HAEMA 2023; **14**(1-4):34-38

Review Article

Post ASH 2022: High-grade B-cell Lymphomas, what's new?

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ABSTRACT:

Diffuse large B-cell lymphoma (DLBCL) is the most frequent subtype of lymphoid malignancy and still remains a significant clinical challenge. However, remarkable progress has been made over the last years with the emergence of novel therapeutic agents and the development of accurate prognostic tools. Some of them were presented in the 65th annual meeting of the American Society of Hematology (ASH) and may be incorporated in clinical practice. Among the most interesting developments are measurement of circulating tumor DNA (ctDNA) as a prognostic factor, early-phase clinical trials evaluating epcoritamab-R-CHOP, glofitamab-R-CHOP and mosunetuzumab monotherapy in frontline therapy and the use of liso-cel or new bispecific monoclonal antibodies in relapsed/refractory disease. This review aims to describe the most significant findings and critically comment on their possible application to clinical practice.

KEY WORDS: *DLBCL, ctDNA, prognosis, frontline treatment, bispecific antibodies, CAR T-cell therapies*

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is usually treated with Rituximab-based chemoimmunotherapy (CI) with curative intention at initial diagnosis. Over the last years, multiple clinical trials and analyses have been carried out and resulted in new therapeutic options both in the first-line setting with the addition of polatuzumab vedotin in the CI and in relapsed/refractory (R/R) disease with the advent of bispecific monoclonal antibodies, chimeric antigen receptor-T (CAR-T) cell therapy and new therapeutic combinations. Furthermore, ongoing research on the molecular background of DLBCL has led to more accurate prognostic and predictive markers that could guide the clinicians towards the best therapeutic strategy. Several abstracts that were presented in the latest 65thannual meeting of the American Society of Hematology (ASH) proposed new therapeutic approaches and assessment tools for a more effective management of DLBCL patients. This review summarizes the most innovative studies concerning prognostic markers and therapeutics in DLBCL.

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Received 21 Sep 2023; Accepted 20 Oct 2023

Developing prognostic factors in first-line therapy

Prognostication in DLBCL is based on clinical examination, basic laboratory and imaging studies, such as contrast-enhanced computer tomography (CT). Three scoring systems are widely used: the International Prognostic Index (IPI), revised IPI (R-IPI), and National Comprehensive Cancer Network IPI (NCCN-IPI), with NCCN-IPI providing the most accurate information compared to IPI and R-IPI.[1] This is also confirmed in a presentation of Sibon, *et al*. at ASH 2022 regarding primary mediastinal large B-cell lymphomas (PMLBCL). In this pooled analysis NCCN-IPI had the best prognostic value over IPI and age adjusted IPI (aaIPI) with progression free survival (PFS) 82% (low + low-intermediate) vs 67% (high

intermediate + high, p=0.01), and 4-year overall survival (OS) 86% vs 78% (p=0.05).[2]

However, integrating molecular features of the tumor into the prognostic scores becomes a need, as the genetic and epigenetic landscape of the disease becomes more understandable. Cell of origin plays a significant prognostic role: multiple studies have shown that patients with the activated B-cell (ABC) disease subtype have significantly poorer outcomes to standard up-front rituximab-containing CI compared to germinal center B-cell (GCB) disease. Regarding the molecular features, the presence of *MYC* rearrangements is associated with a poorer response to up-front R-CHOP. Also, the co-occurrence of either a BCL2 or BCL6 rearrangement in double hit and triple hit lymphomas leads to a poor response to up-front R-CHOP.[3]

