BHS guidelines on the management of relapsed and refractory diffuse large B-cell lymphoma: Part 2

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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.

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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. In the first part, we discussed the treatment options for patients with a first relapse. For patients with a second or later relapse, we already discussed treatment with CAR T-cell therapy. In this second part, we will go on with

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discussing novel treatment options for patients with a second or later relapse, the role of allogeneic stem cell transplantation, secondary central nervous system (CNS) relapse and high-grade lymphoma.

SECOND OR HIGHER RELAPSE

NOVEL TREATMENT OPTIONS

Here, we give a summary of the novel treatment options in R/R DLBCL. However, none are currently reimbursed in Belgium.

LENALIDOMIDE

Data emerging from early clinical trials demonstrated that lenalidomide has a moderate activity against R/R DLBCL either as monotherapy or in association with rituximab (R^2).[6] Lenalidomide is an immunomodulatory agent with pleiotropic anti-tumour activity with potential preferential activity in the ABC subtype of DLBCL.[5] In a phase II/III trial investigating lenalidomide 25 mg daily *versus* investigators choice (IC)(single agent gemcitabine, rituximab, etoposide or oxaliplatin) in 102 patients with R/R DLBCL, lenalidomide patients had a higher overall response rate (ORR) of 28% *versus* 12% in the IC arm.[5,7]

Zinzani *et al.* reported long-term results of a single-center phase II trial (n=23) on the combination of R^2 plus lenalidomide maintenance for eight months. The CR on completion of maintenance phase was 35%. Overall, median duration of response (DoR) of patients in CR was five years.[6]

TAFASITAMAB

Tafasitamab is an Fc-enhanced, humanised, anti-CD19 monoclonal antibody that has shown limited single-agent activity in patients with R/R B-cell lymphoma.[4,8,9] In the ongoing MOR208C201 phase IIa study (n=92) patients received tafasitamab 12 mg/kg intravenously (IV) as monotherapy. The ORR in DLBCL patients was 26%. At median follow-up of 21 months, median progression free survival (PFS) was 2,7 months in DLBCL patients.[8-10] Adverse events (AEs) were mild.[8,10]

However, when combined with lenalidomide, tafasitamab shows promising potential in DLBCL. L-MIND is an open-label, single-arm, phase II clinical trial of tafasitamab plus lenalidomide in R/R DLBCL who were ineligible for high-dose chemotherapy with autologous stem cell transplantation (ASCT).[4,9,11] Patients received IV tafasitamab (12 mg/kg) and oral lenalidomide (25 mg/day) for up to twelve cycles (28 days each), followed by tafasitamab monotherapy until disease progression. Of the 80 patients who received the dual therapy, 43% experienced CR and 18% partial responses. Furthermore, these responses were durable with a median DoR of 21,7 months.[4,9,11] The most common AEs of grade ≥3 were neutropenia (48%), thrombocytopenia (17%) and febrile neutropenia (12%).[11]

These results were confirmed in the RE-MIND study, where the data from L-MIND were compared to a real-world retrospective cohort of lenalidomide monotherapy in R/R DLBCL. [4,9,12] ORR was significantly improved with combination therapy (67%) *versus* lenalidomide monotherapy (34%). CR rates were 40% and 13%, respectively. PFS and OS were also significantly improved with combination therapy (PFS 12,1 months *vs.* 4 months; median OS not yet reached *vs.* 9,4 months). In conclusion, RE-MIND demonstrated significantly improved outcomes with the tafasitamab-lenalidomide combination compared with lenalidomide monotherapy.[9,12]

Although this combination is not reimbursed at the moment in Belgium, a medical need program is now open and patients can be enrolled.

IBRUTINIB

The BTK-inhibitor, ibrutinib, has shown preferential efficacy in the ABC subtype of DLBCL.[5,13] In a phase I/II clinical trial involving 80 patients with R/R DLBCL, ibrutinib (560 mg orally once daily) produced complete or partial responses in 37% of those with ABC DLBCL, but in only 5% of patients with GCB DLBCL. Median DoR was 4,8 months in ABC DLBCL.[13]

A phase Ib/II study of the LYSA group evaluated the safety of ibrutinib in combination with R-DHAP or R-DHAOx. The combination was too toxic (R-DHAP more than R-DHAOx).[14]

A phase II study of ibrutinib R^2 was conducted in 89 R/R non-GCB DLBCL patients and showed an ORR of 47% including 28% in CR. OS was 44% at eighteen months.[15]

