EDITORIAL

Relapse post hematopoietic SCT remains the Achilles heel for the field

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Allogeneic hematopoietic SCT (HSCT) is a well-established treatment modality for patients with high-risk or relapsed hematologic malignancies. The main obstacles to successful HSCT in hematologic malignancies were outlined by E Donall Thomas in 1975 as the lack of suitable available donors, TRM and relapse post transplant.^{1,2} Since then there has been significant progress in addressing donor availability with the establishment of unrelated donor registries, the use of cord blood as a stem cell source and using haploidentical donors.³ Over the past two decades there has been substantial reduction in TRM secondary to improved supportive care and the introduction of reduced-intensity and non-myeloablative conditioning regimens for older patients and those with comorbidities.⁴ Despite all these advances there has been very limited progress in decreasing the incidence of relapse for patients with hematologic malignancies post HSCT. According to data from the Center for International Blood and Marrow Transplant Registry (CIBMTR), relapse is the leading cause of death for recipients of both related and unrelated donor transplant. Relapse contributes to 41% of the deaths in those receiving HLA-identical HSCT and 34% in those receiving unrelated donor HSCT.⁵

Recent studies have identified a group at high risk of relapse by evaluating the impact of minimal residual disease on the outcome post transplant in both ALL and AML.^{6,7} The risk of relapse is 2–3 fold higher in patients who are MRD positive pre-transplant, but patients who are MRD negative prior to HSCT have a relapse rate of 20–30%. Although one in three patients will likely relapse following HSCT, physicians are left with no clear data to guide their management of those patients. Our ability to define a signature of graft-vs-tumor effect or the lack thereof has remained elusive. Thus, preemptive therapy post HSCT has remained limited to those suspected of having a high risk of relapse based on pre-transplant characteristics of the disease using interventions primarily designed for the non-transplant patient. The interaction of these agents (viz. demethylating agents, tyrosine-kinase inhibitors, FLT-3 inhibitors) with the post-HSCT immune system, and potential drug interactions with immunosuppressive agents remain largely undefined.

Several studies have evaluated the outcome of patients with hematologic malignancies who relapse following allogeneic HSCT.^{8–13} In a study by the Seattle group the authors reported on the outcome of 307 adult patients who relapsed following HSCT. The 2-year survival was 3–19% depending on the time from transplant to relapse, with those experiencing relapse > 200 days having the best outcome.¹² In this study interventions did not include a second transplant. In a report by the European Society for Blood and Marrow Transplantation (EBMT) on the outcome of 465 adult patients with ALL, those who experienced post-HSCT relapse had a 5-year OS of 1%.¹³ Kurosawa *et al.*¹¹ reported on 93 adult patients with hematologic malignancies who relapsed following allogeneic HSCT. Sixty-three patients underwent re-induction therapy and 27 (43%) achieved a complete remission. Although the 1-year survival of those receiving a second transplant was better than that of those who did not (51% vs 14%), the 2-year survival was not different. Similar results were

observed in patients who experienced relapse following reduced intensity conditioning.^{9,10}

In a recent study by our group we evaluated the outcome of 160 children with hematologic malignancies who relapsed following allogeneic HSCT. Forty-three (27%) patients did not receive any salvage therapy and all of them died at a median of 1 month. One hundred and seventeen patients received salvage therapy and, interestingly, among the 78 patients with available detailed re-induction therapy 25 different regimens were used.⁸ The number of regimens used in those patients underscores the lack of uniform therapy for children who relapse following allogeneic HSCT. Unlike what has been observed in adult patients, pediatric patients who received a second HSCT had a significantly improved survival compared to those who were treated with salvage therapy without HSCT (35% vs 2%).⁸ It is also clear from our data that there is no consistent approach regarding the preparative regimen, intensity or timing of the second HSCT. A report from the CIBMTR on the outcome following second allogeneic HSCT in patients with acute and chronic leukemia found that patients younger than 20 years and those who relapse > 6 months from the first HSCT have improved survival.¹⁴

In the current issue of the journal, Bejanyan *et al.*¹⁵ report on the clinical outcome of 104 patients with AML who experienced relapse after matched related and umbilical cord blood transplant. Thirty-seven (34%) patients received supportive care and withdrawal of immune suppression and only one patient survived with no evidence of disease. Fifty-two (50%) of the patients received intensive chemotherapy, with and without donor lymphocyte infusion or second HSCT. Although the remission rate was higher among those receiving DLI or second HSCT compared to those receiving chemotherapy alone, the 1-year survival was not different among those groups. Eighty-eight (85%) patients died secondary to relapsed disease. This study, in addition to the prior published studies, underscores the lack of a unified and systematic approach to treating patients who experience relapse post transplant. Patients continue to receive variable chemotherapy approaches and some patients receive DLI while others receive second HSCT. The main challenges for treating post-transplant relapse are represented by the following questions:

1. What is the optimal chemotherapy induction regimen for patients who relapse post transplant? Unfortunately there are several restrictions on enrolling patients who experience relapse post HSCT on cooperative group- or industry-sponsored relapsed studies. The eligibility criteria of many of those studies exclude patients who are early post transplant, those who are on immune suppression or patients with GVHD. When patients are enrolled and reported in such trials they are usually not analyzed separately regarding toxicity and outcome. There is a definite need for a prospective registry, or, more importantly, clinical trials dedicated to this patient population to study the toxicity and effectiveness of re-induction chemotherapy. The molecular heterogeneity of AML needs to be studied in this patient population to better identify the role of genotypic targeted therapy. Patients achieving CR generally have full donor engraftment and some patients develop GVHD upon recovery post induction. Hence patients treated with re-induction chemotherapy should be

monitored for GVHD that occasionally can be attributed mistakenly to re-induction toxicity.

2. What is the role of DLI and 2nd HSCT? There are no randomized or large prospective trials addressing the role of DLI either as primary therapy or as post-induction consolidation therapy. In the study in this issue patients receiving DLI seemed to have improved CR but not OS. When using DLI it is not clear what is the right timing or dosing or schedule of DLI. It is also not clear if DLI has a role as a prophylactic treatment post re-induction therapy, and the risk of developing severe GVHD in this setting is not known. With increased use of cord blood as a stem cell source the use of DLI is not an option. Although third-party viral-specific T-cell therapies have been successfully used to treat post-transplant viral infection, well-matched third-party DLI has not been used to treat post-transplant relapse.¹⁶ Some studies have shown that a second transplant can provide improved remission and OS, but all those studies were retrospective and treating physician bias cannot be ruled out as a contributing factor.^{8,9,11,17}
3. What is the role of targeted immune therapy? Recent studies have investigated the role of chimeric antigen receptor-modified T cells in relapsed and refractory ALL, with preliminary results showing impressive results in patients who have relapse post allogeneic HSCT without increasing the risk of GVHD.^{18,19} Multicenter trials are planned to evaluate this therapy in relapsed patients, including those with post-transplant relapse. Although this therapy is currently limited to patients with ALL, effort is ongoing to widen its indications to other hematologic malignancies.

The National Cancer Institute has sponsored 2 international workshops on the biology, prevention and treatment of relapse following allogeneic HSCT. The committee acknowledged that there are several confounding factors and a lack of clinical studies.^{20,21} Although the most of the focus was on preventing relapse, the committee reported on potential advances in using novel cellular therapies to address relapse. The committee acknowledged the need for prospective well-designed international studies to address the best way to manage post-transplant relapse.

In conclusion, relapse continues to be a major obstacle in the success of allogeneic HSCT for hematologic malignancies. The study in this issue of the journal adds to the published data that there is an urgent need to address the issue of managing relapse post HSCT.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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