BHS guidelines on the management of relapsed and refractory diffuse large B-cell lymphoma: Part 1

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On behalf of the BHS Lymphoproliferative Disease Committee

SUMMARY

Approximately 30-40% of patients with diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS), will relapse or are unable to obtain a complete remission (CR) after frontline treatment. These patients have a poor prognosis and represent a therapeutic challenge. In this article, we reviewed the recent literature to update the practice guidelines of the Belgian Hematology Society (BHS) Lymphoproliferative Disease Committee for the treatment of relapsed or refractory (R/R) DLBCL. In the first part, we will focus on first relapse and the role of CAR T-cell therapy in first and second relapse. In the second part, we will focus on novel treatment options for patients with a second or higher relapse, secondary central nervous system (CNS) relapse and high-grade lymphoma.

(BELG J HEMATOL 2023;14(3):114-21)

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is an aggressive type of B-cell non-Hodgkin's lymphoma (NHL) and represents 30-40% of all non-Hodgkin's lymphomas.[1] DLBCL belongs to the family of large B-cell lymphoma (LBCL) of which DLBCL, not otherwise specified (NOS) is the most represented entity.[2] After first line therapy with chemo-immunotherapy R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), 60-70% of patients will be cured. However, approximately 30-40% of patients with DLBCL will relapse or are unable to obtain a complete remission (CR). These patients have a poor prognosis and represent a therapeutic challenge.[3-5] In particular, patients with primary refractory disease (i.e. an incomplete response or relapse within six months after treatment) have a dismal prognosis with a median overall survival (OS) of only six months. Here, we present the practice guidelines of the Belgian Hematological Society (BHS) Lymphoproliferative Disease Committee for the management of relapsed and refractory (R/R) DLBCL.

FIRST RELAPSE

Despite adequate first line treatment with R-CHOP, 10-15% of the patients will have primary refractory disease and another 20-25% will relapse after initial response, typically in the first two years.[3] This number is higher in the elderly. In patients with a suspected relapse, the diagnosis should be confirmed with a new biopsy and

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Key words: diffuse large B-cell lymphoma, guidelines, refractory/relapsed.

staging should be repeated with the same examinations as the initial work-up. A possible central nervous system (CNS) relapse should also be considered when there are neurological symptoms present.[3,5-7]

ELIGIBLE FOR STEM CELL TRANSPLANTATION (SCT)

For patients under the age of 65-70 years and without major comorbidities high dose chemotherapy followed by autologous stem cell transplantation (ASCT) is currently the standard of care. However, inclusion into clinical trials should strongly be considered as only half of the ASCT-eligible patients in the R/R setting will benefit of high dose chemotherapy.

Commonly used exclusion criteria for ASCT include advanced age (above 70-75 years), comorbidities such as severe pulmonary impairment or left ventricular dysfunction and inadequate social support to assist in aftercare. The Sorror Index is a prognostic tool that can be used to calculate the risk for mortality after transplantation, even if this assessment was initially described for allogeneic SCT.[8] Salvage chemoimmunotherapy is used for cytoreduction and to assess chemotherapy sensitivity. The commonly used salvage regimens are platinum-based (R-DHAP (rituximab, dexamethasone, cytarabine and cisplatin), R-ICE (rituximab, ifosfamide, carboplatin and etoposide), R-GDP (rituximab, gemcitabine, dexamethasone and cisplatin) or R-DHAOx (rituximab, dexamethasone, high-dose cytarabine and oxaliplatin). They have shown similar efficacy in randomised trials.[3-5,9] Vellenga *et al.* evaluated the role of rituximab during remission induction chemotherapy for R/R DLBCL. Before enrollment, all patients were required to have a histologic confirmation of CD20 positivity. Patients were randomised to DHAP-VIM (etoposide, ifosfamide, methotrexate)-DHAP with or without rituximab. After the second chemotherapy cycle, 75% of patients in the R-DHAP arm had responsive disease (CR or partial response (PR)) *vs.* 54% in the DHAP arm. With a median follow-up of 24 months, there was a significant difference in progression-free survival (PFS) (52% *vs.* 31%) in favour of the R-DHAP arm, illustrating the benefit of adding rituximab to chemotherapy.[10]

