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COMMENTARY

Prophylactic donor lymphocyte infusion in patients with high-risk acute myeloid leukemia: ready for prime time?

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Allogeneic hematopoietic cell transplantation (allo-HCT) is the treatment of choice for younger patients with intermediate or high-risk AML in first CR, as well as for younger patients with AML beyond first CR.[1] AML cure following allo-HCT depends in a large part on graft-versus-AML effects mediated by donor immune cells contained in the graft. Although graft-versus-AML effects have been associated with occurrence of GvHD,[2,3] the observation of lower risks of relapse in allo-HCT patients not experiencing GvHD in comparison with patients transplanted with grafts from identical twins, demonstrated that graft-versus-AML effects can occur without clinical GvHD.[2]

In an attempt to extend the use of allo-HCT to older patients and those with medical comorbid conditions, several groups of investigators have carried out allo-HCT after reduced intensity (RIC) or truly nonmyeloablative conditioning regimens.[4,5] These regimens rely on graft-versus-AML effects rather than on chemo/radiotherapy for tumor eradication.[3,6] Remarkably, a recent study by the HOVON/SAKK group demonstrated that RIC/nonmyeloablative allo-HCT improved overall survival (OS) in older (60 years of age or older) patients with intermediate or high-risk AML in comparison with those not transplanted.[7] Nevertheless, disease relapse remained the first cause of death even in RIC/nonmyeloablative allo-HCT recipients.[7]

The outcome of AML patients who relapse after allo-HCT remains poor.[8] Donor lymphocyte infusion (DLI) can result in prolonged CR but only in a minority of patients with low-disease burden.[9] Similarly, an association of DLI and azacitidine induces only a few persistent CR,[10] whereas a second allo-HCT (in a group of highly selected patients) results in a 2-year OS rate of ~20%.[11,12]

Given the poor prognosis of patients who experience relapse after allo-HCT, several groups of investigators have assessed various post-transplant approaches aimed at preventing disease relapse in high-risk AML patients (Table 1). These approaches include decreasing the level of post-grafting immunosuppression,[13] preemptive (i.e., administered in patients with post-transplant evidence of minimal residual disease or low / decreasing donor chimerism levels) or prophylactic administration of disease-specific medications such as demethylating agents[14] or FLT3 inhibitors,[15] or preemptive[16,17] or prophylactic DLI.[18,19]

In this issue of *Bone Marrow Transplantation*, Jedlickova *et al.*[20] report the results of a retrospective analysis assessing the safety and efficacy of prophylactic DLI in a cohort of 46 high-risk AML patients given grafts following a sequential treatment consisting of chemotherapy (FLAMSA) followed by RIC allo-HCT. Post-grafting immunosuppression included cyclosporine tapered from day +60 to +90 and mycophenolate mofetil discontinued by day +45. Criteria for prophylactic DLI included remaining in CR for at least 120 days after transplantation, being off immunosuppression for at least 30 days, absence of GvHD and no antecedent of grade III–IV acute GvHD. The initial dose of DLI was relatively low: 1×10^6 T cells/kg recipient in sibling (MSD) transplant recipients and 0.5×10^6 T cells/kg in unrelated graft (UD) recipients. In the absence of GvHD, DLI were repeated up to three times using escalating T-cell doses (five- to 10-fold increase/DLI) at 4–6 weeks intervals. Specifically, 7 patients were given one, 15 patients two

Table 1. Post-transplant approaches aimed at preventing relapse in high-risk AML patients

Approach	*Mechanisms of action*	*Potential limitations*
Low exposure to CNI the first weeks after transplantation[13]	- Increases GV-AML effects	- Increases risk of GvHD?
Early post-grafting immunosuppression discontinuation[22]	- Increases GV-AML effects	- Increases risk of GvHD?
Demethylating agents[14,23]	- Direct antileukemic activity - Induce expression of tumor antigens by AML blasts	- Hematological toxicity - Induction of regulatory T cells that might affect GVT effects.
FLT3 inhibitors[15]	- Direct antileukemic activity	- Hematological toxicity - Only efficient in FLT3-mutated AML?
Preemptive DLI[16,17]	- Increases GV-AML effects	- Increases risk of GvHD - Request frequent assessment of MRD or of lineage-specific chimerism
Prophylactic DLI[18]	- Increases GV-AML effects	- Increases risk of GvHD

Abbreviations: CNI=calcineurin inhibitor; DLI = donor lymphocyte infusion; GV-AML=graft-versus-AML effects.