Circulating tumor DNA (ctDNA) is a sensitive prognostic factor whose predictive value is already tested in many solid tumors. ctDNA was also recently assessed in patients with R/R DLBCL and it can probably identify patients at high risk of progression.[4] In a prespecified exploratory analysis of the prognostic value of ctDNA in the POLARIX study, Herrera, *et al.* measured plasma ctDNA levels in mutant molecules per mL (MMPM) in patients that received R-CHOP or Pola-R-CHP and a log-fold change of MMPM at Cycle2 day1 (C2D1) vs baseline was used for risk stratification. It was observed that patients having high baseline MMPM, had more probably worse IPI, ABC cell type, ECOG PS>1 and bulky disease (p<0.001). Moreover, patients in both arms that had higher than the median baseline ctDNA levels, presented lower PFS (Pola-R-CHP: HR, 1.96 [1.21–3.18]; R-CHOP: HR, 1.43 [0.92–2.20]) and lower OS (Pola-R-CHP: HR, 2.17 [1.07–4.37]; RCHOP: HR, 2.10 [1.05–4.21]). Comparing ctDNA levels at baseline and after 1 cycle of R-CHOP or Pola-R-CHP they observed that patients who had a ctDNA log fold change (LFC) < 2.5 at C2D1 had a worse outcome concerning PFS and OS (LFC <2.5 vs LFC >2.5, PFS HR 2.89 [1.78–4.69], 24-month PFS estimates 65.7% [58.3–74.0] vs 87.0% [82.0–92.2]; OS HR 1.87 [0.98–3.58], 24-month OS estimates 86.2% [80.8–92.0] vs 91.8% [87.7–96.0]). Also in Pola-R-CHP arm, patients with cleared ctDNA had a better outcome (not cleared vs cleared, PFS HR 2.98 [1.53–5.80]; OS HR 2.74 [1.07–7.02]).[5]

High prognostic value of ctDNA was also confirmed in Roschewski's, *et al.* presentation, where minimal residual disease (MRD) detection via ctDNA was compared to radiographic response and ultimate outcomes such as PFS. One hundred nine patients were genotyped from plasma or tumor tissue, with blood specimens for 80 patients at pretreatment, 52 at C2D1, 53 at C3D1, 12 at C4D1, and 93 at EOT. Clearance of ctDNA after any of the first three cycles of treatment was strongly prognostic factor for PFS (log-rank p=0.0003, Cox HR=15.9). The ultrasensitive detection using PhasED-seq achieved higher sensitivity than PET/CT at EOT. Compared to PET/CT, ctDNA measurement via PhasED-seq achieved higher sensitivity for identifying PFS events (100% vs 50%, p=0.008) with the same specificity (91%).[6] Taking the above into consideration, ctDNA may complement the prognostic role of interim PET to identify low- and high-risk patients during the course of treatment and help clinical decisions. Moreover, thanks to its prognostic value for ultimate outcomes such as PFS, ctDNA can be used efficiently as a surrogate endpoint after DLBCL therapy. However, there are still challenges for clinical utility, such as low sensitivity due to plenty of distinct mutations that have to be recognized, ctDNA's short half-life and high cost.[7]

The role of novel agents in first-line treatment

Over the last decades, R-CHOP remains the backbone of first-line treatment for DLBCL, as between 50% and 60% of all patients with DLBCL are cured with rituximab-based CI.[8] However there is still space for new treatment options. The addition of newer agents to the familiar to physicians R-CHOP regimen may give better results concerning disease free survival (DFS) and OS. An update from REMoDL-B trial, an open label randomized phase 3 trial where R-CHOP + bortezomib (RB-CHOP) was compared to R-CHOP, was presented at ASH 2022. Although the primary analysis found no overall difference in PFS and OS by treatment arm at a median follow-up of 30 months, results from a retrospective analysis after a 5-year follow-up showed improved PFS and OS in ABC lymphomas after RB-CHOP: 5-year PFS of 54% with R-CHOP vs 69% with RB-CHOP (HR, 0.65; 95% CI, 0.43 to 0.98) and 5-year OS 67% with R-CHOP versus 80% with RB-CHOP (HR, 0.58; 95% CI, 0.35 to 0.95; P = .032). Five-year PFS was also higher in molecular high-grade (MHG) lymphomas: 29% versus 55% (HR, 0.46; 95% CI, 0.26 to 0.84). In conclusion, the addition of bortezomib to R-CHOP may be beneficial for patients with ABC and MHG DLBCL in initial therapy. Results of this analysis were also published in the clinical trial updates section of Journal of Clinical Oncology in May 2023.[9]

