Old methods, lasting impact in relapsed/refractory primary mediastinal B-cell lymphoma

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Primary mediastinal B-cell lymphoma (PMBCL) has long been an overlooked "stepbrother" of diffuse large B-cell lymphoma (DLBCL) in terms of evidence-based medical decisions, with diagnostic and treatment-related strategies adopted from the results of large-scale DLBCL trials. In the best-case scenario, a very limited number of PMBCL patients, commonly constituting less than 10% of the study participants, have been included in the cohorts, and in the worst case, they have just been considered ineligible. The majority of studies exclusively focusing on PMBCL are prospective single-arm phase II trials or retrospective multicenter analyses. While the reasons for this are quite obvious, this does not relieve the burden of making decisions regarding the management of patients suffering from this biologically and clinically unique disease. Distinctive characteristics of PMBCL have prompted the design of specific treatment protocols to be applied both in newly diagnosed patients and in the relapse setting. The DA-EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab) dose-intense chemotherapy protocol has proven to be associated with relatively low toxicity and high efficacy, when used as first-line therapy for PMBCL,[1] obviating the need for mediastinal radiotherapy. This has led to the widespread adoption of DA-EPOCH-R, with subsequent real-world analyses recapitulating the initial phase II trial results.[2] Studies examining the use of checkpoint inhibitors with or without anti-CD30 drug-antibody immunoconjugates in relapsed/refractory PMBCL patients have shown fairly good results, with an overall response rate of 41.5% and complete response of 20.8% in the final analysis of the KEYNOTE study[3] and overall response rate of 73%, with complete remission rates reaching 37% in the CheckMate 436 study.[4] These findings ultimately brought about regulatory approval for the use of the evaluated drugs in these populations.

Despite encouraging treatment outcomes in newly diagnosed patients, second-line treatment of relapsed/refractory PMBCL patients still presents a compelling challenge and historical data suggest that these patients' response rates to chemotherapeutic salvage therapy are inferior to those observed in DLBCL (25% *vs.* 48%, respectively).[5] Large prospective clinical trials have clearly demonstrated the survival advantage of salvage therapy followed by autologous stem cell transplant (ASCT) in patients with large B-cell lymphoma.[6] These studies, however, have not included relapsed/refractory PMBCL cases; hence, clinical decisions regarding the use of this approach in the latter population are currently based on relatively small-scale retrospective and registry analyses. Importantly, the results of these analyses are generally favorable, demonstrating a 5-year overall survival (OS) that exceeds 75% in patients with relatively low tumor burden who are chemosensitive to salvage therapy preceding ASCT.[7-9] Notably, in the study from the Memorial Sloan Kettering Cancer Center, including a relatively small cohort of relapsed/refractory PMBCL patients, refractoriness to the first-line therapy emerged as an additional risk factor for poor outcome of salvage treatment and ASCT.

In the current issue of *Haematologica*, Hess *et al*. present the outcomes of 107 PMBCL patients, either relapsed or refractory to DA-EPOCH-R, who were considered eligible for salvage and ASCT.[10] Since DA-EPOCH-R is frequently used nowadays as first-line therapy, the data generated in the discussed study are likely to be highly applicable when choosing the most appropriate salvage therapy for individual patients. This study, in the largest series published to date, demonstrates that patients refractory to DA-EPOCH-R do poorly with chemotherapy salvage ± ASCT and should be offered alternative options, such as T-cell-redirecting therapies or checkpoint inhibitors. On the other hand, patients who relapsed more than 6 months after their initial response to DA-EPOCH-R were shown to respond favorably to salvage therapy (complete remission: 44%), with almost 80% of them proceeding to ASCT and achieving a high 2-year progression-free survival (69%), supporting this as a sound treatment approach for such patients.

