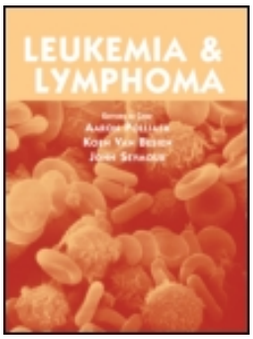

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COMMENTARY

# Salvage chemotherapy and autologous hematopoietic cell transplant in primary refractory diffuse large B-cell lymphoma: progress or better patient selection?

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In this issue of ***Leukemia and Lymphoma***, Telio and colleagues at the Princess Margaret Hospital [1] report their single institution experience using salvage therapy for primary refractory diffuse large B-cell lymphoma (DLBCL). In one of the largest patient series reported to date, they note that while the outcomes of first-line therapy for DLBCL have improved, salvage chemotherapy for subjects with non-responding disease has not had parallel improvements, regardless of the regimen used [2]. These authors used the same definition for primary refractory disease as that employed by Josting and colleagues, i.e. stable or progressive disease at the end of initial therapy, or progression within 3 months of completion of primary therapy [3]. Unlike other publications, Telio and co-authors separately reported on the outcomes of primary refractory patients; as such, this analysis represents a valuable contribution to the literature.

Telio and colleagues [1] also prospectively reported upon the outcome of those patients with primary refractory disease taken to autologous hematopoietic cell transplant (AHCT). Although previous reports indicate that such patients can be salvaged with use of this modality [4,5], there is an inherent selection bias in identifying medically fit patients with sufficiently responsive disease. The Toronto group advocated for salvage chemotherapy with ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) or GDP (gemcitabine, dexamethasone, cisplatin); the response rate was low, and only 28 of 111 patients were able to proceed to transplant. The outcomes in the AHCT group were what one would anticipate, i.e. superior to those subjects who continued to fail to respond to cytotoxic therapy.

Three potential strategies to improve patient outcome are discussed below. The first involves earlier identification of patients unlikely to respond to initial therapy and take this group to non-conventional therapies, e.g. investigational agent therapy or AHCT. Various clinical tools such as the second-line age-adjusted International Prognostic Index (IPI) score can predict outcomes for both relapsed and primary refractory DLBCL [6]. Although some success has been attained with AHCT in the primary refractory setting, many of these patients will fail to have long-term disease-free survival [5]. Attempts at establishing the optimal salvage regimen for primary refractory disease have been unrewarding, including the recent CORAL trial, where Gisselbrecht *et al.* [2] established no survival advantage of R-DHAP (rituximab, cytarabine, cisplatin, dexamethasone) compared to R-ICE (rituximab, ifosfamide, carboplatin, etoposide) chemotherapy in the salvage setting for the patient with relapsed or primary refractory DLBCL.

An alternative strategy includes the use of functional testing such as $^{18}$F-fluorodeoxyglucose positron emission tomography (PET) scanning, so-called risk-adaptive therapy. One conclusion inferred by the Toronto group study is the need at diagnosis to identify the subset of patients with DLBCL who are destined to fail conventional chemotherapy and take this group to AHCT earlier. Several studies have advocated for use of PET scans for interim analysis to predict outcome [7,8]. One example is the phase II, risk-adapted therapy investigation reported by Kasamon *et al.* [7]; 59 patients with newly diagnosed, aggressive B-cell lymphoma underwent PET/computed tomography (CT) scanning after two or three cycles of first-line chemotherapy. Those with negative PET scans proceeded to complete standard therapy, while those patients with positive PET scans received platinum-based salvage chemotherapy and subsequent AHCT. Mid-treatment PET was positive in 33 (56%); 28 subjects received AHCT and had an actuarial 2-year event-free survival (EFS) of 75%. Using intention-to-treat analysis, 2-year EFS was 67% in all PET-positive patients and 89% in PET-negative patients. These investigators, however, found no association between the IPI category and the mid-treatment PET result. This favorable outcome in historically poor-risk patients warrants validation for more definitive investigation

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of treatment modification based on early PET scanning in patients with DLBCL. Other investigators [9], however, have not confirmed the use of post-treatment PET evaluation for outcome prediction. Unresolved issues such as the specific timing of mid-treatment PET and which salvage regimen to use plague this approach.

A third strategy may rely upon gene expression tools to identify the patients with the most resistant tumors. This technique has gained momentum since the initial reports [10], but has not fully penetrated clinical practice. The impact of cell of origin in the relapsed and refractory setting is unknown. Furthermore, it is unclear when and what the next treatment intervention should be. Finally, this supposition implies that the dose-escalation effect of AHCT may overcome inherent tumor resistance, a fact not in evidence.

Telio *et al*. [1] acknowledge that conventional chemo-immunotherapy approaches generally are ineffective in this patient population. The study of newer agents such as lenalidomide and PCI-32765, the Bruton tyrosine kinase inhibitor [11,12], should be explored in this group. In addition, radio-immunotherapy (RIT) is a potent combination of anti-CD20 antibody activity linked to radioisotope emission that may provide a more targeted approach to lymphoma sites and limit toxicities to other tissues. This approach may allow more patients to proceed to AHCT without added toxicities that preclude patients from undergoing a transplant. The use of allogeneic transplants in DLBCL has limited prospective comparisons.

The Toronto group describes the important and often under-recognized disease entity of primary refractory DLBCL. Significant selection bias, however, remains for those who actually undergo AHCT. Future initiatives should focus collectively on the available resources of prognostic factors, imaging modalities and gene expression tools to create a risk-adaptive strategy to identify those who would benefit most from earlier AHCT or alternative therapeutic investigations. Primary refractory DLBCL continues to be a challenging clinical dilemma, and support for additional investigations in this population is warranted.

***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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