutated acute myeloid leukemia

Even after allo-SCT, *FLT3*-mutated AML is associated with a higher risk of early relapse (30%-59%) compared to *FLT3*-wildtype AML.[82,92] Indeed, in a CIBMTR analysis of 511 patients (158 with *FLT3* mutations), there was an increase in relapse rates in *FLT3*-mutated AML (38% *vs*. 28%; P=0.04; relative risk 1.60; 95% CI: 1.15-2.22).[74] Satisfactory treatment of patients with *FLT3*-mutated AML who relapse or progress after allo-SCT, is an unmet need. Chemotherapy or FLT3 inhibitors alone or com-

bined with donor lymphocyte infusions are rarely effective in the long term,[45-50] even though a small proportion of patients who relapse after allo-SCT can achieve long-lasting responses with sorafenib.[52,54,55,57] A second allo-SCT can be offered to only a small percentage of patients and is associated with a rather high non-relapse mortality rate.[111] Several studies have, therefore, investigated the use of post-transplant maintenance with FLT3 inhibitors as a strategy aimed to reduce relapse after allo-SCT.[112]

Midostaurin was not offered as maintenance therapy to recipients of allo-SCT in the RATIFY study,[113] but the RADIUS phase II randomized trial compared post-transplant midostaurin maintenance with standard care in 60 adult patients.[114] Estimated relapse rates at 18 months were 24% in the standard care group and 11% in the midostaurin group (P=0.27).[114] In another prospective phase II study, maintenance midostaurin was also offered to *FLT3*-mutated AML patients undergoing allo-SCT in CR1. In a landmark analysis in patients who were event free at day 100 after transplant (n=116), those who started maintenance therapy within 100 days after their transplant (n=72) had a significantly better OS than those who did not.[115] The main cause of early discontinuation of maintenance midostaurin after allo-SCT (23%) was poor tolerability, mainly as a result of gastrointestinal toxicity.[114]

Sorafenib has been studied as maintenance therapy following allo-SCT, demonstrating benefit with regards to survival and improved outcomes in a phase I study, a pilot study, a single-center study, a multicenter study, a registry study and a randomized study.[60-65,116] A phase I trial (NCT01398501) was conducted in which 22 *FLT3*-ITD AML patients received twelve 28-day cycles of sorafenib 45-120 days after allo-SCT.[61] The maximum tolerated dose was established at 400 mg twice daily. The 1-year progression-free survival (PFS) rate was 85% with a corresponding 1-year OS of 95%. In a pilot study, six patients with *FLT3*-ITD AML received sorafenib (n=5 maintenance, n=1 salvage) after allo-SCT with similarly encouraging results.[116] Five of these patients developed cutaneous corticosteroid-sensitive GvHD within a few days after sorafenib initiation, suggesting a possible immunomodulatory effect, and remarkably all patients had sustained molecular remissions.

In a single-institution, observational study on *FLT3*-ITD AML patients transplanted in CR1, 26 patients who received sorafenib as maintenance treatment after allo-SCT were compared to 55 historical controls who did not.[62] The sorafenib cohort had a better 2-year OS rate (81% *vs*. 62%), improved PFS (82% *vs*. 53%), and lower relapse incidence (8% *vs*. 38%).

In a multicenter study, 27 *FLT3*-mutated AML patients (aged 15-57 years) received maintenance therapy with sorafenib as a single agent after allo-SCT.[60] At a median follow-up of 18 months, 25 patients were in complete remission with full donor chimerism, with 1-year PFS and OS rates reaching 92%. Updated results after a median follow-up of 40 months further demonstrated favorable long-term outcomes in patients receiving sorafenib maintenance therapy, with 2-year PFS and OS rates reaching 73% and 80%, respectively, with an acceptable toxicity profile.[65]

A recent large EBMT registry study assessed outcomes in 462 allografted *FLT3*-mutated AML patients over a median follow-up of 39 months for surviving patients.[63] Twenty-eight patients received post-transplant sorafenib maintenance treatment, initiated at a median of 55 days after transplantation (range, 1-173) at a median dose of 800 mg/day (range, 200-800 mg/day). Thirteen patients in the sorafenib group had chronic GvHD at a median time of 76 days after the initiation of sorafenib (range, 9-194 days). Chronic GvHD was limited in seven patients and extensive in six. On multivariate analysis, post-transplant maintenance with sorafenib significantly reduced the relapse incidence (HR=0.39; P=0.05), and improved LFS (HR=0.35; P=0.01), OS (HR=0.36; P=0.03) and GFRS (HR=0.44; P=0.02). Matched-pair analysis was also performed on 52 patients (26 in the sorafenib group and 26 controls) who engrafted and survived after allo-SCT with no relapse or grade II-IV acute GvHD until sorafenib initiation. The 2-year LFS and OS rates were 79% and 83%, respectively, in the sorafenib group (P=0.02) *versus* 54% and 62%, respectively, in the controls (P=0.007).