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and 24 patients three DLI. The rationale for giving DLI in escalating doses was based on prior observations by Dazzi *et al.*[21] who demonstrated that, in comparison with single-dose DLI, escalating-dose DLI were as efficient but significantly less often complicated by GvHD. The median time from transplantation to first DLI was 160 days. Transplantation outcomes of patients given prophylactic DLI were compared with those of a group of 34 control patients fulfilling the criteria for high-risk AML and prophylactic DLI but who were transplanted during the same time period in centers not administering prophylactic DLI. Seventy percent of DLI patients and 60% of control patients were either refractory or in untreated relapse.

Following DLI, only 4 patients (9%) developed grade II–IV acute GvHD and 5 (11%) extensive chronic GvHD. Seven-year OS was 67% in DLI versus 31% in control patients, respectively, ($P < 0.001$). In a pseudo landmark analysis, starting the day of first DLI in DLI patients and on day +160 in control patients, 6-year leukemia-free survival was 68% in DLI patients versus 38% in control patients ($P = 0.01$). This was owing to a lower risk of relapse in DLI patients (22 versus 53%, $P = 0.004$).

There are some limitations in the study by Jedlickova *et al.*[20] including the diversity of disease status at transplantation, the retrospective design of the study and some differences between DLI and control patients (including the type of conditioning regimen and GvHD prophylaxis). However, the study is informative for several aspects. First, the study shows that prophylactic DLI given in escalating doses starting after day 120 following transplantation are well tolerated with $< 15\%$ of patients developing grade II–IV or extensive chronic GvHD. This might be due to the fact that DLIs were given in escalating doses[21] and were started relatively late after transplantation (and thus at least 30 days after cyclosporine discontinuation). Second, the relapse incidence was significantly lower in DLI than in control patients suggesting that prophylactic DLI prevented relapse. Third, the lower risk of relapse in DLI patients translated into improved leukemia-free survival.

Another prospective study of prophylactic DLI in patients with high-risk acute leukemia has been reported by Liga *et al.*[19] 2 years ago. In that study, patients were given allo-HCT following a low-dose (10–20 mg total dose) alemtuzumab-containing conditioning regimen. The starting dose of DLI was 0.75×10^6 cells/kg (escalated up to 1.5×10^6 $CD3^+$ cells/kg) in MSD recipients and 0.5×10^6 cells/kg (escalated up to 1×10^6 $CD3^+$ cells/kg) in UD recipients. DLI were scheduled to start 2–4 weeks after cyclosporine discontinuation. Main criteria for DLI included no evidence of disease relapse, no history of $>$ grade 1 acute GvHD, no active GvHD at the time of planned DLI and off immunotherapy. Fifteen patients (out of 56 consecutive patients registered) received prophylactic DLI a median of 162 days after allo-HCT. As observed in the Jedlickova *et al.*[20] study, the relapse incidence was very low after prophylactic DLI (none of the 15 patients). However, in contrast to what was observed by Jedlickova *et al.*,[20] 4 of 15 patients died of steroid-refractory GvHD. Reasons for this apparent discrepancy are unclear. One possible explanation might be that the low doses of alemtuzumab given in the Liga *et al.*[19] study impaired the recovery of regulatory T cells. Another possible explanation might be that DLI were given as soon as 2 weeks after cyclosporine discontinuation in the Liga *et al.*[19] study, versus at least 30 days, in the study by Jedlickova *et al.*[20]

Although the data reported by Jedlickova *et al.*[20] are impressive, prospective randomized studies are needed to confirm the benefit of prophylactic DLIs in patients transplanted for high-risk AML, and also to compare strategies of prophylactic versus preemptive DLI.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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