Ibrutinib is being further explored in various combinations.[3,5]

SELINEXOR

Selinexor is an oral selective inhibitor of XPO1-mediated nuclear export and has a broad potential mechanism of action.[4,16] In DLBCL, XPO1 is overexpressed and this correlates with poor prognosis.[16] The multicentre, open-label, phase IIb SADAL study included 127 patients who received selinexor orally at a fixed dose of 60 mg on day 1 and day 3 weekly until disease progression or unacceptable toxicity. The ORR was 28% and the CR rate was 12%. The median DoR was 23 months for patients in CR. In conclusion, selinexor induced durable response in a small group of patients and had a manageable safety profile.[4,16]

VENETOCLAX

A phase I trial of the bcl2-inhibitor venetoclax in 106 patients with R/R NHL showed a limited ORR of 18% in patients with DLBCL.[5,17] Venetoclax is being explored in various combinations.[3,5]

CHECKPOINT-INHIBITORS

The programmed death-1 (PD-1) pathway is an immune checkpoint to attenuate T-cell mediated immune responses and may be exploited by tumours to avoid immune surveillance.[18] Immune checkpoint blockade with the anti-PD1 monoclonal antibody nivolumab demonstrated only modest activity in R/R DLBCL in a phase Ib study, including eleven patients with DLBCL. ORR was 36% among patients with DLBCL, but responses were not durable.[4,5,18] The safety profile was feasible and immune-mediated AEs occurred in 34% of patients.[18]

BISPECIFIC ANTIBODIES

Blinatumomab is a CD3/CD19 bispecific T-cell engaging antibody construct (BiTE) that simultaneously binds CD3+ T-cells and CD19+ lymphoma cells, bringing them into proximity of each other. This leads to T-cell activation and lymphoma cell lysis. In a phase II trial, including 25 patients with DLBCL, blinatumomab monotherapy induced responses in 43% of the 21 evaluable patients and the CR rate was 19%. The median DoR was 11,6 months.[19] Despite the promising results, the development of blinatumomab for DLBCL was halted because of the high rate of serious neurological complications. However, improvements in bispecific antibody engineering have led to the development of fully human or humanised monoclonal antibodies, which have increased half-life and decreased side effects. Several new bispecific antibodies targeting CD20 and CD3 have shown promising results in the treatment of B-cell NHL, like odronextamab, mosunetuzumab, glofitamab and epcoritamab.[20]

Odronextamab is a fully human IgG4-based bispecific antibody. In the phase II study of Bannerji *et al.* 71 patients with DLBCL were treated with step-up doses in week one and week two, followed by a weekly dose of 160 mg from week three to twelve and 320 mg every two weeks from week fourteen onwards. Step-up dosing was used to reduce cytokine release syndrome (CRS) and neurotoxicity. CRS grade ≥3 occurred in 7%. In patients who had not received prior CAR T therapy and were treated at doses ≥80 mg (10 patients), ORR and CR were 60%. Median DoR was 10,3 months. The median duration of CR (DoCR) was 9,5 months and follow-up is still ongoing. In DLBCL patients refractory to prior CAR T therapy and treated at doses ≥80 mg (21 patients), ORR was 33% and CR rate was 24%. Median DoR was 2,8 months. Median DoCR was 4,4 months with ongoing follow-up.[20,21]

Mosunetuzumab is a fully humanised IgG1 bispecific antibody. Mosunetuzumab in a subcutaneous (SC) formulation, which is an approach to minimise CRS, has promising results in a phase I/Ib trial in R/R B-NHL. Twenty-three patients (fifteen patients had an aggressive NHL of which ten patients had DLBCL) received mosunetuzumab SC on day one of each 21-day cycle. All CRS events occurred during the first cycle and were grade 1 (26%) or grade 2 (9%). Among the 22 efficacy-evaluable patients, ORR was 60% and CR rate was 20% in aggressive NHL patients. After a median of 6,9 months, all but one patient remained in CR. There is also an IV alternative with a dose escalation.[20,22]

Glofitamab showed high responses in a phase I dose-escalation and expansion study for 171 patients with DLBCL. A single dose of obinutuzumab was given one week prior to treatment with IV glofitamab to reduce the risk of CRS. CRS was the most common AE and was observed in 50% of all patients with grade ≥3 in 4% of patients. In the phase II part of the study, CR was reached in 25%. Results were consistent among the 52 patients who had previously received CAR T. After a median follow-up of 12.6 months, the estimated twelve months PFS was 37%. The majority (78%) of CR were ongoing at twelve months.[20,23,24]