More recently, preliminary conclusions of a double-blind, prospective trial (SORMAIN) that randomized patients to either maintenance treatment with sorafenib or placebo introduced during the first 60-100 days after allo-SCT provided further support for the use of this drug in this high-risk setting.[64] Eighty transplanted *FLT3*-ITD adult AML patients were randomized 1:1 to receive either sorafenib (up to 400 mg twice daily) or placebo for up to 24 months. After a median follow-up of 42 months, the median RFS was 31 months in the placebo group whereas it was 'not reached' in the sorafenib group (corresponding to a 2-year RFS of 53% *vs.* 85%: HR 0.39; P=0.01). Sorafenib was well-tolerated with toxicities that were generally manageable, mostly by dose reduction. These findings build on previously reported data and confirm that sorafenib maintenance therapy after allo-SCT in *FLT3*-ITD AML patients is both safe and efficient in significantly reducing CIR and improving survival.

In addition to sorafenib's direct anti-leukemic effect, a possible synergism between the drug and alloreactive donor T cells in facilitating long-term disease control has been suggested,[117] and has also been proposed in murine models in which sorafenib apparently exacerbated GvHD.[118] A recent study demonstrated that sorafenib promotes graft-*versus*-leukemia activity in mice and humans through interleukin-15 production in *FLT3*-ITD leukemia cells.[119]

Gilteritinib is also currently being prospectively assessed for maintenance use in *FLT3*-ITD AML after allo-SCT in a phase III, randomized, double-blind, placebo-controlled multicenter trial (NCT02997202).[120] This study aims to enroll 346 adult patients with AML in CR1, randomized 1:1, to receive either gilteritinib 120 mg or placebo for 2 years. In addition, a large phase III randomized study (NCT04027309) by a consortium of several cooperative study groups, including HOVON, AMLSG, SAKK, ALFA, CETLAM, PETHEMA, FILO and ALLG, is anticipated to start enrolling by the end of 2019: patients will be randomized to midostaurin or gilteritinib added to standard induction and consolidation treatment. Patients who achieve complete remission will continue maintenance with either midostaurin or gilteritinib.

Finally, the recent approval of midostaurin for frontline treatment of *FLT3*-mutated AML in the USA and Europe may challenge the role of post-transplant maintenance therapies, including sorafenib. Accordingly, new data should be generated in this setting.[121,122] Most *FLT3*-mutat-

ed AML patients, however, are not currently receiving midostaurin, at least outside the USA and some other countries; therefore, for the foreseeable future, patients may still benefit from sorafenib maintenance treatment after allo-SCT.

Summary of position statement (Table 1)

1- Indications for allogeneic stem-cell transplantation in *FLT3*-internal tandem duplication acute myeloid leukemia

• The indication for allo-SCT is controversial in patients with *FLT3*-ITD who belong to the ELN favorable risk group (low allelic ratio <0.5 with concomitant *NPM1* mutation) and who achieve MRD negativity. Allo-SCT may be delayed until first relapse as recommended by the ELN or performed in CR1 as allowed by NCCN guidelines. Grade level C-II

• In general, all other patients with *FLT3*-ITD AML should be considered for allo-SCT in CR1 if feasible. Grade level B-II

2- Modalities of hematopoietic stem cell transplantation

• Donors should be selected according to EBMT general guidelines[83] including the potential use of cord blood grafts whenever indicated. Grade level B-II

• *In vivo* T-cell depletion decreases the risk of chronic GvHD, without apparently increasing the risk of relapse, in *FLT3*-ITD AML and is therefore an option in this setting. Grade level B-II

• The choice of conditioning has no direct link with *FLT3*-ITD mutation and should be adapted to other individual risk factors such as age, disease status at transplant, and donor type. Grade level B-II

3- Post-transplant maintenance for *FLT3*-internal tandem duplication acute myeloid leukemia

• Post-transplant maintenance therapy with a FLT3 inhibitor for patients who have undergone allo-SCT for *FLT3*-ITD AML is recommended (except for patients with active acute GvHD). In the absence of an appropriate clinical trial, sorafenib could be considered as the preferred option, but other FLT3 inhibitors are attractive and war-

Table 1. Summary of the European Society for Blood and Marrow Transplantation position statement on allogeneic hematopoietic stem-cell transplantation in FLT3-internal tandem duplication acute myeloid leukemia.

