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REVIEW ARTICLE

Improving first-line treatment in diffuse large B-cell lymphoma

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Abstract

R-CHOP remains the standard of care in first-line treatment of diffuse large B-cell lymphoma (DLBCL), the most common lymphoma subtype. Patients who fail this therapy have a poor outcome, with relapse or refractory disease resulting in fatality in the majority.

In this short paper, we summarize recent clinical studies exploring alternative regimens and efficacy of autologous stem cell transplantation (ASCT) consolidations.

In ABC DLBCL, adequately identifying patients with poor prognosis but failed to recognize the patient for molecular target of therapy. Immunotherapy, which may potentially be used in less well genetically characterized patients, is most potent if used relative to chemotherapy protocols, therefore its optional combination remains to be determined. The hope is ultimately to move away from a universal chemotherapeutic mentality towards an individualized approach, be it through the use of a targeted small molecule or a biological drug.

We discuss the role of new monoclonal antibodies such as obinutuzumab, brentuximab vedotin, polatuzumab vedotin and bispecific antibodies (BIABs) in first-line treatment regimens. BIABs which can bind to two different antigens at the same time are under investigation. After neurotoxic blinatumomab, anti-CD20/anti-CD3 BIABs take the lead, and due to their favorable toxicity profile they can be used in elderly patients with comorbidities, causing durable responses in patients with B-cell non-Hodgkin lymphoma who otherwise have limited options, even in those relapsing or refractory to chimeric antigen receptor (CAR) T-cell therapy.

Key words: DLBCL, targeted molecular therapies, immunotherapy

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Diffuse large B-cell lymphoma (DLBCL) belongs to a group of aggressive lymphomas which, if left untreated, progress rapidly and shorten the lives of patients. First-line immunochemotherapy, usually curative in aim, should be implemented as soon as possible.

The first effective regimen was suggested in 1973 by the 'NCN gang of five' (Canellos, Chabner, Schein, DeVita and Young) when doxorubicin was added to the CVP (cyclophosphamide, vincristine, prednisone) regimen. CHOP is the single most effective protocol, and is still used nearly 50 years later with only a few modifications. With its significantly prolonged progression-free survival (PFS) and overall survival (OS), the results hold up well against so-called second generation chemotherapy regimens [1]. Introducing rituximab, a chimeric anti-CD20 monoclonal antibody, was a breakthrough, and has been the only widely accepted CHOP modification so far. This significantly increased the complete response (CR) rate, and improved 10-year PFS and OS [2].

R-CHOP-14, an attempt to intensify the R-CHOP regimen in elderly patients by shortening the interval between

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cycles to 14 days, despite initial German results, proved discouraging in properly planned randomized phase III studies [3, 4]. Efficacy was not superior and toxicity was more pronounced. Therefore, R-CHOP-21 remains the standard of care. An even greater dose escalation was explored in high-risk DLBCL, in R-MegaCHOEP, a four-arm randomized trial with or without subsequent autologous stem-cell transplantation (ASCT) consolidations [5, 6]. Despite the improvement of failure-free survival (FFS) after ASCT, there was no difference in overall survival [6, 7].

An alternative approach is the R-DAEPOCH (dose adjusted rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) protocol [8], aimed at improving the effectiveness of treatment and minimizing side effects. This aims to modulate the dose of individual cytostatics in subsequent chemotherapy cycles depending on their pharmacodynamics and individual toxicity of treatment. However, the only randomized study failed to prove its superior efficacy over an R-CHOP regimen [9]. In a non-randomized setting, the R-DAEPOCH regimen, or early consolidation of first line therapy with ASCT, is supposedly better in DLBCL with 'double hit' and possibly also with double expression of c-myc and bcl-2 or bcl-6 oncoproteins [10]. The Polish Lymphoma Study Group also recommends more intensive (i.e. R-CHOP 14) therapy in PMBCL (primary mediastinal B cell lymphoma) patients.

Our understanding of the molecular complexity of DLBCL has evolved over the years. It was previously considered as a single disease, but gene expression profiling (GEP) analysis has identified three groups based on the cell of origin: an activated B-cell (ABC), a germinal center B-cell (GCB), and a third category termed indeterminate or unclassifiable (type 3), which accommodates cases that do not fit neatly into the other categories [11–13]. Each of these subtypes is subject to a distinct molecular mechanism and oncogenic signaling pathway, and may therefore differ in response to conventional treatment. Chronic, active B-cell antigen receptor signaling, constitutive myeloid differentiation primary response gene 88 (MYD88) signaling, and phosphatidylinositol-3-kinase/serine-threonine kinase (PI3K/Akt/mTOR) pathway, subsequent antiapoptotic nuclear factor-kappa B (NF-κB) pathway and interferon pathway activation, are characteristics of ABC DLBCL [12, 14, 15]. For the GCB subtype, BCL6 and EZH2 are most common [16].

