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Improve R-CHOP in diffuse large B-cell lymphoma, still a challenge.

(1) Fabrice Jardin, MD-PhD

Centre Henri Becquerel, INSERM U1245, Rouen University, Rouen, France

Email address: fabrice.jardin@chb.unicancer.fr; Tel: +33232082465

Since the advent of R-CHOP as the gold standard for the treatment of diffuse large B-cell lymphoma (DLBCL), clinical investigators have constantly tried to improve its effectiveness by adding new drugs and proposing combinations (R-CHOP+ "drug X")¹. This strategy is justified by the great biological heterogeneity of DLBCLs, suggesting that R-CHOP cannot be a universal treatment and that it can instead provide the rational basis for personalized treatment. As such, the molecular classification based on the distinction between Germinal center B-cell like (GCB) and Activated B-cell like (ABC) subtypes has largely dominated the debate and focused efforts in terms of targeted therapy or biomarker research².

To demonstrate the interest of such a strategy, it is necessary to identify the biologically relevant, reliable, reproducible biomarker and to possess the corresponding effective molecule likely to improve the efficacy of the R-CHOP regimen.

The prospective multicenter phase III REMoDL-B trial, reported in this issue by Davies and colleagues, shows that a real-time DLBCL characterization by molecular biology with RNA extracted from FFPE samples and by DASL (cDNA-mediated annealing, selection, extension and ligation) technique is feasible³. Thus, among the 1128 DLBCL eligible patients, 918 (81%) could be effectively classified according to their cell of origin (COO: 26% ABC, 52% GCB and 22% unclassified). Phenotyped patients were subsequently randomized after the first R-CHOP cycle (C1) between R-CHOP and R-CHOP + bortezomib (D1/D8). The primary end-point analysis shows that the addition of bortezomib does not provide any benefit in terms of Progression Free Survival (PFS) /Overall Survival (OS) in the overall population, GCB, ABC or unclassified subtypes. These results support those of a randomized Phase II⁴. However, the authors point out a potential benefit of the combination for double-hits or MYC/BCL2 dual-expressors patients, without achieving statistical significance. Finally, despite overexpression of the NFκB pathway and activating mutations of this pathway in ABC DLBCL, the addition of bortezomib, a proteasome and NFκB pathway inhibitor does not provide any benefit over R-CHOP.

How can these ultimately disappointing results be explained? A relative under-representation of the ABC DLBCL subtype compared to some DLBCL cohorts, a significantly older age of ABC DLBCL patient, and the use of bortezomib only from C2 with a relatively low dosage can impact the efficacy of Bortezomib. These results also suggest that the GCB/ABC dichotomy is probably too simplistic or reductive. Recently, the Phase 3 randomized study Phoenix, which specifically targeted ABC DLBCLs, failed to clearly demonstrate the value of adding ibrutinib (a Bruton tyrosine Kinase inhibitor), to R-CHOP in this setting. However, it is likely that for this trial, the toxicity of this combination after 60 years of age is partly responsible for a negative conclusion since a benefit in OS and PFS is well observed for patients under 60 years of age⁵.

The prognostic impact of the COO classification remains also uncertain and has recently been questioned in two prospective trials⁶. In contrast, recent data from the CAVALLI Phase 2 trial show the value of adding a mimetic BH3, venetoclax, to the R-CHOP in BCL2+ patients, regardless of the GCB/non-GCB subtype, suggesting that a single biomarker (BCL2 expression quantified by immunohistochemistry) may be more relevant than COO molecular determination for patient selection⁷.

New classifications integrating Next Generation sequencing (NGS), FISH or Copy number variation (CNV) data are now available, and may offer other therapeutic or predictive opportunities⁸⁻¹⁰. However, these models are complex, partially overlapping and relatively difficult to apply in a randomized clinical trial or in daily practice. The selection of DLBCL patients on the basis of biological markers before the 1st treatment line therefore remains a crucial and real challenge in 2019.

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