

● ● ● LYMPHOID NEOPLASIA

Comment on Horn et al, page 2253

MYC, BCL2, BCL6 in DLBCL: impact for clinics in the future?

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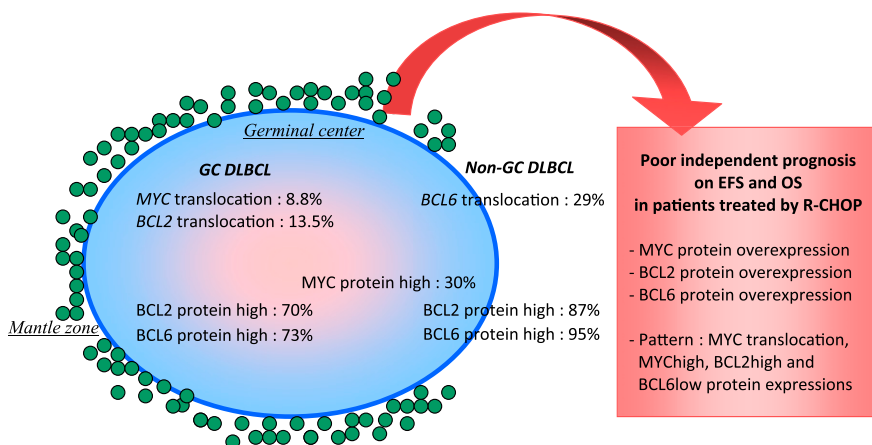
In this issue of *Blood*, Horn et al investigated the prognostic relevance of MYC, BCL2, and BCL6 rearrangements and protein expression in a large series of patients with diffuse large B-cell lymphoma (DLBCL) homogeneously treated in a prospective randomized trial.¹

Diffuse large B-cell lymphoma (DLBCL), the most frequent lymphoma in adults, is a clinically and biologically heterogeneous group of lymphomas associated with diverse response to optimal therapy. Despite major advances in the treatment, particularly with the addition of the anti-CD20 monoclonal antibody rituximab to the standard cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (CHOP), 40% of the

patients still experience early treatment failure defined as refractory disease or relapse after initial response to chemotherapy.² Prognosis is influenced by well-recognized clinical features summarized in the International Prognostic Index (IPI)³ (age 60 years or older, disease stage III/IV, high lactate dehydrogenase, 2 or more extranodal sites of disease, and an Eastern Cooperative Oncology Group performance status of 2 or more) and

by biological parameters, such as the BCL2, BCL6, TP53, and LMO2 protein expressions, that taken individually have an equivocal prognostic relevance. In addition, gene expression profiling studies have provided prognostic relevant information with a major division on the basis of the cell of origin of DLBCL into germinal center B-cell (GCB)-like disease and activated B-cell (ABC)-like disease.⁴ However, relapses occur at nearly the same rates in patients with GCB-like DLBCL and in patients with ABC-like DLBCL,⁵ suggesting the existence of additional oncogenic events of importance in resistance to therapies.

In this context, MYC in concert with BCL6 and BCL2 appear to have a role to play in refractory/relapsed DLBCL. MYC translocation is a defining feature for Burkitt lymphoma (BL) and is required for the diagnosis. However, emerging data showed that MYC gene aberrations are not limited to BL because DLBCL and other lymphomas can also harbor this genetic abnormality. In DLBCL, MYC aberration is found in less than 10% of the cases at diagnosis⁶ and in almost 20% at first relapse.⁷ In contrast to BL, MYC aberration usually occurs with complex karyotypes and with other cooperating genetic lesions such as BCL2 and BCL6 rearrangements, defining the so-called “double-hit” and “triple-hit” DLBCL. The MYC aberration is associated with a more aggressive phenotype and poor outcome, including shorter progression-free and overall survival (OS). The MYC protein acts as a transcription factor that regulates more than 15% of all cellular genes to promote cellular proliferation via metabolic and angiogenic mechanisms. MYC protein overexpression (>40%) was recently identified in about 30% of DLBCL cases.⁸ The cutoff of 40% was found to be the optimal cutoff for predicting survival⁸ and the cutoff of 70% was optimal for predicting the presence of MYC rearrangement.⁹ It was also suggested that



MYC, BCL2, and BCL6 rearrangements and protein expression regarding cell of origin classification and their prognostic impact in patients with DLBCL treated by R-CHOP. MYC and BCL2 rearrangements were more frequently observed in GCB-DLBCL and BCL6 translocation was more frequently observed in non-GCB-DLBCL, whereas at the protein level, no significant difference with respect to MYC overexpression was noted between GCB- and non-GCB-DLBCLs. The survival analyses showed that, taken individually, MYC, BCL2, and BCL6 protein overexpression was associated with an adverse prognosis, independently of the IPI score. The pattern associating MYChigh, BCL2high, BCL6low, and MYC rearrangement was highly predictive of the prognosis, independent of the IPI score.

