Allogeneic stem cell transplantation for *FLT3* mutated acute myeloid leukemia in first complete remission: does age really matter?

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Since its first discovery[1] and initial report on the prognostic impact in patients with FMS-related tyrosine kinase 3 (*FLT3*)-mutated acute myeloid leukemia (AML),[2] a large amount of data has been accumulated which have helped devise the best therapeutic approach for patients with this disease. Constitutive activation of *FLT3* by internal tandem duplications (ITD) occurs in approximately 20-30% of patients with cytogenetically normal (diploid) AML (CN-AML), the most frequent molecular aberration in patients with AML, while the less common mutations (7%) are those found in the tyrosine kinase domain (*FLT3*-TKD).[3,4] The presence of *FLT3*-ITD mutations is widely accepted as a poor prognostic factor in CN-AML owing to its chemoresistance, high risk of relapse and short relapse-free survival (RFS), whereas the prognostic impact of *FLT3*-TKD mutation remains unclear.[3,5-7]

Although evidence from a large meta-analysis indicated that patients with either cytogenetic high- or intermediate-risk AML benefit from allogeneic hematopoietic stem cell transplantation (AHCT),[8] until recently, the role of AHCT in patients with *FLT3*-ITD-mutated AML remained a matter of debate, as post-transplant outcomes were inconsistent between studies.

In a study by Gale *et al.*, the outcomes of adult AML patients treated according to the United Kingdom Medical Research Council (UK MRC) protocols were analyzed. Results from the donor-*versus*–no donor analysis of patients with *FLT3*-ITD-mutated AML showed a significantly lower relapse rate in patients with a donor, but overall survival (OS) was not significantly improved when compared with the no donor group. The authors concluded that the presence of an *FLT3*-ITD mutation should not influence the decision to proceed to transplantation. However, in total only a small number of patients received an allograft, and only 37 of the 68 *FLT3*-ITD-positive patients (54%) with donors actually received an allograft in first complete remission (CR1) in this study. Moreover, this analysis may be subject to selection bias as there was no direct comparison between *FLT3*-ITD patients receiving allografts and those receiving chemotherapy alone.[9]

On the contrary, several more recent studies indicate that AHCT is likely the best consolidation therapy for patients with *FLT3*-ITD-mutated AML, and should be performed as soon as possible in CR1.[10-13] In a study by DeZern and colleagues, there was significantly better RFS of *FLT3*-ITD-mutated AML patients treated with AHCT as compared to the non-transplant group (54 months *vs*. 8.6 months),[12] while a study from the MD Anderson Cancer Center, which compared post-remission treatment with consolidation chemotherapy and AHCT in 227 *FLT3*-mutated AML patients who achieved CR1 after induction chemotherapy, showed that AHCT reduced the risk of relapse and improved both RFS and OS regardless of *NPM1* status and *FLT3* allelic ratio.[10]

Moreover, our group analyzed the outcomes of 200 *FLT3*-mutated AML patients (either ITD or TKD mutations) treated with AHCT with various donor types, including haploidentical donor transplants.[11] This study showed a dramatic increase in the relapse rate and progressively worse progression-free survival (PFS) for patients transplanted beyond CR1, suggesting, again, that patients benefit the most from receiving ASCT in first remission, and that the lack of a human leukocyte antigen (HLA)-matched donor should not be a limitation to transplantation, as haploidentical transplants had similar survival with HLA-matched donor transplants.[11]

Albeit several advances have been made to improve outcome after AHCT, mortality related to the procedure is still a major concern. The initial hope was that the development of *FLT3* inhibitors would have provided a dramatic effect on *FLT3*-mutated AML, and perhaps delay or reduce the need for transplantation, similar to the effect of tyrosine kinase inhibitors in patients with chronic myeloid leukemia; however, this was not realized. Thus far, several *FLT3* inhibitors have been studied in *FLT3*-mutated AML as part of induction, consolidation as well as post-transplant maintenance therapy.[14,15] Most recently, the results of a randomized, placebo-controlled trial of induction and consolidation chemotherapy with or without midostaurin for newly diagnosed *FLT3*-mutated AML patients (the RATIFY study) indicated a survival benefit for patients receiving midostaurin, and resulted in the FDA approval of this drug, in combination with chemotherapy, for induction and consolidation treatment of those with newly diagnosed *FLT3*-mutated AML. Although AHCT was not mandated in this protocol, more than half of patients received AHCT at some point during the disease course. Even though patients were not randomized to receive AHCT, results from the analysis, starting from time at transplant, showed a remarkable difference in the survival of midostaurin-treated patients who underwent AHCT in CR1 compared to those on the placebo arm, suggesting not only that midostaurin associated with induction chemotherapy might help provide deeper responses but may also improve transplant outcomes, especially for those who received transplantation in first remission.[15] Nevertheless, as of yet there is no evidence to demonstrate that midostaurin, or any other *FLT3* inhibitors, can provide survival benefit over AHCT in *FLT3*-ITD-mutated AML.