Epcoritamab is administered SC, leading to a gradual increase in drug levels and lower peak in plasma cytokine levels. A phase I/II dose-escalation study included 45 patients with DLBCL. Epcoritamab was well tolerated. CRS grade 1 or 2 were observed in 58% of patients; there were no grade ≥3 events. In eighteen patients with DLBCL receiving epcoritamab ≥12 mg, ORR was 67% and CR was 33% with a median follow-up of 8,3 months in DLBCL patients.[20,25] In the dose-expansion cohort (n=157), the ORR was 63%, and CR was 39%. At a median follow-up of 10,7 months, the median DoR was twelve months (not reached among complete responders).[26]

Although, none of these bispecific antibodies is currently reimbursed in Belgium.

The advantage of bispecific antibodies, in comparison to CAR T, is the availability for immediate treatment, circumventing the need for apheresis and genetic alteration of T cells *ex vivo*. Bispecific antibodies also exhibit a favourable toxicity profile in comparison to CAR T. The efficacy of bispecific antibody therapy relies on the patient's endogenous T-cells; therefore, it remains unclear how bispecific antibodies improve outcome for heavily pre-treated patients who have poor quality T-cells to begin with. Bispecific

antibody therapy is however an advantage for those unable to receive CAR T-cells for limitations in T-cell collection or *ex vivo* manipulation. A practical advantage of bispecific antibodies is the ease of administration via subcutaneous products (for example epcoritamab and mosunetuzumab) and that they could be given for a limited duration (glofitamab and mosunetuzumab).[22,24,27]

LONCASTUXIMAB TESIRINE

Loncastuximab tesirine is a CD19-directed antibody-drug conjugate with promising phase I single-agent antitumor activity in NHL and Food and Drug Administration (FDA) approved. The LOTIS-2, a multicentre single-arm phase II trial, enrolled 145 patients with heavily pre-treated DLBCL. Patients received loncastuximab tesirine up to one year or until disease relapse, progression or unacceptable toxicity. The ORR was 48% with a CR of 24%. Median DoR was 10,3 months. Median PFS was 4,9 months and median OS 9,9 months. The most common grade ≥3 AEs were neutropenia (26%), thrombocytopenia (18%) and increased gamma-glutamyltransferase (17%). In conclusion, loncastuximab tesirine has substantial single-agent antitumor activity and produces durable responses with an acceptable safety profile.[28]

An important remark is that it is not yet known whether the CD19 antigen can be targeted with a different anti-CD19 therapy after disease progression following a previous CD19-directed therapy. There are concerns regarding antigen masking and the potential for selection pressure of the prior therapy. To date, evidence and knowledge about the sequencing of anti-CD19 therapy are limited. Therefore, use of anti-CD19 therapy as bridging for CAR T therapy is not recommended.[29]

ROLE OF ALLOGENEIC STEM CELL TRANSPLANTATION

Although allogeneic SCT (allo SCT) can be a curative option, it is complicated by a high treatment related mortality and the role of allo SCT in R/R DLBCL is currently uncertain with relatively few published data and a lack of consistent findings.[30] In a real-world evaluation of the Belgian Federal Cancer Registry of 1888 newly diagnosed patients with DLBCL between 2013 and 2015, 252 went on to second line treatment. Forty-four patients received an autologous transplant but only ten received an allotransplant.[31]

Today, allo SCT is reserved for a selection of fit patients, usually in case of relapse after ASCT. However, considering the availability of novel treatment options, maybe allo SCT will be reserved for patients relapsing after innovative immunotherapies. Reviewing the literature on allo SCT reveals that long-term OS in the 20-50% rate is possible.[32] For example, the study of Thomson *et al.* included 48 patients who received a transplantation with reduced-intensity-conditioning (RIC) and reported an OS as high as 48% at four years.[5,30]

The 25-30% rate of non-relapse mortality (NRM) remains the greatest drawback. The implementation of less-intensive preparative regimens like RIC could mitigate this.[5,32] Robinson *et al.* reviewed the outcome of 4210 patients with R/R DLBCL that underwent an ASCT or allo SCT as their first transplant procedure. Two hundred thirty patients underwent an allo SCT. The 4-year NRM rate was 7% for ASCT, 20% for RIC allo SCT and 27% for myeloablative conditioning (MAC) allo SCT. The 4-year OS was 60%, 52% and 38% for ASCT, RIC and MAC respectively. After adjustment for confounding factors, NRM was significantly worse for patients undergoing an allo SCT whilst there was no difference in relapse incidence.[5,33] In conclusion, this study failed to prove that allo SCT is superior to ASCT in any salvage setting in patients with R/R DLBCL and more studies are warranted.[33]

Recommendation: At second or higher relapse, we recommend treatment with CD19 directed CAR T (axi-cel or tisa-cel) for fit patients. For unfit patients or at relapse after CAR T there are no curative treatment options available. If treatment is considered a clinical trial should be preferred. Palliative care is recommended when there are no new promising treatment options available.

