Differential Therapy for Diffuse Large B-Cell Lymphoma with Different Cells of Origin

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Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid neoplasm. By gene expression studies three subtypes have been identified, the activated B-cell (ABC)-like DLBCL, the germinal center (GC)-like and the primary mediastinal large B-cell lymphoma. ABC- and GC-like DLBCL differ with respect to the cells of origin, pathogenetic mechanisms and prognosis. Because classical gene expression studies require fresh (-frozen) biopsy material, surrogate markers for the assignment to the ABC- and GC-like subtypes are warranted, which are applicable to formalin fixed paraffin embedded (FFPE) biopsy samples. Immunohistochemistry of FFPE using antibodies against CD10, BCL-6 and MUM-1 has been reported to allow the assignment of DLBCL to the GC- and non-GC subtype [1], and many studies have shown that the classification on the basis of the cell of origin is an independent prognostic factor for patients who are treated with CHOP or CHOP-like regimens.

Zhang et al. [2] report in this issue of ONKOLOGIE the results of a retrospective analysis of the role of the GC and non-GC subtype of DLBCL on the outcome of patients who had been randomly assigned to classical 3-weekly (CHOP-21) or bi-weekly CHOP (CHOP-14). The authors show that patients suffering from DLBCL of the non-GC type had a significantly better outcome with CHOP-14 compared to CHOP-21, while this was not the case for patients with GC type DLBCL. Even though R-CHOP has become the standard treatment for DLBCL world-wide, the results of Zhang et al., obtained in the 'pre-rituximab era' or a 'non-rituximab area', respectively, are interesting and definitely deserve publication, because this is the first study to address the differential effect of interval reduction of the CHOP regimen for the outcome of GC type and non-GC type DLBCL and the first study suggesting that a differential therapeutic approach to GC and non-GC DLBCL could be helpful. In the original study of CHOP-14, it had been shown that patients with elevated pre-treatment LDH had the greatest benefit from CHOP-14 [3]. Unfortunately, no multivariate analysis was performed by Zhang et al., so we do not know whether the putative cell of origin as defined by immunohisto-

chemistry was an independent factor for the beneficial effects of interval reduction of CHOP. Apart from the retrospective nature of the analysis, there are several other points that have to be kept in mind when interpreting the study of Zhang et al.: 1st, the number of patients in this study is very small, yielding large confidence intervals; 2nd their study population consists of 63.8% non-GC type and 36.2% GC type patients, which is an atypically high proportion of non-GC type DLBCL; 3rd, the results of the non-GC type patients under CHOP-14 were clearly inferior to those observed in the German study [4], despite the fact that the patients in the Chinese study were much younger (51 years vs. 67 years); 4th the value of the 'Hans Classifier' [5] as a surrogate marker for the distinction of GC-type and non-GC type of DLBCL has been challenged; 5th, one has to keep in mind that the positive predictive value of the immunohistochemical approach in comparison to gene expression-based classifications is only 87% for the GC and 73% for the non-GC phenotypes with a misclassification of 20% [6]; 6th, the Lunenburg consortium observed unexpectedly highly variable results and very poor reproducibility in scoring for almost all markers, and particularly poor agreement was found for BCL-6 which is included in the Hans classifier [7].

In summary, the study of Zhang et al. has raised more questions than it has delivered answers. Similar problems are inherent to a recently published study from the NIC [8]. This study which included only 15 patients with GC and 12 with ABC DLBCL, suggested that the addition of bortezomib to a R-CHOP-like regimen improved results only in ABC, but not in GC DLBCL compared to the R-CHOP-like regimen alone.

What we are left with is the duty to address the issue of differential treatment for DLBCL of different cells of origin in appropriately designed prospective trials using validated methods to distinguish the GC from the non-GC type of DLBCL.

Conflict of Interest

Niels Murawski: none.
Michael Pfreundschuh: Roche advisory board Rituximab.

References

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