The randomised phase III CORAL trial included 396 R/R DLBCL and compared R-DHAP *vs.* R-ICE followed by ASCT in chemosensitive patients. Both salvage regimens resulted in a similar overall response rate (ORR) (63%) and CR rate (38%).[4,5,11] Long-term results showed no significant difference in event-free survival (EFS) (51% *vs.* 43%) and OS (34% *vs.* 26%) after four years in the R-DHAP compared to R-ICE arm.[12] However, R-DHAP resulted in more grade 3-4 hematologic and non-hematologic toxicities (including renal impairment).[7] The randomised phase III LY.12 trial included 619 patients with R/R aggressive lymphoma and compared the platinum-containing regimens R-DHAP and R-GDP followed by ASCT. The ORR after two cycles of R-DHAP or R-GDP was not significantly different (44% *vs.* 45%) and no differences were observed in EFS or OS.[4,13] Furthermore, GDP had a more favourable toxicity profile characterised by less febrile neutropenia, fewer platelet transfusions, lower hospitalisation rate compared to R-DHAP.[5,13,14]

Unfortunately, the severe adverse events (AEs) caused by cisplatin in these regimens may lead to dose reduction and dose delay compromising ASCT. Manconi *et al.* investigated a modified R-DHAP regimen including oxaliplatin instead of cisplatin (R-DHAOx). Oxaliplatin was designed to reduce the cisplatin-related toxicities, especially nephrotoxicity and mucositis. Fifty-three patients with R/R DLBCL were treated without any renal impairment. After two courses, the ORR was 60% (CR 49%). Twenty-two patients proceeded to stem cell collection and ASCT was performed in 21 of these patients. This trial suggest that R-DHAOx has a response rate comparable to cisplatin-containing regimens and improved toxicity profile.[15]

Tixier *et al.* retrospectively assessed the toxicity profiles in 276 patients with R/R Hodgkin and NHL lymphomas with platinum salts (cisplatin, carboplatin and oxaliplatin) plus DHA (dexamethasone, cytarabine). Renal failure was mainly reported in cisplatin regimens. Cisplatin was also associated with auditory toxicity. Neurotoxicity must be monitored with oxaliplatin.[16] However, it should also be added that a warning was published in 2018 concerning a possible relationship between oxaliplatin exposure before ASCT and a higher risk of sinusoidal obstruction syndrome.[17,18]

In conclusion, the choice of the platinum derived salvage regimen may depend on institutional preference and the adverse event profile.[3,5] In chemosensitive patients we recommend a consolidation with ASCT. Sensitivity encompasses CR, but also PR after two cycles. In the latter situation, proceeding to ASCT is still preferred, although CAR T therapy could be discussed at this point.[19] Approximately 40-50% of patients have an initial response to salvage therapy and will proceed to ASCT with an overall cure rate of 25-30% for all patients in the rituximab-era.[3-5] BEAM (carmustine, etoposide, cytarabine and melphalan) is the standard conditioning regimen for R/R DLBCL. The addition of rituximab to BEAM could be beneficial.[5] Following ASCT, two large, randomised trials failed to show benefit of rituximab maintenance therapy.[5,12,20]

Recommendation: For fit patients, eligible for ASCT, we recommend induction chemoimmunotherapy (three to four cycles of a platinum-based regimen) followed in chemosensitive patients by a BEAM-based autologous SCT as consolidation. If possible, inclusion in a clinical trial should be preferred.

NOT ELIGIBLE FOR ASCT

About half of the R/R patients are no longer candidates for ASCT due to poor performance status, advanced age or comorbidities. For this category of patients, single- or multi-agent chemoimmunotherapy with an acceptable safety profile has frequently been used with a palliative intent.[3,5] Inclusion into clinical trials for sufficiently well and willing patients should again be strongly encouraged.

