R-CHOP: Does One Size Fit All in Diffuse Large B Cell Lymphoma?

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R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) has justly emerged as the standard of care for the treatment of diffuse large B cell lymphoma (DLBCL) based on three large randomized clinical trials all showing improved overall survival compared to CHOP alone [1–3]. Two additional studies have assessed whether R-CHOP given every 14 days would improve outcomes compared to the traditional 21-day schedule, each showing no incremental benefit to dose-dense administration [4, 5].

So R-CHOP on a 21-day cycle is the optimal treatment for all patients with DLBCL. Or is it? DLBCL is a heterogeneous disease including diverse variants such as T cell histiocyte rich B cell lymphoma (THRBCL), primary mediastinal B cell lymphoma (PMBCL), and the molecular subtypes germinal center-like DLBCL and activated B cell-like (ABC) DLBCL, among others. Certain subsets of DLBCL may not have been included in sufficient numbers in randomized trials to date to fully understand whether the results observed in DLBCL as a whole can be broadly applied to less common DLBCL variants.

In this issue of *Acta Haematologica*, Kim et al. [6] seek to address this question specifically for THRBCL, an uncommon morphologic variant of DLBCL. Pathologically, THRBCL is distinguished from traditional cases of DLBCL based on the paucity of large malignant B cells surrounded by an inflammatory microenvironment composed predominantly of polyclonal T lymphocytes,

with or without histiocytes [7]. Clinically, THRBCL has historically been observed to occur at a younger age than traditional DLBCLs, and with a tendency to present at an advanced stage with preferential involvement of the spleen, liver and bone marrow. Prior to rituximab, patients with THRBCL appeared to have similar prognoses as their stage-matched DLBCL counterparts. Does this hold true in the rituximab era? Kim et al. [6] report their matched-pair analysis comparing outcomes between THRBCL and DLBCL patients treated with R-CHOP. Among 11 patients with THRBCL and 33 patients with DLBCL, they find complete response rates of 91 and 97%, respectively, with both groups having an excellent 3-year event-free survival of 81%. Though this study is clearly too small to definitively answer this question, it does offer the first glimpse at THRBCL outcomes with R-CHOP in the modern era, and encouragingly suggests that the benefits of R-CHOP in DLBCL can be extrapolated to the THRBCL variant. Studies including larger numbers of patients to validate this finding would be helpful.

Ongoing questions remain about whether R-CHOP has been established as the standard of care in other subsets of DLBCL. PMBCL is a distinct clinical variant of DLBCL occurring primarily in young patients with a median age in the thirties and presenting predominantly with bulky limited-stage disease in the mediastinum. This disease has historically demonstrated an increased rate of chemotherapy resistance compared to DLBCL, necessi-

tating the use of mediastinal radiation [8–11]. PMBCL has represented only a small minority of patients included in randomized trials to date, so the preponderance of data in this disease is retrospective in nature. Though outcome of DLBCL does appear improved in the rituximab era [12, 13], modern R-CHOP still appears to be insufficient therapy for many patients with PMBCL, with a rate of primary refractory disease that approaches 20% [14], and with the majority of patients achieving remission still relying on radiation consolidation. A recent phase II trial of dose-adjusted EPOCH-R suggests improved outcomes and reduced need for radiation in PMBCL, further suggesting that R-CHOP may not represent the optimal chemotherapy platform in this particular variant of DLBCL [15].

Ultimately, the next great advances in the treatment of DLBCL will not be a one-size-fits-all approach like R-CHOP, but rather therapies that exploit the unique biological differences among heterogeneous subsets within

DLBCL. This may include targeting the NF- κ B and JAK-STAT pathways that are critical to the biology of PMBCL [16, 17], or targeting the microenvironment in the setting of THRBCL. Subset-directed therapy has already shown promise within molecular subsets of DLBCL based on the cell of origin, where ABC-like DLBCLs appear to preferentially benefit from NF- κ B inhibition with bortezomib, BTK inhibition with ibrutinib, or immunomodulation with lenalidomide, all of which warrant further investigation [18–20]. A significant additional ongoing challenge in DLBCL is the so-called ‘double-hit’ variant harboring dual translocations of both MYC and BCL2, where R-CHOP appears to be woefully inadequate therapy.

Though R-CHOP indisputably remains the standard of care for the majority of patients with DLBCL in the modern era, ongoing attention to variants within DLBCL is warranted, as future advances are likely to rely on therapies targeting discrete biologic subsets of disease rather than DLBCL as a whole.

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