The ABC subtype shows a much worse prognosis with R-CHOP [17, 18]: 10–20% of DLBCL patients will be resistant to first-line chemotherapy, and a further 30–40% will relapse after gaining complete remission [19]. Therefore, ABC DLBCL patients may be regarded as presenting an unmet medical need for a new, more efficient first line regimen. Dysregulation of the important oncogenic drivers of ABC DLBCL, such as IRAK4, BTK, MYD88, PI3K, and NF-κB, makes them a suitable potential target. Recent phase III studies exploring the role of adding new agents to an R-CHOP regimen have been negative and failed to meet their primary target.

One of the first examples of this strategy investigated the role of bortezomib, a pleotropic proteasome inhibitor inhibiting IκB degradation, which appeared to be a suitable candidate for blocking NF-κB. The PYRAMID study [10] and the ReMoDL-B trial [20] both interrogated the merits of bortezomib plus R-CHOP in ABC-DLBCL. Neither reached their primary endpoints.

The PHOENIX study was a phase III clinical trial investigating the role of ibrutinib, a BTKi (Bruton tyrosine kinase inhibitor) added to R-CHOP in patients with non-germinal center diffuse large B-cell lymphoma. In the final analysis, with a median follow-up of 34.8 months, there were no differences either in EFS or in OS [21, 22], and therefore the study was declared negative, having not reached its primary targets.

However, in a subgroup analysis of patients under the age of 60, significant (nearly 10%) improvements in EFS, PFS and OS in the experimental arm were demonstrated. This discrepancy was explained by increased toxicity of the combination in patients over 60, which resulted in a higher rate of treatment discontinuation and a lower dose intensity in the experimental group. The ESCALADE study is an ongoing protocol with acalabrutinib, a second generation BTKi, featuring non-GCB DLBCL patients under 65. This study will probably lead to approval of acalabrutinib in this indication, although it does not address the most important question. GEP-based subtypes are not unique clinical entities. BTKi should have been investigated in the MCD genetic subtype only which accounts for c.25% of ABC DLBCL cases and as much as 75% of patients with PCNSL (primary central nervous system lymphoma) [23]. The MCD subtype has a particularly bad prognosis, and involves MYD88 and CD79B mutation both prone to BTKi [11].

Molecularly targeted drugs may address only very well and adequately characterized disease subtypes. Immunotherapy, and in particular immunomodulating agents and monoclonal antibodies, may be useful in a broader context. ROBUST [24, 25] was a multicenter, international, randomized, double-blind, placebo-controlled, phase III protocol run in 257 global sites assessing R-CHOP with lenalidomide (R2-CHOP) versus R-CHOP in ABC subtype DLBCL [26]. Although ROBUST did not meet the primary or secondary PFS endpoints for R2-CHOP, it had certain promising conclusions: positive trends for PFS favoring R2-CHOP were observed in patients with higher risk IPI ≥3 and the safety profile of R2-CHOP was consistent with that previously observed. It was disappointing that the study did not confirm the previous phase II results from the Mayo Clinic. Comparing the two studies, one should note that results of the R2-CHOP arm were comparable, while R-CHOP results were significantly better in a phase III study. It appears that in

a multicenter setting, fewer high risk cases were included, and that the average time from diagnosis to therapy initiation was prolonged.

The currently recruiting FIRST-MIND study is evaluating tafasitamab, a humanized anti-CD19 monoclonal antibody with a modified constant region (Fc) that increases Fc-γ receptor binding affinity or the addition of tafasitamab to lenalidomide in addition to R-CHOP in intermediate and high-risk DLBCL [27, 28]. Under this protocol, it is mandatory to initiate treatment within four weeks of diagnosis, to increase the number of high-risk patients and better reflect real life settings. Tafasitamab in combination with lenalidomide in relapsed or refractory DLBCL patients showed an overall response rate of 54% and complete remission rate of 32%, with median progression-free survival of 16.2 months [29].

In other investigated first-line treatment regimens, the role of new monoclonal antibodies such as obinutuzumab, brentuximab vedotin, polatuzumab vedotin and bispecific antibodies have been assessed.