A multi-agent regimen that has been used frequently is R-GemOx (rituximab, gemcitabine and oxaliplatin).[3,5,21] Several phase II trials have shown efficacy and a good safety profile in R/R DLBCL.[5,21,22] The largest multicentre phase II trial by Mounier *et al.* (n=49) showed an ORR of 46% (CR 38%) after eight cycles of R-GemOx.[5,21] The median duration of response (DoR) was ten months with a 5-year PFS and OS of 13% and 14%, respectively.[21] R-GemOx was well tolerated with low rates of febrile neutropenia (4% of all administered cycles), although 73% of patients developed grade ≥3 neutropenia. Ninety-two percent of patients experienced platelet toxicity (44% had at least one grade 3 episode). Oxaliplatin-induced neurotoxicity was the most common non-hematologic AE (grade ≥3 in 15% of patients).[21] These data were confirmed by a large retrospective analysis (n=192) showing a CR of 33%. The median PFS was five months and median OS was ten months. However, in patients obtaining CR the median PFS and OS were 22 and 40 months, respectively.[23]

Another well-tolerated salvage regimen with moderate activity is R-benda (rituximab, bendamustine 120 mg/m^2). The multicentre phase II study of Ohmachi *et al.* (n=63) assessed the efficacy and safety of six cycles in patients with R/R DLBCL who were unfit for ASCT. ORR and CR were 63% and 37%, respectively. Median PFS was 6,7 months. Toxicities were mostly hematologic (7% grade 3, 0% grade 4).[24] The trial of Vacirca *et al.* included 59 patients and administered six cycles of R-benda (bendamustine 90 mg/m^2 or 120 mg/m^2). ORR was 46%, but CR was only achieved in 15%. The median PFS was only 3,6 months.[25]

The antibody-drug conjugate polatuzumab vedotin (Pola) (a humanised anti-CD79b monoclonal antibody armed with mono-methyl auristatin E) also showed promising activity, both as single agent and in combination with R-benda.[4,5] Pola-R-benda demonstrated a median OS of 12,4 months compared with 4,7 months for patients receiving only R-benda. CR was 40% for patients treated with Pola-R-benda *versus* 18% for patients treated with R-benda.[26] Although DoR is quite short (9,5 months), this could be used as a bridge to further therapy, such as CAR T. However, the use of bendamustine before apheresis needs to be further assessed due to the risk of lymphodepletion.[27] This triplet has been FDA (Food and Drug Administration) and EMA (European Medicines Agency) approved as third line therapy but is not reimbursed in Belgium.[4,5]

Patients with R/R disease who are not suitable for transplantation and have localised disease may benefit from involved field radiotherapy, both for disease control and/or symptom palliation.[28,29]

Recommendation: For unfit, elderly patients that are transplant-ineligible we recommend treatment with six to eight cycles of R-GemOx at first relapse. If possible, inclusion in a clinical trial should be preferred.

ROLE OF CAR T AT FIRST RELAPSE

Cellular immunotherapy with autologous T-cells genetically engineered to express chimeric antigen receptors (CARs) or T-cell receptors (TCR), in order to redirect their cytotoxic specificity towards tumour cells, is a promising new treatment.[3-5,30] Currently, there are three anti-CD19 CAR T-cells used in the treatment for R/R DLBCL. Their general structure is similar in that all use the same single-chain variable fragment targeting CD19 and use CD3-zeta-chain for intracellular signalling. However, they use different combinations of transmembrane and costimulatory domains.[31]

Recently, three international phase III randomised trials investigated the use of CAR T for second line treatment in LBCL *vs.* ASCT, challenging the role of ASCT as standard of care (SOC) in second line.

The ZUMA-7 trial randomly assigned 180 patients with LBCL that were refractory to or had relapsed no more than twelve months after first line chemoimmunotherapy to receive axicabtagene ciloleucel (axi-cel, an autologous anti-CD19 CAR T) or SOC. SOC consisted of two or three cycles of chemoimmunotherapy, followed by high dose chemotherapy with ASCT in responding patients. The primary end-point was EFS. At a median follow-up of 25 months, the median EFS was significantly superior for axi-cel compared to SOC (8,3 months *vs.* 2,0 months). CR was achieved in 65% in the axi-cel group and 32% in the SOC group. The most reported AE of grade ≥3 was neutropenia (69% in the axi-cel group *vs.* 41% in the SOC group). Cytokine release syndrome (CRS) grade ≥3 occurred in 6% of the axi-cel group (92% any grade) and neurologic events

grade ≥3 occurred in 21% of the axi-cel group *vs.* 1% in SOC. Bridging was not allowed in ZUMA-7.