CENTRAL NERVOUS SYSTEM RELAPSE

CNS relapse is a rare, but devastating event occurring in 5% of patients. The prognosis is dismal with a median OS of two to five months. It can occur as an isolated event or in combination with systemic relapse.[34-38] CNS dissemination usually occurs early during first line chemotherapy or throughout the first year of follow-up.[35-38] The brain parenchyma is involved in 40-50% of the patients, the leptomeninges in 30-40% and both in 10-15%.[35,37,38] Treatment should consist of drugs effective in penetrating the blood brain barrier and should treat systemic disease if necessary.[35] Several phase II trials have been published; however, there are no randomised trials to guide treatment in this setting.[34-38]

The Italian multicentre phase II trial of Ferreri *et al.* enrolled 38 patients with aggressive B-cell lymphoma and secondary CNS involvement at diagnosis (sixteen patients) or relapse (22 patients). The patients were treated with high doses of methotrexate and cytarabine followed by an intensification phase consisting of Rituximab, cyclophosphamide, cytarabine and etoposide supported by ASCT.

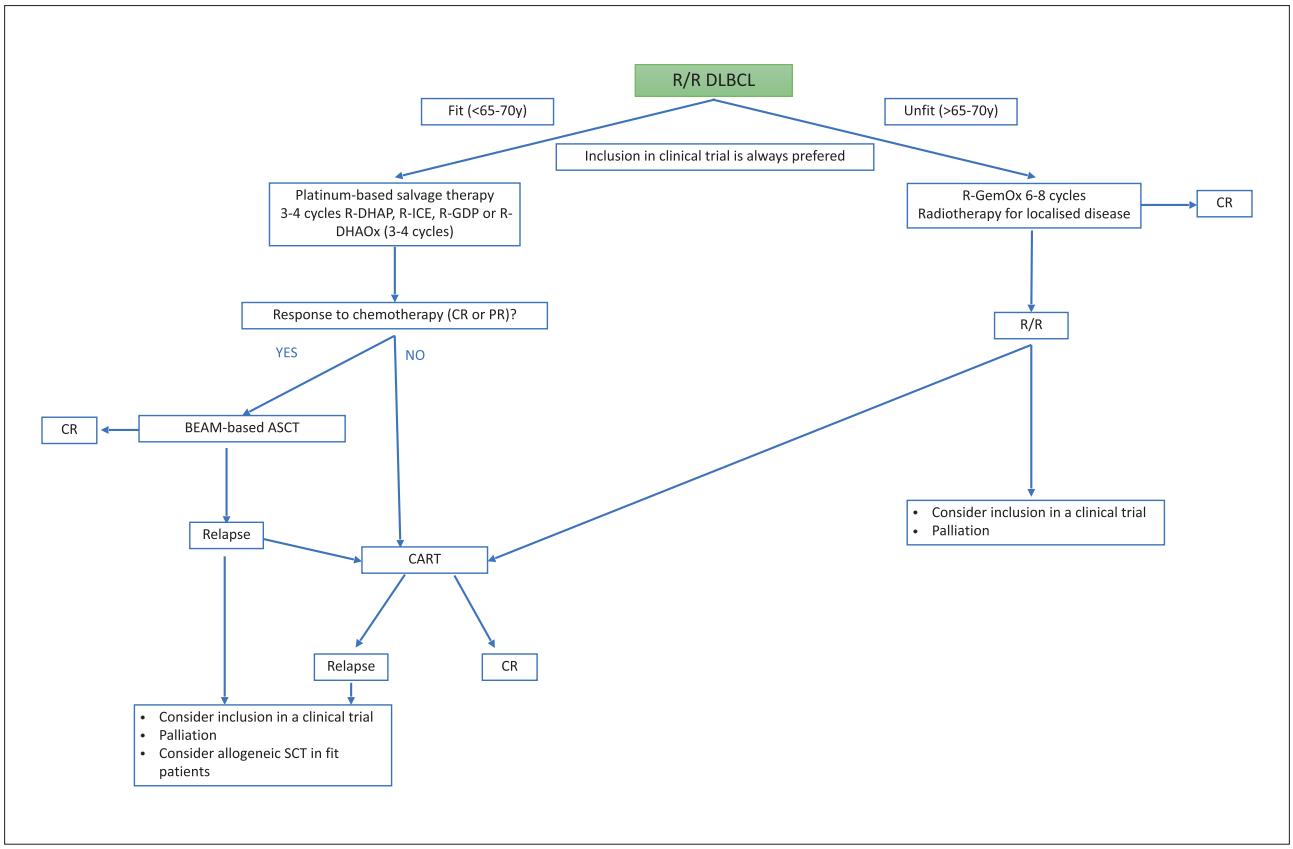

FIGURE 1. Approach to treatment in R/R DLBCL.

Abbreviations: R-DHAP: rituximab, dexamethasone, high-dose cytarabine and cisplatin; R-ICE: rituximab, ifosfamide, carboplatin and etoposide; R-DHAOx: rituximab, dexamethasone, high-dose cytarabine and oxaliplatin; R-GDP: rituximab, gemcitabine, dexamethasone and cisplatin; BEAM: carmustine, etoposide, cytarabine and melphalan; R-GemOx: rituximab, gemcitabine, oxaliplatin; CAR T: chimeric antigen receptor T-cell; ASCT: autologous stem cell transplantation.

Treatment included eight doses of rituximab and four doses of intrathecal liposomal cytarabine. Twenty patients underwent ASCT. Toxicity was usually hematologic and manageable. Sixty-three % of patients achieved a CR. At a median follow-up of 48 months, seventeen patients remained relapse free. The 2-year event free survival (EFS) was 50%. Five-year overall survival rate was 41% for the whole series and 68% for patients who received ASCT.[37]