MYC protein overexpression had poor prognostic impact when BCL2 protein was coexpressed.⁸

The study by Horn et al¹ took advantage of a large series of elderly patients (age 61–80 years) homogeneously treated in a prospective trial with CHOP or rituximab plus CHOP (R-CHOP) to analyze the prognostic impact of MYC, BCL2, and BCL6 at both the gene level and the protein level. First, the description of the distribution of the oncogenic events and the deregulation of the protein expression is of great interest. MYC translocation and MYC protein overexpression (>40%) were detected in 8.8% and 31.8% of the cases, respectively. MYC translocation was associated in double-hit or triple-hit aberrations with BCL2 and/or BCL6 rearrangements in 60% of these cases. MYC overexpression occurred independently of MYC translocation in 30% of the cases. In terms of cell of origin, MYC and BCL2 rearrangements were more frequently observed in GCB-DLBCL and BCL6 translocation was observed more frequently in non-GCB-DLBCL, whereas at the protein level, no significant difference with respect to MYC overexpression was noted between GCB- and non-GCB-DLBCLs. Second, and more importantly for clinical practice, the survival analyses showed that, taken individually, MYC translocations in the whole group of patients as well as MYC, BCL2, and BCL6 protein overexpression in the R-CHOP group were associated with an adverse prognosis, independently of the IPI score (see figure). Moreover, the pattern associating MYChigh, BCL2high, BCL6low, and MYC rearrangement was highly predictive of the prognosis, independently of the IPI score.

Why is this report significant in routine practice for DLBCL patients? The pivotal importance of this report is that the authors identified in elderly patients treated with R-CHOP a worse group within the IPI high-risk group (3–5 adverse prognostic parameters) with 3-year event-free survival and OS of only 15.6% and 41.6%, respectively. Whether these results will also be true in young patients (younger than age 60 years) in whom intensity of treatment may be different still has to be proven.

Regarding the physiopathology of these oncogenic events, why should MYC be diagnostic in BL but prognostic in DLBCL?

One possible explanation is that these diseases are molecularly distinct as reflected by gene expression profiling.¹⁰ Moreover, by using small interfering RNA against MYC, it was shown that MYC target genes modulate a completely different and unique set of genes in BL compared with DLBCL, with the nuclear factor κ B pathway being one distinguishing set of affected genes.¹⁰ This may explain the profound negative prognostic significance of MYC expression in DLBCL.

In addition to the fact that DLBCL is described in the World Health Organization classification with 18 subentities, choice of treatment is still based on clinical features only. Clearly, because of the recent identification of GCB-like and ABC-like DLBCL subtypes as well as the outstanding analysis reported by Horn et al¹ describing the major impact of MYC, BCL2, and BCL6, we can argue that the classification of DLBCL is changing. New entities with clinical relevance are emerging. In the near future, this will have a major impact on defining the most appropriate treatment to propose to patients with DLBCL. The number of ongoing clinical trials attests to the search for novel targeted agents tailored toward these specific molecules or pathways.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

● ● ● CLINICAL TRIALS & OBSERVATIONS

Comment on Jourdan et al, page 2213

MRD in AML: time for redefinition of CR?

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In this issue of *Blood*, Jourdan and colleagues from the French AML Intergroup demonstrate the prognostic value of minimal residual disease (MRD) in adult patients with core binding factor (CBF) acute myeloid leukemia (AML).¹

Currently, the most important prognostic factors for AML are based on cytogenetics and molecular abnormalities, which are assessed at diagnosis.² Although these factors have been shown to be of utmost importance in risk stratification, the treatment outcome of patients within the thus-defined risk groups is still highly variable. New prognostic factors that, apart from diagnosis parameters, may include treatment and response related factors are needed.

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MRD, defined as the persistence of leukemic cells after chemotherapy at numbers below the sensitivity detection level of routine morphology, represents the sum of the effect of all relevant cellular resistance mechanisms, pharmacokinetic resistance, dosage and compliance, and other unknown factors affecting the effectiveness of treatment. Relapses still are a major cause of dismal outcome in AML treatment and are generally thought to be the result