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# EDITORIAL

## Allogeneic hematopoietic stem-cell transplantation in patients with acute myeloid leukemia in first complete remission: new answers for an old question

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Allogeneic hematopoietic stem-cell transplantation (allo-SCT) has an established role in the treatment of patients with acute myeloid leukemia (AML). Although the majority of adult patients diagnosed with AML will enter a complete remission (CR) with standard induction chemotherapy, most will suffer disease relapse despite the use of consolidation chemotherapy, and less than 40% will be cured.[1] The curative potential of allo-SCT is mediated by the administration of high-dose chemoradiotherapy and by induction of graft-versus-leukemia effect (GVL) by donor immune-competent cells. However, SCT may be associated with significant rates of therapy-related morbidity and mortality (TRM) due to regimen-related toxicities, graft-versus-host disease (GVHD) and the immune deficiency status after SCT.

The role of allo-SCT in AML in first CR has been debated for more than two decades with no definite conclusions. Numerous studies addressed this issue by using genetic randomization, selecting patients with an HLA-matched sibling donor to allo-SCT, while those with no donor received autologous SCT or consolidation chemotherapy. Results were most often analyzed by an 'intent-to-treat' analysis to avoid biases such as the selection of healthier patients to allo-SCT, as well as those who did not suffer early relapse, thus making the results of allo-SCT more optimistic. However, this approach results in relatively high dropout rates with significant percentage of patients not receiving their assigned treatment, making it difficult to detect differences among the various therapeutic approaches. As a role, patients having standard myeloablative allo-SCT at first CR can expect leukemia-free survival (LFS) of 50–65%, relapse rates of 20% and TRM rates of less than 20%. Results are significantly inferior in those transplanted at a more advanced stage with higher rates of both TRM and relapse translating into inferior survival.

The landmark large-scale study reported by Zittoun *et al*[2] showed 4-year LFS estimates of 55, 48 and 30%, in recipients of allo-SCT, autologous SCT and intensive chemotherapy, respectively. The large EORTC-GIMEMA AML-10 study[3] reported that patients entering first CR who had a matched sibling donor had a better 4-year LFS than patients with no donor (52.2 *vs* 42.2%, $P=0.04$); however, overall survival (OS) rates were similar. The difference was more pronounced in younger patients (age 15–35 years) and those with poor-risk cytogenetics. Similarly, the large UK MRC 10 study[4] reported improvement in relapse rate and LFS, but not in OS in patients with a donor. In this study, significant benefit was limited to young patients and those with standard risk cytogenetics (55% in the donor group *vs* 44% in the no donor group, $P=0.02$). The US intergroup study[5] failed to detect any advantage of SCT over chemotherapy; however, when the data were reanalyzed based on cytogenetic stratification,[6] patients with poor-risk cytogenetics did benefit from allo-SCT in first CR (LFS 44 *vs* 11%). A few conclusions can be drawn from these series of studies comparing allo-SCT, autologous SCT and intensive chemotherapy in first CR. In all studies, relapse rates were lowest with allo-SCT reflecting the major role of GVL in curing AML. TRM rates were uniformly higher with allo-SCT. This translated to superior LFS with allo-SCT in some studies and equivalent LFS in others, but not inferior in any study. OS was most often not significantly different, in part reflecting the ability to salvage some patients not allocated to allo-SCT by SCT after relapse. Stratification by cytogenetics emerged as the most valuable tool in planning consolidation therapy and the timing of SCT. It is a common practice that patients with favorable cytogenetics do not require allo-SCT at first CR. Patients with unfavorable cytogenetics have an extremely poor outcome with standard chemotherapy, which can be overcome by allo-SCT, at least in some studies,[3,6] and they may be candidates for early SCT. The approach to patients with standard risk cytogenetics remains controversial as the reduction of relapse rate with standard myeloablative allo-SCT is offset by an increase in TRM.

