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COMMENTARY

Hodgkin lymphoma, allogeneic transplant and the graft-versus-tumor effect: size does matter

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By limiting the effects of cumulative toxicity, reduced intensity conditioning (RIC) has allowed the delivery of allogeneic transplant (alloSCT) and, by inference, the graft-versus-tumor (GVT) effect to patients who have been previously heavily treated, including those patients who have disease recurrence after autologous stem cell transplant (autoSCT). AlloSCT following RIC is now increasingly offered to patients with Hodgkin lymphoma (HL) that has relapsed after high dose chemotherapy and autoSCT. However, at the present time it remains unclear which clinical features of relapsed HL best determine who might benefit most from alloSCT.

Overall, registry data suggest that durable disease-free survival can be achieved in 30–40% of patients undergoing alloSCT [1]. However, the additive effects of transplant-related mortality and early disease progression post-alloSCT result in a precipitous fall in survival in the first 6 months. Therefore, whilst capturing the GVT effect against HL is the immunological aim of alloSCT, developing criteria to improve patient selection would allow improved HL control, avoid unnecessary toxicity in those unlikely to benefit, and allow more cost-effective utilization of this intensive therapy.

In this issue of *Leukemia and Lymphoma*, Sobol and colleagues from the Loyola University Medical Center suggest that a simple assessment of HL lesion size pre-alloSCT may be a straightforward means by which to determine the setting in which alloSCT is most effective [2]. In their analysis of 31 patients, a dose-attenuated form of BEAM (BCNU, etoposide, cytarabine, melphalan) was used as RIC, followed by infusion of stem cells from adult donors (42% human leukocyte antigen [HLA]-matched siblings; 71% peripheral blood). To augment the GVT effect they used a strategy of low dose methotrexate and Thymoglobulin as graft-versus-host disease (GVHD) prophylaxis and undertook an early and rapid withdrawal of tacrolimus. In the reported cohort, complete responses post-alloSCT were seen in 81%, which in itself is an impressive response rate in a heavily

pretreated group, many of whom would have likely received BEAM or similar conditioning for prior autoSCT. Non-relapse mortality was acceptable (13% at 1 year), and the 1-year relapse rate of 36% with no relapses beyond 3 years compares very favorably to other published series.

The most interesting observation in this analysis, however, is the ability for pre-alloSCT burden to act as a predictor of overall survival (OS) post-alloSCT. More fascinating still is that the effect of disease burden was independent from the effect of disease response as a predictor of outcome. Chemosensitivity has long been held as a prerequisite for efficacy of transplant in lymphoma. In this current analysis Sobol *et al.* describe for the first time in HL that the size of the residual lesion was the best determinant of post-alloSCT outcome. Using a cut-off of 2 cm they defined two cohorts of patients: those with minimal residual disease (< 2 cm) and those with gross residual disease (> 2 cm). Chemosensitivity was defined as a partial remission or better to salvage chemotherapy. Despite chemo-refractoriness, the cohort of patients with minimal residual disease had a 4-year OS of 71%, whilst the patient cohort with gross residual disease had a 4-year OS of 8% irrespective of whether chemosensitivity was present or not.

Overall, the implications of these findings are that the immunologically driven GVT effect following RIC alloSCT is either possible and/or effective only in the setting of low-burden HL. Further, as the efficacy of alloSCT in HL is wholly immunological, the presence of chemosensitivity is irrelevant.

The microenvironment of HL lesions is known to be potentially immunosuppressive through mechanisms including galectin-1 expression [3], transforming growth factor β (TGF- β) expression [4], PD-1 expression [5] and generation of regulatory T cell populations [6]. It is likely that high HL bulk is a surrogate marker for those lesions that are most resistant to immunological control and therefore, by extension, insensitive to the GVT effect of alloSCT.

Our own unpublished experience for alloSCT outcome in HL is also in line with the observations of Sobol and colleagues. We have found that the 4-year OS of patients transplanted with any measurable disease pre-alloSCT is 15% compared to 88% in those without any measurable lesions.

It remains to be seen whether the prognostic influence of disease size remains predictive in those patients receiving alternative-donor alloSCT, such as those using cord blood units or haploidentical donors. Similarly, the immunological consequences in HL remain unknown in the setting of disease progression after prior exposure to intensified chemotherapy regimens such as BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), or those regimens incorporating novel agents such as brentuximab vedotin (BV). Furthermore, the optimal use of BV as an immunological adjunct warrants more exploration, as it clearly has the capacity to bridge patients to curative alloSCT and to augment the efficacy of post-alloSCT donor lymphocyte infusions, perhaps by reducing disease mass to a minimal state that is sensitive to allogeneic immunological control [7,8].

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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