The HOVON 80 phase II trial included 36 patients with DLBCL and a CNS relapse. Treatment consisted of two cycles of R-DHAP alternating with high-dose methotrexate (MTX) and was combined with intrathecal rituximab. Responding patients received a third R-DHAP-MTX cycle followed by busulfan and cyclophosphamide myeloablative therapy and ASCT. The ORR after two R-DHAP-MTX cycles was 53% with 22% achieving CR. Forty-two percent underwent ASCT. One year OS was 25%. In conclusion, this treatment did not result in improved outcome in secondary CNS relapse, especially when systemic disease was present.[36] The German phase II trial of Korfel *et al.* included 30 patients with secondary central nervous system lymphoma (SCNSL), with or without systemic relapse.[34,36]

This study showed much better results compared to the HOVON 80 trial.[36] In the German trial, an intensive approach with drugs penetrating the blood-brain barrier (high dose MTX, ifosfamide, cytarabine and thiotepa) was used, combined with intrathecal liposomal cytarabine. Induction chemotherapy was followed by high-dose chemotherapy with carmustine, thiotepa and etoposide and ASCT. After ASCT, there was a CR In 63% patients, partial remission (PR) in 8% and progressive disease (PD) in 29%. Two-year OS was 63%.[34] The difference with the HOVON 80 study is that in the German study, 80% had isolated CNS relapse, whereas in the HOVON 80 study this was only 44%. This could explain the better results in the German trial.[36]

The MARIETTA trial, an international single-arm phase II trial, enrolled 79 patients with DLBCL and CNS involvement at the time of primary diagnosis or at relapse. Seventy-five patients were assessable and received three courses of

KEY MESSAGES FOR CLINICAL PRACTICE

1. DLBCL is an aggressive type of B-cell NHL. Thirty to forty percent of patients with DLBCL will relapse or are unable to obtain complete remission after frontline treatment. These patients have a poor prognosis and represent a therapeutic challenge.
2. If possible, inclusion in a clinical trial should always be preferred.
3. For patients with a first relapse that are fit (younger than 65-70 years old, no major comorbidities) the best treatment option is re-induction with chemoimmunotherapy (R-DHAP, R-DHAOx, R-ICE or R-GDP) followed by high dose chemotherapy (BEAM) and autologous stem cell transplantation.
4. Unfit or elderly patients with a first relapse should be treated with immunochemotherapy such as six to eight cycles of R-GemOx.
5. At second or higher relapse, therapy with CD19-directed CAR T is recommended for fit patients. For unfit patients or relapse after CAR T, there are no curative options (even not allogeneic stem cell transplantation).