It is conceivable that if TRM rates were reduced while relapse rates remain unchanged, then the benefit of allo-SCT over standard therapy will increase. Much progress has already been achieved in making myeloablative SCT safer, by the use of more tolerable regimens[7,8] and by improving supportive care. However, the most significant progress in this direction is the development of nonmyeloablative and reduced-intensity conditioning (RIC). The use of RIC has been rapidly expanding over the last decade and vast experience was gained in the related and unrelated setting.[9,10] Initial studies showed the feasibility of this approach.[11–13] RIC regimens were designed to be sufficiently immune suppressive to allow donor cell engraftment, yet to be less toxic and more tolerable than standard myeloablative regimens. Engraftment serves as a platform for adoptive cellular immunotherapy and induction of GVL as the primary goal of therapy. RIC regimens allowed extension of allo-SCT to elderly and medically infirm patients who were not candidates for allo-SCT before. These initial studies included patients with different diseases and different status at SCT and disease outcome was therefore difficult for interpretation. A few studies enrolling only patients with AML followed, showing evidence for potent GVL in this disease.[14–16] These outcomes are still based on small and selected samples. So far no randomized studies were conducted to establish the role of RIC compared with standard chemotherapy and with myeloablative conditioning.

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In this issue of *Leukemia*, Mohty *et al* report their experience with RIC in patients with high-risk AML in first CR, ineligible for standard myeloablative conditioning.[17] In all, 35 patients with a donor were 'genetically randomized' to receive allogeneic RIC SCT, of whom 25 patients actually received the transplant. A total of 60 patients were 'randomized' to no SCT. The 4-year LFS was significantly better in the donor group compared to the no donor group in an 'intention-to-treat' analysis (54 *vs* 30%, $P=0.01$). TRM rates were relatively low at 12% and there was also advantage in OS. The 2-year LFS of transplanted patients was 75%. Similarly, in a group of 22 patients with AML/MDS in first or second remission transplanted with RIC at our center, the 2-year LFS was 75% (95%, CI 52–97%), no patient died of TRM; however, five relapsed (Shimoni *et al*. *Blood* 2004; **104**: 635; abstract).

The study by Mohty *et al* adds significant data to the field of RIC, by showing for the first time in a 'randomized' design that RIC can improve the outcome of high-risk AML, in patients not eligible for ablative conditioning, over that achieved with standard chemotherapy. It supports the primary indication for which RIC was initially designed, to substitute for myeloablative conditioning in those considered not good candidates for standard SCT, but in need for allo-SCT to control high-risk leukemia.

Furthermore, this trial gives some important directions for further studies. The study, despite its limited size, shows relatively low relapse rates in patients with high-risk AML that seems similar to what one may expect after myeloablative conditioning. Considering the lower TRM rates, this may imply that RIC may also be of benefit in patients who are eligible for myeloablative conditioning. In our study (Shimoni *et al*, as above), patients in remission having RIC because they were not eligible for standard allo-SCT had a trend for better outcome than eligible patients having myeloablative therapy, despite being older and with comorbidities. Obviously, this important question can only be answered in prospective trials comparing myeloablative and RIC SCT. Furthermore, one can expect relapse and TRM rates to be even lower in standard risk AML. Therefore, although, as discussed above, it is not established whether standard allo-SCT in first CR improves overall outcome in standard-risk AML due to increased TRM, RIC allo-SCT with its lower TRM may. This important question may also be resolved by trials comparing RIC and chemotherapy in standard risk patients both eligible and not eligible for myeloablation.

In most similar studies, OS was not improved reflecting in part the ability to salvage patients with SCT after relapse. Mohty *et al* did show improvement of OS in this group of patients. This may reflect the fact that patients not eligible for myeloablative therapy are less likely to be candidates for SCT after relapse. RIC has a very limited role in active leukemia (Shimoni *et al*, as above; 14). Patients in relapse may not respond to salvage chemotherapy or may acquire additional comorbidities during therapy precluding any allo-SCT after relapse. Therefore, first CR may be viewed as a window of opportunities for curative therapy in these patients. This may be of utmost value in older patients. AML has a worse outcome in the elderly and they are less likely to tolerate multiple consolidation chemotherapy courses. Early RIC allo-SCT is therefore more appealing in this group. After a decade of experience in RIC, it is time to move ahead and plan large-scale comparative trials to define its role in various settings. This issue paper by Mohty *et al* is a first step in this direction.

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