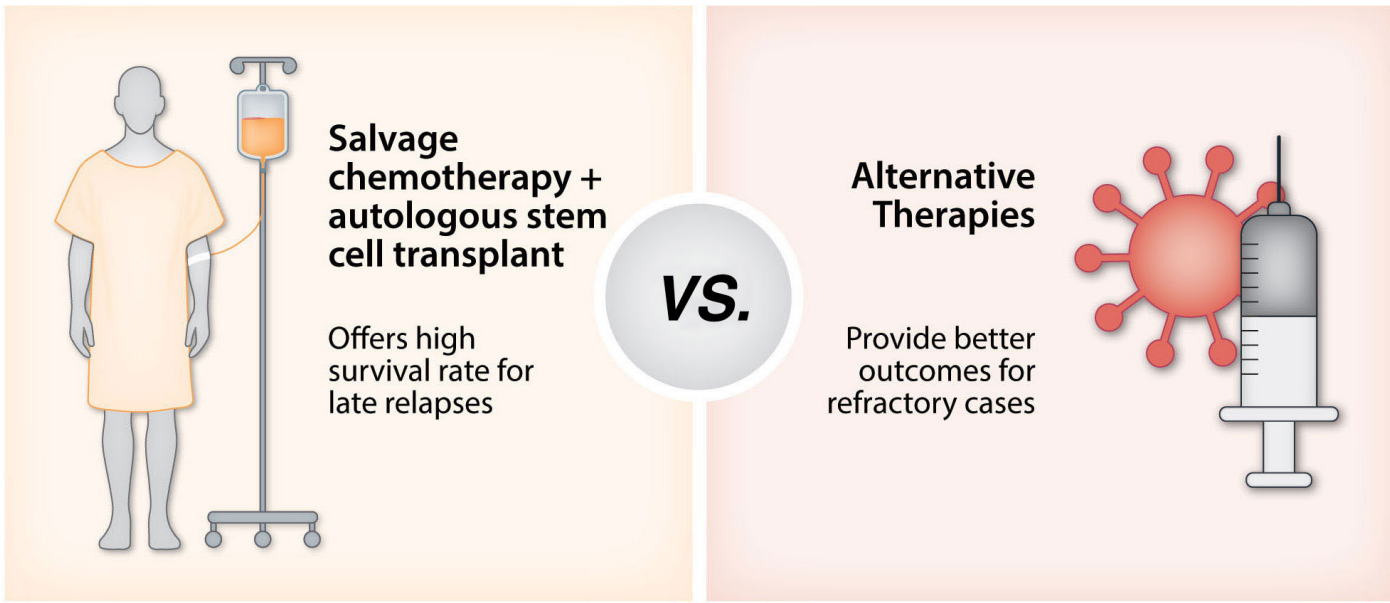

Figure 1. Choosing the most appropriate treatment strategy for relapsed/refractory primary mediastinal large B-cell lymphoma after first-line DA-EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab).

The most impressive survival outcomes were observed in transplanted patients with chemosensitive disease (5-year progression-free survival: 85%; 5-year OS: 88%).

While the results documented in the cohort of relapsed PMBCL patients achieving a good response to salvage therapy followed by ASCT are indeed encouraging, it is noteworthy that only 44% of patients in the intent-to-treat cohort had undergone ASCT. Yet, the projected OS for the whole cohort is relatively high (5-year OS: 78%), a finding that underlines the curative potential of other treatment strategies in this setting. One of such strategies, chimeric antigen receptor T-cell therapy, was also evaluated in the study by Hess *et al*., demonstrating exceedingly good results (57% complete remission rate and estimated 5-year OS of 71%), which are comparable to those reported in the pivotal ZUMA 1 study for a small cohort of PMBCL patients.[11]

The favorable survival data from the currently discussed study by Hess *et al*., as well as other studies, suggest that even relapsed/refractory PMBCL patients have a reasonable chance of being cured. Notwithstanding the substantial benefit of salvage therapy and ASCT in specific subgroups of patients, the decision to proceed with this approach should always be mindfully weighed against late complications of high-dose chemotherapy, particularly in the era of novel immunotherapies.

Disclosures

No conflicts of interest to disclose.

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