E3. PROGNOSTIC FACTORS WITH THERAPEUTIC IMPLICATION IN DIFFUSE LARGE B-CELL NON-HODGKIN LYMPHOMA`S

Hortensia Ioniţă, Ioana Ioniţă
University of Medicine and Pharmacy „Victor Babeş", Timişoara, Department of Hematology, Timişoara, Romania

The International Prognostic Index (IPI), originally established to predict outcome of patients with aggressive lymphoma treated in the pre-rituximab era, DLBCL with MYC breakpoints (including double-and triple hit DLBCL), expression of MYC together with BCL2 protein, patients presenting with skeletal involvement, central nervous system (CNS) involvement during the course of disease, represent a subpopulation with an almost always fatal course.

A major improvement in treatment outcome has been achieved by adding rituximab to CHOP-like regimens. The revised IPI or "R-IPI" has three risk groups as suggested by Sehn *et* a/. treated with R-CHOP. The differences became smaller between the four risk groups under R-CHOP, demonstratrated that the IPI is still valid in the R-CHOP era and has a significant prognostic power.

ln the Mega-CHOEP trial, young patients with aalPI of 2 had a 3-year survival of 90%, and aalPI of 3 73% after 8 X R-CHOEP-14. In young patients, only the high-risk group with a 3-year survival of less than 75% represents a clinically relevant risk group. Related to toxicity of CHOP- 14 and CHOEP-14, combinations with targeted therapies like bortezomib, lenalidomide or ibrutinib are currently being evaluated in this population of young patients with high-risk DLBCL.

In elderly (age 61-80 years) DLBCL patients, with a 3-year overall survival of 88% for low-risk, 78% for low-intermediate, 67% for high-intermediate and 58% for the high-risk group, all but the low- risk group have a high risk of failure and must be improved. The increased toxicity in elderly patients as hematotoxicity, and strategies pursued include dose-dense of rituximab, adding other CD20 monoclonal antibodies or antibodies directed against targets other than CD20, addition of lenalidomide to R-CHOP, or lenalidomide or enzastaurin for maintenance therapy.

In a study of morphological and immuno-histochemical biomarkers in elderly patients treated both with and without rituximab within the RICOVER-60, immunoblastic morphology emerged as a robust, significantly adverse prognostic factor. In multivariate analysis adjusted for the factors of the has been confirmed to be a valid prognosticator for patients receiving rituximab, with the differences between the four risk groups (low, low-intermediate, high-intermediate and high) being smaller, yet significant compared to the pre-rituximab era.

Apart from the IPI, there are other subsets of diffuse large B-cell lymphoma (DLBCL) that are characterized by criteria not included in the IPI or are too rare to be recognized in multivariable analyses. This applies to: very old patients (>80 years), histological subgroups like DLBCL with immunoblastic or plasmablastic morphology, Epstein-Barr (BV)-positive B-cell diffuse large B- cell lymphoma of the elderly, the germinal center versus the non-germinal center subgroups,
IPI, the immunoblastic subtype was an independent predictor for EFS.

EBV-positive B-cell diffuse large B-cell lymphoma of the elderly is an EBV-positive clonal B-cell lymphoid proliferation that occurs in patients over 50 years of age and predominantly in elderly patients without any known immunodeficiency or prior lymphoma. These patients are diagnosed at older age, present with elevated LDH, poor performance status, B symptoms, and frequent skin and lung involvement. B symptoms and age over 70 years, but not IPI, appear to be reliable prognostic factors.

Age is one of the strongest prognostic factors in the IPI, not related to increasing comorbidities of elderly patients, but also because adverse biological features like the ABC-type and MYC breaks are enriched in the elderly population. While the IPI discriminates between patients aged 60 years or under and those over 60 years, a modification of the IPI, the IPI for elderly patients or E-IPI, was suggested using 70 instead of 60 years as a cut-off point to delineate older age as a risk factor. There are fewer prospective data available for octogenarians or nonagenarians, even though this population of DLBCL patients is increasing fast.

Male gender is a negative prognostic factor in (elderly) patients treated with rituximab, because female patients have a higher benefit from the addition of rituximab to CHOP chemotherapy than male patients. This is due to the slower rituximab clearance in elderly females that results in higher serum levels, longer serum half-life elimination time. No pharmacokinetic data are available for young DLBCL patients.

Bulky disease was an independent risk factor in the MInT study in young patients with an aalPI of 0 or 1 and bulky disease, despite the fact that nearly all patients with bulky disease had received radiotherapy to the respective area. For elderly patients with bulky disease, the results of the RICOVER-noRX study also suggest a

benefit of additional radiotherapy, at least in patients achieving a PR or less. While skeletal involvement (localized or diffuse) was not a risk factor in the pre-rituximab era, it evolved as such when rituximab was given. Involvement of the central nervous system (CNS) is a serious and mostly fatal complication of DLBCL and remains to be so in the rituximab era. Several retrospective studies suggest that iv. HD-MTX can reduce the incidence of CNS involvement in patients at increased risk. The situation is less clear in younger patients for whom a group at significant risk for CNS involvement (elevated LDH, advanced stage) develops CNS disease in only 6.5% of the cases.

Chromosomal instability and changes confer a worse prognosis, and the expression of certain microRNAs and proteins has been reported to be associated with a favorable (BCL6, CD10, HIF-la, HLA-DR, IRF4/MUM1, LM02; CD30) or an adverse (BCL2, CD5, indolamine 2,3-dioxygenase, high Ki-61, mutated p53, VEGFR2, Skp2) outcome.

In contrast to «single molecules, the analysis of the entire exome by GEP studies identified three biologically and prognostically relevant subtypes of DLBCL: the activated B cell (ABC)-like DLBCL, the germinal center (GC)-like, the mediastinal large B-cell lymphoma based on cell-of-origin (COO) gene signatures, with the activated B-cell (ABC) type being associated with an inferior outcome compared to the germinal center (GC) type.

ABC- and GC-like DLBCL differ with respect to the cell of origin, pathogenetic mechanisms and prognosis: the GC/non-GC was shown to be a prognostic factor independent of the IPI in patients treated with CHOP only, the GEP added to the predictive power of the IPI, the IPI added to the predictive power of the GEP in patients treated with CHOP-R.

In many B-cell lymphomas, chromosomal translocations are biological and diagnostic hallmarks of the disease. A subset of these lymphomas has structural aberrations affecting the myc locus that is associated with a poor prognosis independent of clinical risk factors. MYC- break positive DLBCL cases may also co-express high levels of BCL2, and up to half of these cases have a concurrent translocation involving BCL-2. These double-hit (DH) lymphomas are defined by a chromosomal breakpoint affecting the MYC/8q24 locus in combination with another recurrent breakpoint, *e.g.* a t(14; 18)(q32;q21) involving BCL2.

Regimens effective in Burkitt's lymphomas that incorporate HD-MTX such as the (CODOX-M/IVAC regimen), will improve the outcome of DH lymphomas.

In contrast to MYC translocations, observed in 5% of the cases and had a median OS of less than one year, MYC protein expression was associated with an inferior PSF and OS only when BCL2 protein was co-expressed. The patients with DLCBL co-expressing MYC and BCL2-proteins by IHC have a poor prognosis.