The ZUMA-7 trial concluded that axi-cel therapy led to significant improvements, in comparison with SOC, in EFS and response, with the expected levels of high-grade toxic effects. The trial showed that axi-cel could be an effective second line treatment for refractory high-grade lymphoma or relapsing within twelve months of therapy.[32]

The BELINDA trial randomly assigned 322 patients with high-grade lymphoma that was refractory to or progressing within twelve months after first line therapy to receive tisagenlecleucel (tisa-cel, an autologous anti-CD19 CAR T) or salvage chemotherapy followed by ASCT. The primary end-point was EFS.[35] Bridging therapy was allowed with the same regimens as from the SOC arm (R-DHAP, R-GDP or R-ICE). Unlike the ZUMA-7 trial, the BELINDA trial failed to show superiority of tisa-cel to SOC with EFS of three months in both groups.[33]

The third trial (TRANSFORM) included 184 patients with LBCL with primary refractory disease or progression within twelve months of first line therapy. Patients were randomly assigned to receive lisocabtagene maraleucel (liso-cel, an autologous anti-CD19 CAR T) or SOC (salvage chemotherapy with R-DHAP, R-ICE or R-GDP and ASCT). The primary end-point was EFS, which was significantly improved in the liso-cel group (10,1 months) compared with the SOC group (2,3 months). The most common grade ≥3 AEs were neutropenia (80% in the liso-cel group *vs.* 51% in the SOC group), anaemia (49% *vs.* 49%), thrombocytopenia (49% *vs.* 64%) and prolonged cytopenia (43% *vs.* 3%). Grade 3 CRS and neurological events occurred in 1% and 4% of patients in the liso-cel group, respectively. Bridging was also allowed with the same regimens as the SOC arm.[34]

Possible explanations for the different outcomes between ZUMA-7 and TRANSFORM (superiority of CAR T) *vs.* BELINDA (no superiority of CAR T) can be found in the different study design. Bridging with the same regimens of the SOC arm was allowed in BELINDA and TRANSFORM, but not in ZUMA-7. ZUMA-7 permitted corticosteroids for disease stabilisation. BELINDA and TRANSFORM allowed crossover from the SOC to the CAR T arm. Because bridging was not allowed in ZUMA-7, this may have introduced a selection bias in favour of patients with less aggressive biology. Real-world studies indicate that approximately 50% of patients will receive bridging therapy. The BELINDA trial failed to show superiority of CAR T, but it should be noted that the highest use of bridging chemotherapy (83%) was reported in BELINDA, indicating that patients included in this trial had high-risk disease.

Another difference between the three trials is how they defined their primary end-point, which was EFS. In addition to death and disease progression, all three trials included stable disease at different time points as events (day 150 in ZUMA-7, week 12 in BELINDA and week 9 in TRANSFORM). Initiation of new therapy was considered an event in ZUMA-7 and TRANSFORM, but not in BELINDA.[35]

In the phase II ALYCANTE study, 40 patients that were transplant ineligible received axi-cel as second line treatment in R/R LBCL. At three months, 92,5% of patients showed a CR and 67,5% a complete metabolic response on PET-CT with an excellent tolerance in this frailer population.[36]

Additional studies are needed to assess which patients may obtain the most benefit from each approach.[33] Currently, CD19-directed CAR T is not reimbursed at first relapse in Belgium, but EMA approved the extension of the reimbursement criteria for axi-cel for second-line treatment. This will be a game changer for patients relapsing less than twelve months after first line therapy, even for unfit patients that are considered ineligible for ASCT because of their age, for example.

SECOND OR HIGHER RELAPSE

Patients with disease resistant to primary and salvage chemoimmunotherapy or relapsing after transplantation have an extremely poor prognosis.[37] The SCHOLAR-1 study, an international multi-cohort retrospective NHL study, evaluated outcome of patients with R/R DLBCL. Relapse was defined as progressive or stable disease as best response at any point during chemotherapy (>4 cycles of first line or 2 cycles of later line therapy) or relapse ≤12 months from ASCT. Objective RR was 26% (CR 7%) to the next line of therapy and the median OS was 6,2 months. Twenty percent of patients were alive at two years.[38] Inclusion in a clinical trial is the preferred way to go, if possible.

