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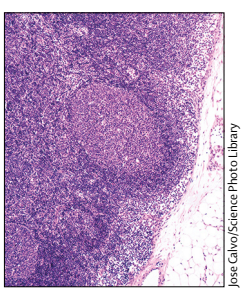
Improving R-CHOP in diffuse large B-cell lymphoma is still a challenge

Since the introduction of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) as the gold standard for the treatment of diffuse large B-cell lymphoma , clinical investigators have constantly tried to improve its effectiveness by adding new drugs and proposing combinations (ie, R-CHOP plus drug X).[1] This strategy is justified by the great biological heterogeneity of diffuse large B-cell lymphomas, suggesting that R-CHOP cannot be a universal treatment but can instead provide a rational basis for personalised therapy. As such, for the past decade molecular classification on the basis of the distinction between germinal centre B-cell-like and activated B-cell-like subtypes has largely dominated the debate and focused efforts in terms of targeted therapy and biomarker research.[2]

To show the potential of such a strategy, biologically relevant, reliable, reproducible biomarkers and a corresponding effective molecule that are likely to improve the efficacy of the R-CHOP regimen need to be identified.

The prospective multicentre phase 3 REMoDL-B trial, reported in *The Lancet Oncology* by Andrew Davies and colleagues,[3] shows that real-time characterisation of diffuse large B-cell lymphoma is feasible by use of molecular biology with RNA extracted from formalin-fixed paraffin-embedded (FFPE) samples and cDNA-mediated annealing, selection, extension, and ligation techniques.[3] Among the 1128 eligible patients in this trial, 918 (81%) were effectively classified according to their cell of origin (244 [27%] activated B cell, 475 [52%] germinal centre B cell, and 199 [22%] unclassified). Phenotyped patients were subsequently randomly assigned (1:1) after the first R-CHOP cycle to receive either R-CHOP or R-CHOP with bortezomib (RB-CHOP). The primary outcome analysis showed that the addition of bortezomib does not provide any benefit in terms of progression-free survival in the overall population (30-month progression-free survival 70·1% [95% CI 65·0–74·7] with R-CHOP *vs* 74·3% [69·3–78·7] with RB-CHOP; adjusted hazard ratio 0·84, 95% CI 0·64–1·11; p=0·23), with the same conclusion drawn in the secondary outcome analyses in the germinal centre B-cell, activated B-cell, and unclassified subgroups. These results support those of a randomised phase 2 trial by Leonard and colleagues.[4] However, Davis and colleagues point out a potential benefit of the combination for patients with double-hit lymphoma or dual-expressor lymphoma (ie, *MYC* and *BCL2*), although this benefit was not significant. The results show that despite overexpression of the nuclear factor (NF)-κB pathway and activating mutations of this pathway in activated B-cell diffuse large B-cell lymphoma, the addition of bortezomib—a proteasome and NF-κB pathway inhibitor—does not provide any benefit over R-CHOP.[3]

How can these ultimately disappointing results be explained? A relative under-representation of the activated B-cell subtype as compared with previous cohort studies in diffuse large B-cell lymphoma,[5] substantially older patients in the activated B-cell subgroup, and the use of bortezomib only from the second cycle onwards, with a relatively low dose, might all have affected the efficacy outcome of the addition of bortezomib. These results also suggest that the dichotomy of the germinal centre B-cell and activated B-cell subtypes of diffuse large B-cell lymphoma is probably too simplistic or reductive. A phase 3 randomised study (Phoenix)[6] that specifically targeted the activated B-cell subtype did not clearly show the value of adding ibrutinib (an inhibitor of Bruton's tyrosine kinase) to R-CHOP in this setting. However, the toxicity of this combination in patients aged 60 years and older is probably partly responsible for the negative conclusion since a benefit in overall survival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and progression-free survival was observed for patients younger than 60 years.[6]

The prognostic effect of the cell-of-origin classification also remains uncertain and has been questioned in two prospective trials.[5] Data from the CAVALLI phase 2 trial[7] showed a benefit in adding the BH3 (BCL2 homology 3) mimetic venetoclax to R-CHOP in patients positive for BCL2, irrespective of whether they had the germinal centre or non-germinal centre B cell subtype of disease, suggesting that a single biomarker (BCL2 expression quantified by immunohistochemistry) might be more relevant than cell-of-origin molecular determination for patient selection.[7]

New classifications that integrate next-generation sequencing, fluorescence in-situ hybridisation, or copy number variation data are now available and might offer other therapeutic or predictive opportunities.[8–10] However, these models are complex, partially overlapping, and relatively difficult to test in a randomised clinical trial or apply in daily practice. The selection of diffuse large B-cell lymphoma patients on the basis of biological markers before the first treatment therefore remains a crucial challenge.

Fabrice Jardin
Department of Clinical Hematology, Centre Henri Becquerel, INSERM U1245, Rouen University, Rouen 76038, France
fabrice.jardin@chb.unicancer.fr

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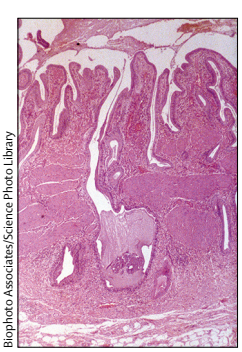
Adjuvant capecitabine in biliary tract cancer: a standard option?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In *The Lancet Oncology*, John Primrose and colleagues[1] have tackled the question of adjuvant treatment for a rare cancer: biliary tract cancer, an unresolved question to date. Although a meta-analysis (of mostly retrospective data) has suggested improved overall survival with adjuvant treatment (especially chemotherapy in patients with node-positive disease and adjuvant radiation-based therapy after R1 resection),[2] older randomised studies were not sufficiently statistically powered to define a standard of care,[3,4] and two recent randomised studies did not show a significant benefit of gemcitabine[5] or gemcitabine plus oxaliplatin (GEMOX regimen).[6]

In the randomised, phase 3, BILCAP study, 753 patients were screened across 44 UK centres between 2006 and 2014, of whom 447 patients with curatively resected cholangiocarcinoma or muscle-invasive gallbladder cancer and preserved performance status (Eastern Cooperative Oncology Group 0 or 1) were randomly assigned to receive oral capecitabine for 24 weeks or observation.[1] Unfortunately, the study did not meet its primary endpoint: the median overall survival by intention-to-treat was 51·1 months (95% CI 34·6–59·1) in the capecitabine group compared with 36·4 months (29·7–44·5) in the observation group (hazard ratio [HR] 0·81, 95% CI 0·63–1·04; p=0·097).

Should capecitabine be considered as ineffective as gemcitabine[5] and GEMOX[6] in the other two recent adjuvant trials? Probably not. In fact, despite being