Taken together, the available evidence suggests that AHCT ameliorates the prognostic impact of *FLT3*-ITD mutations, and is the preferred consolidation treatment for younger AML patients with *FLT3*-ITD mutations after achieving CR1.

Transplantation for older patients is being increasingly performed worldwide. Data from the Center for International

Blood and Marrow Transplant Research (CIBMTR) showed an increased number of transplants for older patients,[16] including alternative donor transplants,[17] with outcomes similar to those of HLA-matched donors.[18] Multiple studies have demonstrated that AHCT can provide long-term survival benefit in elderly AML patients with high risk for disease relapse, and advanced age *per se* should not be used as a contraindication for AHCT. Questions remain, however, as to whether older patients with *FLT3*-ITD-mutated AML would benefit from AHCT in CR1, considering the fact that AML is a disease that is most often encountered in the older population and the majority of reports on AHCT outcomes of *FLT3*-ITD-mutated AML were performed in patients younger than 60 years.

In this issue of *Haematologica*, Poiré and colleagues examined the role of AHCT in a large cohort of *FLT3*-ITD-mutated AML patients, aged 60 or over, reported on behalf of the Acute Leukemia Working Party (ALWP) of the European Group for Blood and Marrow Transplantation (EBMT).[19]

In addition to a very promising long-term survival post-transplant result of 56% at two years for patients in CR1, this study has brought up some compelling findings regarding *FLT3*-ITD-mutated AML in the elderly that are worth highlighting. First, increasing age as well as conditioning regimen intensity did not seem to influence non-relapse mortality (NRM). In this cohort, the majority of patients received a reduced-intensity conditioning regimen (82%), with an acceptable NRM at 2 years of only 20% for all patients (18% for patients in CR1), which is particularly low for a registry-based study. This implies that AHCT is feasible for older patients with *FLT3*-ITD-mutated AML, and adds to a growing body of evidence that AHCT should not be denied because of advanced age alone. Not surprisingly, disease status at transplant was strongly associated with a higher risk of relapse and worse survival, similar to the findings in younger patients,[11] while the best outcomes were seen in patients in molecular remission before transplant and those transplanted within 42 days of diagnosis.[19] In this cohort, approximately two-thirds of patients relapsed within two years when transplanted beyond first remission. These results confirm the importance of early AHCT, which should be performed without delay once morphologic remission is achieved.

Nevertheless, the benefit of AHCT for those beyond first remission or with relapse/refractory diseases was less pronounced due to a very high relapse rate. The incorporation of *FLT3* inhibitors before and/or after transplant might help improve the outcomes of these patients. Unfortunately, the RATIFY study on the efficacy of midostaurin only included patients younger than 60 years,[15] whereas the use of sorafenib in combination with induction chemotherapy for an elderly group of patients seemed to be associated with a lower remission rate and unacceptable toxicity.[20] We hope that newer *FLT3* inhibitors will improve the safety profile and further enhance outcomes in these patients.

In spite of these encouraging outcomes, several issues have not been addressed in the current study: the effect of *FLT3* allelic ratio on transplant outcomes of elderly patients with *FLT3*-ITD-mutated AML, since evidence indicates that it can influence post-transplant outcomes in younger patients,[13] outcomes of patients with *FLT3*-TKD mutations, which were not included in this study, and the use of haploidentical donor transplants, as more patients are transplanted with a haploidentical donor when a HLA-matched donor is not available.