Different approaches that could be considered for second or higher relapse patients are a recently CD19-directed CAR T-cell therapy, novel agents and a palliative approach.

CAR T

Three anti-CD19 CAR T-cell products have demonstrated efficacy after two relapses in DLBCL with a remarkably long response duration in patients who achieve CR.[31,35,39-43] Currently, axi-cel and tisa-cel are FDA and EMA approved, liso-cel is only FDA approved. Axi-cel and tisa-cel are also reimbursed in Belgium for the treatment of R/R DLBCL in adults after two or more lines of systemic chemoimmunotherapy.[3-5] Criteria for treatment with axi-cel or tisa-cel are

summarised in *Table 1*. In Belgium, reimbursement criteria between Yescarta (axi-cel) and Kymriah (tisa-cel) are slightly different: Yescarta is also reimbursed for primary mediastinal B-cell lymphoma (PMBCL), Epstein-barr virus positive DLBCL and high grade B-cell lymphoma (HGBCL), NOS or with *MYC/BCL6/BCL2* rearrangement, whereas Kymriah is not reimbursed for these criteria.

These three products have been associated with ORR and CR in the range of 52-82% and 40-54% respectively and long DoR (axi-cel 4-year OS 44%, liso-cel 2-year OS 50%, tisa-cel 36 months OS 84% for patients still in CR at six months).[3,39,41,43]

The ZUMA-1 trial, a multicentre phase II trial, included 111 patients with DLBCL, PMBCL or transformed follicular lymphoma (FL) who had refractory disease despite undergoing prior therapy. Patients received axi-cel after receiving a conditioning regimen of low-dose cyclophosphamide and fludarabine. At twelve months, ORR was 82% and CR was 54%. [37] The median follow-up of ZUMA-1 was 27 months. The estimated 2-year PFS was 72% among those with CR at three months, suggesting that achievement of CR at three months might be predictive of long-term response durability.[31] The most common AEs of any grade were pyrexia (85%), neutropenia (84%) and anaemia (66%). CRS occurred in 93% of patients with grade ≥3 in 13%; neurologic events occurred in 64%, 28% were grade ≥3, being the highest in comparison to other CAR T.[37] The long-term OS data showed that, with over four years of follow-up, median OS was 25,8 months and the 4-year OS was 44%. These results confirm that response is durable in patients reaching CR.[39]

The JULIET trial, an international phase II study of tisa-cel involved adult patients with R/R DLBCL who were ineligible for or had disease progression after ASCT. Ninety-three patients were infused with tisa-cel. The median follow-up was fourteen months. The best ORR was 52% and 40% had a CR. The relapse-free survival at twelve months was 65%. Among the 35 patients who were in remission at three months, the estimated probability of remaining in remission at twelve months was 81%, which again suggests that responses at three months are usually durable. The most common AEs of any grade were CRS (58% any grade, 22% grade ≥3), anaemia (48%), pyrexia (35%), neutropenia (34%), thrombopenia (33%) and diarrhea (32%). Neurologic events of any grade occurred in 21%; 12% were grade ≥3.[44]

In 2020, the results of the TRANSCEND study (evaluating the activity and safety of liso-cel) were published. The TRANSCEND trial is a multicentre study that enrolled adult patients with R/R DLBCL, double hit or triple hit lymphoma, PMBCL or FL grade 3B. Liso-cel was administered to 269 patients. Of 256 patients included in the efficacy-evaluable set, the ORR was 73% and CR 53%. The median DoR was not reached at median follow-up of twelve months. The most common grade ≥3 AEs were neutropenia (60%), anaemia (37%) and thrombocytopenia (27%). CRS and neurological events occurred in respectively 42% (grade ≥3 in 2%) and 30% (grade ≥3 in 10%) of patients.[45] Cross-trial comparisons of efficacy, toxicity and durability of these anti-CD19 CAR T-cell therapies are difficult because of differences in patient populations, baseline characteristics, conditioning regimen, follow-up times and methods.

