# Better understanding and new challenges in high grade lymphomas

Diffuse large B-cell lymphoma (DLBCL), comprise the most commonly diagnosed non-Hodgkin lymphoma. Approximately 60–65% of patients can be cured with standard front-line therapy R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). However, the progress in the understanding of the disease has led us to appreciate its underlying heterogeneity. The 2016 World Health Organization (WHO) classification of lymphoid malignancies recognizes several distinct entities within the group of DLBCL characterized by unique pathological, molecular and biological features. This leads to the identification of subgroups of patients with different prognosis and thus intention to personalize treatment. The first new challenge we face in DLBCL is the correct diagnosis, which, as the understanding of the unique and multiple biological and molecular features evolves, this task becomes more complex and should ideally be performed by expert hematopathologist, which lack in different areas of the world. The diagnosis of DLBCL, NOS, should include cell of origin (CCO); germinal centre B-cell (GCB) or activated B-cell (ABC)/non-GCB subtypes. Although the optimal way to determine COO are gene expression profiling techniques, due to the availability of immunohistochemistry (IHC) and the reduced cost, the Hans algorithm is the most widely used method. This algorithm stratifies patients based on 3 separate IHC stains for CD10, BCL6, and MUM1. It has been reported that the concordance between the Hans algorithm and Lymph2Cx assay, a digital gene-expression based test for COO assignment in formalin-fixed paraffin-embedded tissue, is around 70%, so there may be some discrepancy depending on the method used. With the emergence of novel therapies that have selective biological activity in either COO group, this identification is becoming increasingly important. Another important information gained by using IHC is expression of MYC and BCL2, this isolated dual protein expression (DPE) without underlying chromosomal rearrangements is a distinct and adverse prognostic factor in DLBCL predicting inferior survival compared to patients without DPE. The WHO does not consider DPE as a separate entity.

Therefore, after the pathologic diagnosis is finished, COO must be specified and to make a definite diagnosis of high-grade B-cell lymphoma, not otherwise specified (HGBL, NOS); one should perform FISH of *MYC*, *BCL2* and *BCL6* to exclude HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements. These are new challenges we face trying to keep up excellence in diagnosis. Availability of FISH, the cost of this technique and the need of quick results to decide treatment with this information, is a present struggle in many hematological units. Patients with HGBL-DH/TH comprise around 10% of newly diagnosed DLBCL, with less than 20% estimated long term survival after standard treatment with RCHOP, and better outcome if treatment is intensified from diagnosis. Thus, this important molecular feature in a small number of patients raises the challenge of determining which patient warrants FISH testing. For almost two decade, after the introduction of Rituximab, R-CHOP has been the standard of care for first line treatment in all DLBCL. Today we have several validated prognostic tools to stratify patients into risk groups; however, the impact of these tools on improving outcomes has been limited. With the growing evidence of the heterogeneity of this disease, many attempts have been made to target specific subgroup and improve outcome. The substitution of Rituximab by Obinutuzumab or the addition of Etoposide, Bortezomib, Lenalidomide or Ibrutinib has not modified OS, and thus have not changed the widely accepted use on R-CHOP in first line for most patients with DLBCL. Present and ongoing studies are exploring the significance of pretreatment and dynamic ctDNA (circulating tumor DNA) measurements for predicting outcomes and in the future might be useful for response-adapted therapy. For patients with relapse or refractory disease, intensive salvage strategies including autologous stem cell transplantation (ASCT) provide the best chance for cure in the second-line setting, although only 50% of these patients will be transplant eligible, and 40–50% of those who undergo ASCT will eventually relapse after this procedure. Recent progress in molecular biology has led to a better understanding of the oncogenic drivers of DLBCL, resulting in the development of a large number of targeted therapies undergoing evaluation in phase I and II trials in this setting. Lenalidomide and new target therapies as Venetoclax, Ibrutinib and Polatuzumab (Pola) are available options. In a phase II randomized study, the combination of Pola plus bendamustine (B) and rituximab was compared to BR alone in transplant-ineligible patients with relapsed/refractory DLBCL. With 40 patients included in each arm, the PET-CR rate was higher with Pola-BR *vs.* BR alone, 40% *vs.* 18%, respectively. Similarly, the median OS was significantly improved with Pola-BR (12.4 *vs.* 4.7 months).

With these results, Polatuzumab has been approved for second line therapy. Nivolumab, has shown impressive activity in classical HL but efficacy in DLBCL as a single agent was less remarkable. In a recent phase II single arm study including 121 patients with rel/refr DLBCL, the ORR was 10% and 3% in patients who had failed ASCT and transplant-ineligible patients, respectively (median DoR, 11 and 8 months, respectively). There is still an unmet need for patients with relapsed refractory DLBCL and a significant proportion of them will eventually die of progressive disease. Chimeric antigen receptor (CAR) T-cell therapies, such as tisagenlecleucel and axicabtagene ciloleucel, offer a possible cure for these patients and has been approved by the FDA for third line treatment, with on-going studies in second line.

On hand with this great step forward in the treatment of relapsed/refractory patients, we face this other challenge of providing active treatment in the correct time and trying to make this salvage therapy available worldwide. The better understanding of DLBCL is leading to new diagnostic and treatment opportunities. Our greatest challenge lies in trying to prevent that these advances lead to a widening gap in therapeutic opportunities between people with different economic resources.

In this issue, we present the current state of diagnosis and treatment of DLBCL. We have carefully selected experts in the each topic to provide an instructive review of the literature and their personal interpretation of the data. We hope this focused issue provides readers with analyzed information that will help them face or overcome the mentioned challenges with useful and evidenced based information.

## Acknowledgments

## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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