In conclusion, although there are no prospective randomized studies to specifically compare the role of allogeneic transplantation with conventional chemotherapy for *FLT3*-ITD AML patients in CR1, sufficient evidence from several retrospective analyses clearly suggests that allogeneic stem cell transplantation can provide survival benefit in all age groups, which now includes older patients, and should be considered as a preferred consolidation strategy at least for patients with *FLT3*-ITD-mutated AML in CR1. Future studies are needed to clarify the impact of hematopoietic cell transplantation comorbidity index (HCT-CI) on the survival of these patients, the role of *FLT3* inhibitors with initial therapy as well as in post-transplant maintenance therapy in the older age group as well as the use of other therapeutic approaches like natural killer (NK) cell therapy, to further improve the outcomes of these patients, especially those with more advanced disease.

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Large granular lymphocyte cells and immune dysregulation diseases – the chicken or the egg?

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In less than 1% of patients suffering from rheumatoid arthritis (RA), a condition known as Felty syndrome (FS) can develop.[1,2] FS, first described by the American physician Augustus Roi Felty in 1924, is characterized by the triad of RA, (unexplained) neutropenia, and splenomegaly, and is more common in people aged 50 years and over. In spite of the clear association with RA, the common underlying cause of all three characteristic symptoms remains largely elusive. It is known that FS shows an overlap with a rare type of T-cell leukemia, called T-cell large granular lymphocyte (T-LGL) leukemia, which also typically presents in elderly individuals with a median age of 60 years. In fact, T-LGL leukemia patients can show all the features that FS patients have, albeit at varying frequencies, thus making the differential diagnosis between LGL leukemia and FS problematic at times.[3] An additional complication to that of the overlapping clinical features is the fact that both conditions share the presence of LGL cells.

Based on the overlapping features, Savola and colleagues explored a potential common pathogenic mechanism between FS and LGL leukemia. In this issue of *Haematologica* they report on a cohort of 14 FS patients, which were evaluated by next-generation sequencing (NGS) technology for the occurrence of somatic mutations in the *STAT3* and *STAT5B* genes.[4] Both of these genes have been notably implicated in a subset of the $CD8^+$ $TCR\alpha\beta^+$ T-cell type of LGL leukemia, and the occurrence of *STAT3* mutations in LGL leukemia is strongly associated with RA and neutropenia.[5-7] Indeed, in >40% of FS cases somatic *STAT3* hotspot mutations were found, which is at a rate comparable to LGL leukemia cases. The fact that the *STAT3* variant allele frequencies were lower in FS can be explained by the smaller T-cell clone sizes in FS patients. Nevertheless, LGL cell proportions were increased in FS patients, and in two cases the LGL cell numbers additionally fulfilled the criteria for LGL lymphocytosis. Taken together, these observations firmly support the idea that FS and LGL leukemia are part of a disease spectrum with a common pathogenesis, in

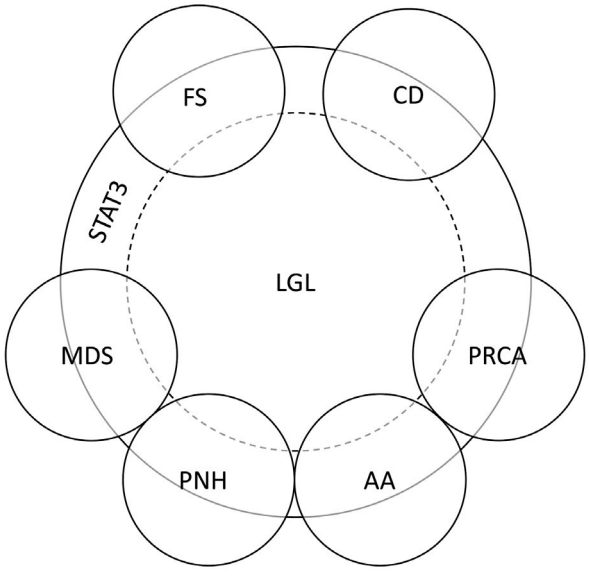

Figure 1. Overlap between LGL leukemia / proliferation and immune dysregulation diseases and conditions that show an increase of LGL cells and/or the presence of *STAT3* mutated cells. AA: aplastic anemia; CD: celiac disease; FS: Felty syndrome; MDS: myelodysplastic syndrome; PNH: paroxysmal nocturnal hemoglobinuria; PRCA: pure red cell aplasia; LGL: large granular lymphocyte.