TABLE 1. Inclusion criteria for treatment with axi-cel (Yescarta) and tisa-cel (Kymriah) according to current reimbursement in Belgium.

Treatment criteria for axi-cel (Yescarta) and tisa-cel (Kymriah)
Histological proven diagnosis of • DLBCL, NOS • DLBCL associated with inflammation • HHV8+ DLBCL • PMBCL (only axi-cel) • Transformed follicular lymphoma • HGBCL, NOS or with MYC/BCL2/BCL6 rearrangements (only axi-cel) • EBV+ DLBCL (only axi-cel)
Chemotherapy-refractory disease or relapse after at least two regimens of chemotherapy (including rituximab and anthracyclines)
ECOG PS 0-1
Preferably: • ANC >1000/µL and ALC>100-300/µL • No corticosteroids for at least 72 hours before apheresis • Adequate kidney (creatinine clearance >30 mL/min/1,73m²), liver, pulmonary and cardiac (LV EF> 40%) function
CNS involvement is a relative contra-indication and needs to be discussed patient per patient

NOS: not otherwise specified; HHV8: human herpes virus 8; PMBCL: primary mediastinal B-cell lymphoma; HGBCL: high-grade B-cell lymphoma, EBV: Epstein barr virus, ECOG: Eastern cooperative oncology group; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; CNS: central nervous system.

Due to differences in study design, the proportions of patients who eventually received CAR T-cell therapy relative to the number enrolled in the trial differed substantially between the three trials and could be relevant when considering the feasibility of therapeutic administration outside trial settings. Bridging chemotherapy after apheresis was allowed in both JULIET and TRANSCEND, which further confounds comparisons with ZUMA-1 and obscures the treatment effect of tisa-cel or liso-cel.[31]

The PILOT trial evaluated the activity and safety of liso-cel in R/R LBCL in patients not eligible for ASCT. Of the 61 patients receiving liso-cel, ORR was 80% (CR 54%). The Eastern Cooperative Oncology Group (ECOG) score of the patients receiving CAR T was ≤2. The trial concluded that liso-cel is a potential second line treatment for transplant-ineligible patients.[46]

Meanwhile, there are real-world data of patients treated with commercially available axi-cel. In the study of Nastoupil *et al.*, 298 underwent leukapheresis and 275 received axi-cel. One hundred and twenty-nine patients (43%) would not have met ZUMA-1 eligibility at the time of leukapheresis. Best ORR and CR rates were 82% and 64%, which is comparable to the ZUMA-1 trial. For the 275 patients that received axi-cel, 12-month PFS and OS estimates were 47% and 68%, respectively. The safety profile was also comparable with ZUMA-1.[47]

The real-world retrospective French DESCAR-T study analysed the outcome of 809 patients with R/R DLBCL after ≥ two previous lines of treatment who had a commercial CAR T-cell order for axi-cel or tisa-cel. The best ORR/CR was 80%/60% *vs.* 66%/42% for patients treated with axi-cel compared to tisa-cel, respectively. The 1-year PFS and 1-year OS were 47% and 64% for axi-cel compared to 33% and 49% for tisa-cel. Grade 1-2 CRS was significantly more frequent with axi-cel than with tisa-cel without significant differences for grade ≥3 CRS. However, ICANS was significantly more frequent with axi-cel than with tisa-cel (14% *vs.* 3% grade ≥3, respectively). This real-world matched comparison study concluded a higher efficacy but also a higher toxicity of axi-cel compared to tisa-cel in third or later line treatment for R/R DLBCL.[48]

Vercellino *et al.* tried to identify risk factors that may predict failure after CAR T. Characteristics of 116 patients were analysed. With a median follow-up of 8,2 months, 55 patients failed treatment. Twenty-seven (49%) were early progressors within the first month after infusion. The identified risk factors for early progression were ≥2 extranodal sites, increased CRP and high total metabolic tumour volume.[49]

Another important remark is that CAR T therapy is very expensive treatment due to costly production process.[50] CAR T therapy is feasible for sufficiently fit patients with a reasonably low rate of progressive disease as time is required to engineer the T-cells (approximatively four weeks). For patients for whom CAR T is not an option considering the age or the rapid progression of the disease, a palliative approach or a novel therapy can be chosen.

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