Chemoimmunotherapy has been the most significant step in recent years to improving overall survival (OS) and progression-free survival (PFS) rates in patients with diffuse large B-cell lymphoma - (DLBCL).[1] Despite this major therapeutic advance, a significant proportion of patients will relapse or remain refractory to initial chemoimmunotherapy. The pivotal PARMA trial confirmed the place of high-dose chemotherapy and autologous stem cell transplant (ASCT) as the optimum salvage treatment.[2] In the post-rituximab (Rituxan) era, patients with relapsed and refractory disease represent a different population than what was studied in the PARMA trial.[3] In this article, Hernandez-Ilizaliturri and Czuczman highlight the difficulty in managing such patients with salvage therapy and ASCT and raise the need for incorporating newer agents and strategies in this heterogeneous patient population.

The incidence of rituximab resistance in DLBCL and its implications in the current therapeutic era are not known. Several investigators have shown improved response rates by adding rituximab to salvage regimens such as DHAP (dexamethasone, high-dose cytarabine [Ara-C], cisplatin [Platinol]) and ICE (ifosfamide, carboplatin, etoposide), although the data on rituximab re-treatment are sparse. The long term results of the Groupe d’Etude des Lymphomes de l’Adulte (GELA) group’s LNH98-5 study[4] and the recent report by Martin and colleagues on behalf of the Grupo Espanol de Linfomas/Trasplante Autologo de Mdula sea (GEL/TAMO)[5] raise important questions about the efficacy of rituximab use in salvage therapy in an era when R-CHOP (rituximab, cyclophosphamide, doxorubicin HCl, vincristine [Oncovin], prednisone) is accepted as standard of care for induction therapy. The salvage therapy of choice and the role of rituximab re-treatment remain to be elucidated.

As pointed out by the authors, in a recently reported interim analysis of 200 patients of a planned total of 400 from the Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL), the factors affecting event-free survival included second-line age-adjusted International Prognostic Index (IPI), relapse less than 12 months since first-line treatment, and prior rituximab exposure.[6] This heralds an important conundrum, suggesting that patients who do not respond to rituximab-containing regimens in first-line therapy may be much more difficult to salvage with rituximab-containing chemotherapy.

Mechanisms and Patient Subgroups

The exact mechanism of rituximab resistance is not entirely clear, although several tumor-associated and host-associated mechanisms have been proposed.[7] Newer-generation monoclonal antibodies targeting CD20 have shown promise in relapsed indolent B-cell lymphoma. Promising results have been outlined with radioimmunotherapies, and their incorporation into conditioning regimens is being investigated.[8] Dacetuzumab targeting CD40 and other monoclonal antibody drug conjugates have shown modest promise in rituximab-refractory patients.[9] Additionally, it is apparent that some patients acquire rituximab resistance, possibly through the hyperactivation of ERK1/2 and NF-κB pathways and from overexpression of BCL-2; biologics targeting these pathways are under assessment in the salvage therapy setting.[10]

Patients in whom first-line therapy fails may be categorized into four distinct groups: those with early and late relapses after complete remission, partial responders, and those with refractory disease.
The outcome is significantly different in each subgroup. True refractory patients occasionally benefit from salvage regimens but generally have a poor outcome, even with aggressive regimens. Partial responders and those with early relapses sometimes benefit from non-cross-resistant salvage regimens and might be offered ASCT. Hence, early identification of patients in these subgroups who might benefit from more aggressive front-line therapy is critical. The available prognostic indices, newly identified biomarkers, and radiologic response criteria might be useful in making this differentiation.

### Prognostic Considerations

The IPI is a validated scoring system for predicting the survival rate of patients with newly diagnosed aggressive lymphoma. More recently in the setting of relapsed or refractory disease, the IPI at commencement of salvage therapy is predictive for OS and PFS. Hamlin et al found that patients with a second-line age-adjusted IPI of 0 had a 4-year PFS and OS of 69% and 83%, respectively, vs 25% and 26% for an IPI of 2 or 3. In the GEL/TAMO study, Martin and colleagues also validated second-line age-adjusted IPI as a prognostic factor.

Positron-emission tomography (PET) scan has been used effectively in identifying early relapses and treatment failures both after initial chemotherapy and after salvage chemotherapy. Despite several limitations of midtreatment PET, there is considerable hope that risk-adapted therapy using PET may improve outcomes, and clinical trials to address this potential are needed. A promising risk-adapted strategy was recently reported in a phase II trial by the Memorial Sloan-Kettering Cancer Center group. After four cycles of dose-dense R-CHOP, patients with negative PET or those with positive PET but negative biopsy received ICE for three cycles, whereas patients with a positive PET who had biopsy confirmation of residual disease received ICE for two cycles, followed by R-ICE and ASCT. Interestingly, only 4 (13%) of 31 PET-positive patients had a positive biopsy. Moskowitz et al concluded that the false-positive rate of interim PET could be up to 87% with dose-dense treatment, particularly when rituximab is used, but urged caution about extrapolating this technique outside of a clinical trial.

PET positivity after salvage chemotherapy is similarly predictive of outcome after ASCT, independent of age-adjusted IPI. Further assessment of the role of PET in risk-adapted salvage treatment will be needed, particularly in light of a recent Eastern Cooperative Oncology Group analysis that demonstrated a lack of consistency in reporting PET results for patients with DLBCL on clinical trials.

Gene-expression profiling has identified two different subtypes with distinct prognostic implications in de novo DLBCL. However, research to date assessing prognostic biomarkers for relapsed/refractory DLBCL has been limited. Hitherto undefined biologic entities seem to play a predominant role in determining response to salvage therapy. Identification of genetic subtypes, prognostic biomarkers, and subsequent targeting therapies in poor prognostic groups are needed to improve response rates in relapsed disease.

### Novel Agents

As mentioned by the authors, novel agents are being evaluated in relapsed/refractory disease. We have studied one such agent—fostamatinib disodium, an oral inhibitor of Syk kinase—and found it to be well tolerated in a phase II study of 68 patients with heavily pretreated relapsed or refractory DLBCL. Treatment results demonstrated a complete or partial response in 22% of 23 patients, with a similar fraction of patients demonstrating stable disease.

Other agents including enzastaurin (a protein kinase C inhibitor) and bevacizumab (Avastin) have shown modest response rates in phase II studies. These agents have limited overlapping toxicities and could enhance responses in combination with current salvage regimens. In addition to the use of biologics and targeted therapy, better conditioning regimens, and consideration of maintenance therapy are being explored. Consolidation of response with maintenance rituximab after ASCT is part of the ongoing CORAL study.

### Conclusions

Aside from ASCT as standard of care for relapsed chemotherapy sensitive patients, there is little consensus regarding management of relapsed/refractory DLBCL. Several treatments highlighted by the authors are under assessment. Targeted therapies are evolving, and their incorporation into current salvage strategies are under investigation. Identification of biomarkers and biologic
pathways are needed for new drug development. Furthermore, the ability to define high-risk subgroups that might benefit from a newer approach in the front-line setting when disease is more responsive will be paramount to improving DLBCL treatment. Since a majority of patients with large cell lymphoma can be expected to be cured, the impetus to enroll in clinical trials is often lacking. Identification of high-risk features in the de novo setting, and enrollment in appropriate clinical trials in order to improve salvage treatment and overall outcome remain key priorities.

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**References:**
of Syk, is well-tolerated and has significant clinical activity in diffuse large B cell lymphoma (DLBCL) and chronic lymphocytic leukemia (SLL/CLL) (abstract 3). Blood 112(11):3-4, 2008.


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