Indication for allo-SCT in *FLT3* mutated AML	Transplant indication is controversial in patients with *FLT3*-ITD who belong to the ELN favorable risk group (low allelic ratio <0.5 with concomitant *NPM1* mutation) and who achieve MRD negativity. Allo-SCT may be delayed until first relapse as recommended by the ELN or performed in CR1 as allowed by NCCN guidelines. In general, all other patients with *FLT3*-ITD should be considered for allo-SCT in CR1 if feasible.
Modalities of allo-SCT	Donor selection according to EBMT general guidelines. *In vivo* T-cell depletion decreases the risk of chronic GVHD without an apparent increase in the risk of relapse in *FLT3* mutated AML and is therefore an option in this setting. The choice of conditioning has no direct link with *FLT3* mutation and should be adapted to other individual risk factors such as age, disease status at transplant, and donor type.
Post-transplant maintenance	Post-transplant systemic maintenance therapy with a FLT3 inhibitor for patients who underwent allo-SCT for *FLT3*-ITD AML is recommended (except for patients with active acute GvHD). In the absence of an appropriate clinical trial, sorafenib could be considered as the preferred option, but the role of other FLT3 inhibitors warrants investigation. Maintenance treatment should be initiated as soon as possible after disease evaluation, including MRD assessment, especially in patients with MRD-positive AML before or after allo-SCT, provided there is adequate hematologic reconstitution. The recommended post-transplant maintenance is sorafenib at a dose of 400 mg/day in two divided doses. Patients with MRD-positive disease may receive 800 mg/day in two divided doses, to be adapted according to tolerance. Sorafenib should be transiently discontinued in the case of GvHD requiring systemic treatment with corticosteroids, but may be cautiously resumed once remission of GvHD is documented. Ongoing studies will determine whether midostaurin, gilteritinib or other FLT3 inhibitors will become additional alternatives in this setting. Maintenance therapy duration is not firmly established, but a minimum of 2 years is recommended, depending on tolerance.

Allo-SCT: allogeneic hematopoietic stem cell transplantation; FLT3: FMS-like tyrosine kinase 3; AML: acute myeloid leukemia; FLT3-ITD: FLT3-internal tandem duplication; ELN: European LeukemiaNet; NPM1: Nucleophosmin 1; MRD: minimal residual disease; CR1: first complete remission; NCCN: National Comprehensive Cancer Network; EBMT: European Society for Blood and Marrow Transplantation; GvHD: graft-versus-host disease..

rant further investigation in larger prospective studies. Grade level B-II

• Maintenance therapy should be initiated as soon as possible after disease evaluation, including MRD assessment (whenever feasible), especially in patients with MRD-positive AML before or after allo-SCT, provided there is adequate hematologic reconstitution. Grade level B-II

• Sorafenib should be transiently discontinued in the case of GvHD requiring systemic treatment with corticosteroids, but may be cautiously resumed once remission of GvHD is documented. Grade level B-III

• If choosing sorafenib, the recommended post-transplant maintenance dose is 400 mg/day in two divided doses. Patients with MRD-positive disease may receive 800 mg/day in two divided doses, to be adapted according to tolerance. Grade level B-III

• One potential challenge is the lack of approval of sorafenib for AML and its off-label use may not be reimbursed in many/most countries. Ongoing studies will determine the role and modalities of use of midostaurin, gilteritinib or other FLT3 inhibitors in this setting.

• The duration of maintenance therapy is not firmly established, but a minimum of 2 years is recommended, depending on tolerance. Grade level B-III

• Monitoring is recommended for potential drug-drug interactions and long-term side effects.

Aspects to be resolved

• Standardization of *FLT3*-ITD allelic ratio in terms of technique and cut-off level

• Indication for allo-SCT in patients with *FLT3*-ITD AML who belong to the ELN intermediate risk group (high allelic ratio ≥0.5 with concomitant *NPM1* mutation) and who achieve MRD negativity.

• Time of withdrawal of immunosuppression

• Pre-emptive *versus* prophylactic donor lymphocyte infusion

• Post-transplant maintenance with FLT3 inhibitors outside *FLT3*-ITD AML (immunomodulatory and off-target effects)

• Impact of post-transplant maintenance therapy on immune reconstitution and environment

• Combination of post-transplant FLT3 inhibitors with other drugs such as hypomethylating agents

• Monitoring of patients receiving post-transplant FLT3 inhibitors for potential extramedullary relapse or aggressive clone selection.

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