Bispecific monoclonal antibodies have been successfully introduced into the management of R/R B-cell lymphomas, including DLBCL. In the near future, these novel agents may play a role in first-line therapy as well. Glofitamab, a CD3 X CD20 bispecific monoclonal antibody possessing a novel 2:1 structure with bivalency for CD20 on B cells was proved to be efficient and is FDA and recently EMA approved for R/R DLBCL patients. Apart from heavily pretreated patients, glofitamab was also tested as first-line therapy in combination with R-CHOP

in previously untreated DLBCL patients and preliminary results were presented at ASH 2022. This phase Ib study included 56 patients with DLBCL stage III/IV and median IPI 3 and ORR 93,5% and CR 76,1% were reached. It is worth mentioning that no serious event of cytokine release syndrome (CRS grade 3-5) was observed, but neutropenia was present (48,2%) and neurologic events (39,3%) that were not related to ICANS.[10]

Although R-CHOP is considered as efficient and safe for most of DLBCL patients, a significant proportion of patients are not eligible for anthracycline therapy due to cardiac comorbidities. Furthermore, although new therapeutic agents are being developed for DLBCL patients, many of them are not available for the elderly and patients with comorbidities, since this population is less included in clinical trials. Mosunetuzumab, a CD20 X CD3 bispecific monoclonal antibody, has been tested in a phase I/II clinical trial in those patients and results 1 year after the end of treatment were presented in ASH 2022 by Topp, *et al.* In this trial, 54 patients participated with a median age of 83 years and an IPI ≥2 in 81% of the patients. Patients received a median of 8 cycles of mosunetuzumab monotherapy and responses following the end of treatment were ORR 43% and CR 35%, with a median duration of CR 15,8 months. The 12-month PFS was 39% and main adverse events included neutropenia (15%) and CRS grade 1-2 (26%).Taking the above into consideration, mosunetuzumab may be a therapeutic option for the elderly and for patients with comorbidities having newly diagnosed DLBCL.[11]

Patients with primary central nervous system lymphoma (PCNSL) eligible for intensive treatment approaches are currently treated with high-dose methotrexate (HD-MTX) based induction immune-chemotherapy followed by consolidative high-dose chemotherapy and ASCT (HDC-ASCT) .The efficacy of the MATRix regimen followed by ASCT has been proved in IELSG32 trial on May 2022.[12] Results of MATRix/IELSG43 trial were presented by Illerhaus *et al.*, where 260 fit patients with newly diagnosed PCNSL received induction therapy with 4 cycles of MATRix and then were allocated to either R-DeVIC or HDC-ASCT. There was a difference in PFS and OS between the two arms: 79% (95% CI 71-86%) after HDC-ASCT and 53% (95% CI 43-62%) after R-DeVIC (HR 0.42; p=0.0003). The 3-year OS was 86% (95% CI 78-91%) for HDC-ASCT arm and 71% (95% CI 61-78%) for R-DeVIC arm (HR 0.47; p=0.01), without any difference on neurocognitive functions between arms. This phase III trial confirms HDC-ASCT as the standard consolidation therapy for fit PCNSL patients.[13]

Progress has also been made in the treatment of PMLBCL. A pooled analysis of 5 prospective clinical trials was presented at ASH 2022 by Sibon, *et al.* regarding a comparison among R-CHOP21, R-CHOP14 and R-ACVBP. 290 patients with a median age of 35 years, having received one of the above regimens were evaluated after a median follow up of 42 months. PFS and OS of the 290 pts were 80% and 85%, respectively. For patients treated with R-CHOP21, R-CHOP14 and R-ACVBP, 4-y PFS was 64%, 78% and 86% (p=0.004), and 4-y OS was 73%, 89% and 88% (p=0.031), respectively. In multivariate analysis including NCCN-IPI and treatment, both factors remained independently prognostic for PFS and OS. Permanent treatment discontinuation for toxicity occurred in 5 patients (all in R-ACVBP group).Taking into consideration both efficacy and safety of each regimen, the authors concluded that R-CHOP14 without RT may be the preferred choice as first-line treatment for younger patients with PMBCL.[2] However, the issue of superiority of R-CHOP14 versus R-CHOP21 remains unclear[14-15], while more intensive CI regimens such as R-da-EPOCH without RT seem more effective in controlling the disease.[16-17] Therefore, further, prospective randomized trials are warranted to clarify the best frontline treatment for patients with PMLBCL.