The GOYA study comparing G-CHOP to R-CHOP used obinutuzumab, a second generation anti-CD20 monoclonal antibody, instead of rituximab. The results showed a comparable safety profile, but did not significantly improve investigator-assessed PFS compared to R-CHOP in these patients [30].

Early phase II results of brentuximab vedotin, an anti-CD30 monoclonal antibody linked to monomethyl auristatin E (MMAE), a microtubule disrupting agent, have been encouraging. An acceptable safety profile and high efficacy (CR with an estimated annual PFS of 82%) was demonstrated in a subgroup of DLBCL patients with CD30 antigen on the surface of neoplastic cells [31, 32].

Even more exciting have been consistent polatuzumab vedotin (pola) results. This is an anti-CD79b antibody-drug conjugate with MMAE. This compound is approved in relapsing/refractory DLBCL, after a phase II randomized study comparing bendamustine +rituximab +pola (BR-Pola) with a BR regimen. The response rate was 70% (BR-Pola) versus 33% (BR) [33], and median PFS and median OS were significantly prolonged. In a phase I study, setting an optimal dose of polatuzumab vedotin in combination with R-CHOP, an acceptable safety profile in previously untreated DLBCL patients was demonstrated [34]. Of the 10 DLBCL patients enrolled, seven had an end-of-treatment response: five CRs, one partial response (PR), and one data unavailable [35]. This regimen was properly explored in the Polarix study, a randomized, placebo-controlled, double-blind phase III trial in newly diagnosed DLBCL patients with IPI ≥2, comparing R-CHOP to Pola R-CHP (polatuzumab vedotin, rituximab, cyclophosphamide, vincristine, prednisone) [36]. A similar study (POLAR BEAR) is being conducted in elderly patients subjected to an R-mini CHOP regimen with reduced doses of cytostatics. Preliminary results will be published in 2022 [37].

So far, little is known about bispecific antibodies (BIABs), which may represent the future. They are antibodies that can bind to two different antigens at the same time. They 'combine' the target (tumor cell) and the effector cell of the immune system (lymphocyte or macrophage), promoting the destruction of the target cell. Blinatumomab is the first CD19/CD3 bispecific T-cell engager antibody construct approved for the treatment of refractory Philadelphia chromosome-negative acute B-lymphoblastic leukemia. However, the development of all other BIABs directed against CD19 has been halted, due to neurotoxicity adverse events [38].

In their place, we have anti-CD20/anti-CD3 BIABs: mosunetuzumab, odrenextamab, epcoritamab and glofitamab, to name only the compounds most advanced in their development. They all lead to durable responses in patients with B-cell NHL, who otherwise have limited options, even those relapsing or refractory to chimeric antigen receptor (CAR) T-cell therapy [39]. Their favorable toxicity profile allows them to be used in elderly patients with comorbidities, as demonstrated in the recent report summarizing the results of a first line chemotherapy-free regimen [40]. Their potential role in PR consolidation, or as an additional compound added to Pola-R-CHOP, is currently being investigated in multicenter randomized studies.

Numerous attempts have been made to improve the first-line treatment of DLBCL patients. Using new compounds, adding to or replacing an R-CHOP regimen, is probably more effective than escalating the dose or intensity of classical chemotherapy. Molecularly targeted drugs such as BTKi have proved to be effective in very well characterized genetic subsets of patients which cannot be identified by the routine histopathological methods used in 2021. In this respect, the ABC DLBCL subtype describes patients with an adverse prognosis, but cannot be used to select patients for targeted therapies. Immunotherapy may be effective in less accurately defined genetic subtypes, but its mechanism of action may be compromised by intensive chemotherapy regimens. Obinutuzumab is evidently a 'better' monoclonal antibody than rituximab, but CHOP abrogated its efficacy, as demonstrated in the GOYA study [30]. We are still exploring the role of lenalidomide added to a (modified) R-CHOP regimen, but the most fascinating results in DLBCL so far were achieved in the L-MIND protocol, where it was combined only with the monoclonal antibody tafasitamab.

Our patients with DLBCL still await solutions to improve their outcome. The failure of several phase III studies has proved that this is the only way to verify the new protocols. Although ASCT consolidation is widely used in high-risk DLBCL patients, none of the randomized studies has confirmed its efficacy. Furthermore, this idea is no longer being explored in any ongoing clinical trial.

Author'scontributions

Equal contribution in design of the article and preparing manuscript.

Conflict of interest

None.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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