MATRix (Rituximab, high-dose methotrexate, cytarabine, thiotepa, intrathecal chemotherapy consisting of liposomal cytarabine or conventional triple-drug chemotherapy) followed by three courses of RICE (Rituximab, etoposide, ifosfamide, carboplatin and intrathecal chemotherapy) and carmustine-thiotepa and ASCT. Thirty-nine percent had a CR after MATRix-RICE. Thirty-seven patients who responded had ASCT. At the end of the regimen, 61% had an objective response with a median DoR of 26 months. Two-year OS was 46%. Grade 3-4 toxicity was most commonly hematologic with neutropenia in 61% of patients, thrombocytopenia in 60% and anaemia in 35%.[35]

Recommendation: Given the lack of prospective trials, no treatment recommendations can be made for DLBCL with CNS relapse. However, based on expert opinion, treatment should include chemotherapy penetrating the blood-brain barrier such as high dose methotrexate and cytarabine, and would be preferentially followed by ASCT.

HIGH-GRADE B-CELL LYMPHOMA WITH *MYC* AND *BCL2* AND/OR *BCL6* TRANSLOCATION

The revised WHO classification of 2016 moved all aggressive B-cell lymphomas with a *MYC* translocation and a concurrent translocation of *BCL2* and/or *BCL6* into a single diagnostic category: the double- and triple hit lymphomas (DHL and THL).[39,40] In the fifth edition of the WHO criteria of 2022, DLBCL/high-grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* rearrangements are still a separate entity. DLBCL/HGBL with *MYC/BCL6* are now classified as a subtype of DLBCL, NOS or HGBL, NOS.[2] DHL and THL represent a group with poor outcome to conventional chemotherapy (R-CHOP). More intensive treatment regimens improve the outcome of double- and triple-hit lymphomas and there is a preference for DA-EPOCH-R based on phase II trials.[39,40,41]

Patients with DHL/THL and refractory disease or relapse after an initial response have a poor outcome when treated with the conventional approach of re-induction with R-ICE or R-DHAP followed by high dose chemotherapy and ASCT.[40,41] The 4-year PFS and OS were significantly lower in the MYC positive (MYC+) DLBCL patients (simple hit and complex hits) than those in the MYC negative (MYC-) with rates of 18% *vs.* 42% and of 29% *vs.* 62%, respectively.[41] This may be partly explained by the fact that DHL/THL patients have possibly received more intensive chemo-immunotherapy regimens than R-CHOP in the up-front setting.[39]

There is limited data on the benefits of allogeneic transplantation in this patient population and these are all small subsets of patients. The retrospective study of Herrera *et al.* including 78 patients concluded that DHL/THL status did not affect allo SCT outcome. Although, in order to gain benefit from an allogeneic approach, patients must first achieve an adequate and durable response to re-induction therapy.[42] There is new promising data from the use of CAR T-cell therapy in DHL/THL with high response rates in small numbers of patients.[39,40] Both the ZUMA-1,

JULIET and the TRANSCEND trial included patients with high grade lymphomas, showing similar benefits compared to DLBCL, NOS, although these studies were not powered to detect differences in these subgroups.[43,44,45]

The single institution real-world cohort of R/R aggressive B-cell lymphomas of Chafouri *et al.* demonstrated similar efficacy outcomes to those of the ZUMA-1 and JULIET trials and published real-world studies. It suggests that DHL/THL patients could benefit from CAR T-cell therapy.[46]

Recommendation: Given the lack of prospective trials, no treatment recommendations can be made for R/R DHL/THL.

CONCLUSION

We conclude that the standard therapy for transplant-eligible patients with R/R DLBCL at first relapse remains platinum-based chemotherapy followed by ASCT. For the unfit patients, R-GemOx can be used with palliative intent. After two lines of chemoimmunotherapy, CD19 directed CAR T-cell therapy is reimbursed in Belgium and provides a long-term cure in approximately 40%. Promising novel therapies are being developed and whenever possible, it is important to include patients in clinical trials. Due to the broad genetic landscape in DLBCL, we expect that in the future more targeted therapies will be available. The upcoming fifth edition of the WHO classification of Haematolymphoid Tumours reorganised the different lymphoid tumours, which will make the reimbursement of therapies much more complex in the future.[2] The International Consensus Classification is another recent classification proposal.[47]

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