Recent advances in R/R disease

CD19 chimeric antigen receptor (CAR) T-cell therapy represents a breakthrough for patients with R/R DLBCL, inducing sustained remissions, with the main representatives being axicabtagene ciloleucel and tisagenlecleucel. In phase III TRANSFORM study, administration of lisocabtagenemaraleucel (liso-cel), an autologous CD19-directed CAR-T product, demonstrated superior efficacy over standard-of-care (SOC) with salvage chemotherapy followed by ASCT. Patients in the liso-cel arm underwent lymphodepletion with fludarabine/cyclophosphamide followed by liso-cel at a target dose of 100 x10^6 CAR T cells. Median (95% CI) EFS was not reached (NR; 9.5–NR) for liso-cel arm versus 2.4 months (2.2–4.9) for SOC arm. CR rate and PFS met statistical significance; CR rate was 74% for liso-cel arm versus 43% for SOC arm ($p < 0.0001$) and median PFS (95% CI) was NR (12.6–NR) for liso-cel arm versus 6.2 months (4.3–8.6) for SOC arm (HR, 0.400; $p< 0.0001$). These data reinforce liso-cel as a second-line treatment in patients with primary refractory or early relapsed DLBCL, and more data are awaited from TRANSFORM trial.[18]

In recent years, treatment with bispecific monoclonal antibodies has been just as rising as CAR-T cell therapy. Huchings, *et al.* presented data of 61 patients with R/R DLBCL who were in CR after the end of treatment (EOT) with glofitamab and had received ≥3 previous lines of therapy. The median duration of CR follow-up was 18.1 months. From 53 patients who had reached 6 months

follow-up post-EOT; the majority of patients with a CR at EOT (45/61; 74%) remained in CR, 1/61 (2%) had experienced progressive disease (PD), and 8/61 (13%) remained in follow-up but had not yet reached 6 months. At 12 months post-EOT, 34/61 (56%) patients remained in CR, 1/61 (2%) had experienced PD, and 17/61 (28%) remained in follow-up but had not yet reached 12 months. Only one patient experienced PD between 12 and 18 months post-EOT. The median duration of CR had not been reached. Glofitamab therefore appears to achieve deep remission in these patients, even after multiple lines of treatment.[19]

Another CD20XCD3 bispecific monoclonal antibody, odronextamab, has given encouraging results regarding its clinical activity and safety in R/R follicular lymphoma and R/R DLBCL patients who have relapsed following CAR-T cell therapy in ELM-1 trial.[16] Results from the final analysis of the R/R DLBCL cohort from ELM-2 trial were presented in ASH 2022. In ELM-2 trial, 141 R/R DLBCL patients with a median of 2 prior lines of therapy, received odronextamab and achieved ORR and CR 52% (66/127) and 31% (39/127) respectively with durable response, having a median duration of CR at 17.9 months (95% CI: 9.2–NE). The most common adverse events were low grade CRS (53%) which resolved with tocilizumab and supportive treatment, pyrexia (41%), and anemia (34%). The above findings make odronextamab a promising option for the management of R/R DLBCL patients.[21]

CONCLUSION

The latest ASH meeting, though presented clinical trials and studies, shed light to new aspects of prognostication and therapeutics that will soon have an impact on clinical practice. Novel molecular prognostic methods are gaining ground in initial and interim risk assessment of DLBCL patients. Bispecific monoclonal antibodies have already proved their efficacy on R/R disease and the potential for their use in frontline therapy as monotherapy or in combination with R-CHOP is being evaluated. As for R/R DLBCL, CAR-T cell therapy remains a promising treatment with potential to achieve durable remission and an increasingly well-known safety profile. However, more studies are necessary to fulfill the unmet needs of bridging therapy for the R/R patients in order to reach CAR-T cell therapy. Finally, more frontline options for the elderly patients are needed.

Conflict of Interest: None

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