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Frontline therapy in primary mediastinal B-cell lymphoma: when salvage outcomes redefine the meaning of intensity. Comment on: Outcomes of patients with relapsed or refractory primary mediastinal B-cell lymphoma after frontline DA-EPOCH-R

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We read with great interest the article by Hess et al., reporting the largest real-world cohort to date of patients with relapsed or refractory primary mediastinal B-cell lymphoma (PMBCL) following frontline DA-EPOCH-R therapy.[1] Their analysis provides sobering insights, particularly the poor outcomes observed in refractory disease, with a complete remission (CR) rate of only 19% and a 2-year progression-free survival (PFS) of 30%. These findings are not only clinically relevant in the salvage setting but also raise fundamental questions regarding the assumptions that currently guide frontline treatment selection in PMBCL.

The optimal frontline treatment for PMBCL remains a subject of ongoing debate.[2] Over the past decade, DA-EPOCH-R has emerged as a commonly used frontline option in many centers, influenced by early single-arm studies reporting high cure rates and the potential to omit consolidative radiotherapy.[3,4] However, as real-world data have matured, it has become apparent that treatment intensity alone does not guarantee durable disease control and must be balanced against toxicity, feasibility, and the downstream consequences of treatment failure.[5] In this context, the study by Hess et al. demonstrates that failure after DA-EPOCH-R is associated with inferior outcomes, thereby challenging the assumption that intensified frontline therapy necessarily offers a therapeutic safety net.[1]

In this context, large multicenter real-world analyses provide an important complementary perspective. Across contemporary practice, CR rates, PFS, and overall survival (OS) appear comparable between R-CHOP and DA-EPOCH-R, while DA-EPOCH-R is consistently associated with higher toxicity and treatment delays or hospitalizations. Importantly, among patients achieving PET-negative complete metabolic response after R-CHOP, consolidative radiotherapy has not been shown to improve outcomes, supporting a radiation-free, PET-adapted approach.[5] These observations suggest that effective frontline disease control may be achievable without routine escalation to highly intensive regimens.

The data presented by Hess et al. further refine this discussion by highlighting the vulnerability of patients who fail to achieve an optimal response to DA-EPOCH-R. Among those who subsequently developed relapsed or refractory disease, 62% had not achieved CR initially, and early relapse within six months was associated with dismal salvage outcomes.[1] This underscores a critical implication: patients who do not respond deeply to DA-EPOCH-R upfront face substantial treatment-related toxicity and limited curative options thereafter.

Recent single-center and multicenter experiences reinforce the importance of response depth over dose intensity. Noel et al. reported excellent long-term survival outcomes with DA-EPOCH-R in a highly selected cohort; however, only 71% achieved complete metabolic response at the end of treatment, and dose escalation beyond level 2 conferred no survival advantage.[3] Crucially, all relapses occurred among patients with PET-positive disease, suggesting that DA-EPOCH-R is most effective when deep metabolic response is achieved early and that its therapeutic margin may be narrower than historically assumed.

Prospective and large-scale real-world data further emphasize the complexity of frontline decision-making in PMBCL. The IELSG37 trial demonstrated that radiotherapy can be safely omitted in patients achieving complete metabolic response after immunochemotherapy, regardless of the specific regimen used.[6] Post-hoc analyses comparing R-CHOP-21 with dose-intensive regimens revealed no significant differences in long-term PFS or OS despite differing PET response rates.[2] Importantly, many patients with PET-positive findings ultimately required additional systemic therapy, blurring the distinction between initial disease control and cumulative treatment burden.

The unifying theme emerging from these datasets is that depth of response, not nominal regimen intensity, defines outcome in PMBCL. This principle is most clearly illustrated in the salvage setting, where Hess et al. observed that no patient achieving CR prior to autologous stem cell transplantation subsequently relapsed. When frontline and salvage data are viewed together, the primary goal of initial therapy should be to maximize the likelihood of achieving CR with acceptable toxicity, rather than defaulting to the most intensive regimen available.

Taken together, these findings challenge a “one-size-fits-all” approach to PMBCL. While DA-EPOCH-R remains a highly effective option when optimally delivered and deep metabolic responses are achieved, its real-world toxicity, variable deliverability, and the devastating prognosis associated with treatment failure warrant careful consideration. Modern R-CHOP, integrated within PET-adapted strategies, may offer comparable frontline disease control for many patients, with lower toxicity and without compromising curative potential.

Ultimately, optimizing PMBCL care requires aligning frontline strategy not only with efficacy, but also with tolerability and a clear-eyed understanding of salvage outcomes. The integration of frontline and salvage-setting evidence should guide a more individualized and pragmatic approach to initial therapy selection. We commend Hess et al. for their contribution and hope that these data will stimulate renewed discussion on optimal frontline management of PMBCL.

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