THE STANDARD OF CARE IN RELAPSED REFRACTORY CD30+ LYMPHOMA

***Martin Hutchings**

Department of Hematology, Rigshospitalet, Copenhagen, Denmark
**Correspondence to hutchings@dadlnet.dk*

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ABSTRACT

CD30-positive (CD30+) lymphomas are a heterogeneous group of hematological malignancies that share the same antigen. Over recent decades, advances in therapeutic management of these diseases have considerably improved clinical outcomes. Overall, the two main CD30+ lymphomas - Hodgkin's lymphoma and systemic anaplastic large cell lymphoma - are associated with a favourable prognosis after first-line therapy. Nevertheless, optimal therapeutic strategies are needed to manage relapsed or refractory CD30+ lymphomas. The introduction of novel targeted approaches, such as brentuximab vedotin (BV), expands the therapeutic armamentarium and provides new perspectives in terms of clinical efficacy despite heavily pretreated disease, with reasonable toxicity to patients whose quality of life is often impaired by the disease and repeated treatments. The standard of care (SoC) for these malignancies is being refined and will be clarified with results from ongoing and upcoming Phase II/III clinical trials. Clinical studies are currently assessing the use of BV in a broad range of CD30+ lymphomas. Over time, frontline strategies and SoC will be refined in order to improve outcomes for patients with relapsed disease, while allowing clinicians to expand patient selection and provide long-term remission in a wide variety of clinical settings.

Keywords: Lymphoma, CD30, brentuximab, Hodgkin's lymphoma, systemic anaplastic large cell lymphoma.

INTRODUCTION

CD30-positive (CD30+) lymphomas are a heterogeneous group of hematological malignancies that share the CD30 antigen. While advances in the therapeutic management of these diseases have considerably improved clinical outcomes, optimal therapeutic strategies are still needed to manage relapsed or refractory CD30+ lymphomas. This article aims to review the current evidence and rationale on CD30-targeting strategies, including results from brentuximab vedotin (BV) clinical studies, and to provide an overview of the standard of care (SoC) in main clinical settings.

CD30+ LYMPHOMAS

CD30 is a leukocyte activation marker membrane receptor that is physiologically involved in many signalling pathways through its interaction with tumour necrosis factors in activated B and T cells.[1] It is expressed in a range of lymphomas including: Hodgkin's lymphoma (HL), systemic anaplastic large cell lymphoma (sALCL), primary cutaneous ALCL (pcALCL), primary mediastinal B cell lymphoma, adult natural killer (NK)/T cell leukaemia/lymphoma, mycosis fungoides, and some cases of diffuse large B cell lymphoma, primary effusion lymphoma, and anaplastic diffuse large B cell lymphoma.[2-6] This antigen can also be found in other malignancies, such as lymphomatoid papulosis, embryonal carcinoma, and mast cell neoplasm.[6,7] CD30 is consistently expressed in classical HL and sALCL, and is therefore an interesting therapeutic target for those diseases.

HL

HL is a relatively common and highly curable B cell lymphoma characterised by lymphadenopathies spreading in a contiguous manner, causing systemic symptoms and affecting the immune system's ability to fight infection. The large, multinucleated cells and CD30+ Hodgkin's and Reed-Sternberg cells are the hallmark of classical HL.[3] Displaying a bimodal age distribution, HL is the most common malignancy in adolescents and young adults, and also occurs in the elderly.[8]

This disease is highly curable with approximately 80-90% of patients achieving long-term remission following chemotherapy with or without radiotherapy.[9] Young HL patients have better long-term clinical outcomes than elderly patients: 5-year overall survival (OS) rates are of about 96% in the former versus 88% in the latter.[8] Two subgroups of patients carry a particularly poor prognosis: patients aged 60 and older and those with refractory or relapsing disease after second-line therapy.[9,10] These two clinical settings represent an unmet need which is the focus of extensive clinical research.

Despite a generally good prognosis, it is also important to expand the therapeutic armamentarium of HL in children and adolescents, where treatment-related adverse events are of particular concern. A focus on the long-term effects of the treatment and the quality of life (QoL) of survivors is of crucial importance in this subpopulation.[11]

sALCL

sALCL is a rare and aggressive mature T cell non-Hodgkin's lymphoma (NHL) that is characterised by CD30-expressing large pleomorphic cells that can be found in lymph nodes.[4] Another form of ALCL – pcALCL – is distinct from sALCL in terms of both its clinical and biological presentations.[4] A majority of patients, primarily younger, express the protein anaplastic lymphoma kinase (ALK),[12,13] while older adults are more commonly ALK-negative.[14] ALK positivity coupled with low-risk factors is linked to a better prognosis and an overall good long-term response to treatment than ALK negativity with high-risk factors, as evidenced by highly significant 5-year OS differences.[15] Similarly to HL, sALCL patients with refractory or relapsing disease carry a poor prognosis, regardless of ALK status. Novel therapeutic options are required to address these clinical settings.

CD30 AS A THERAPEUTIC TARGET

As previously mentioned, CD30 is expressed in a range of malignancies, but is absent from most normal cells, which allows for specific targeting of cancerous cells with immunotherapy. Under physiological conditions, CD30 is found on the surface of activated T and B cells, but not on their resting forms.[16,17]

CD30-Targeted Immunotherapy

Over the last decades, targeted immunotherapy has become increasingly important in treatment strategies for many malignancies and has enabled a marked improvement of clinical outcomes. The singular expression profile of CD30 led to the development of several monoclonal antibodies in the treatment of refractory or relapsing HL and sALCL.[18]

Despite impressive preclinical results, the first clinical outcomes were disappointing. Two monoclonal antibodies, MDX-060 and SGN-030, were evaluated in Phase I/II clinical trials in patients with either refractory or relapsing HL or sALCL. In both studies, results for MDX-060[19] and SGN-030[20] showed limited activity and objective responses (8% and 9% of patients, respectively), with fewer complete responses ([CR]; 6% and 3% of patients, respectively).

Recent advances in antibody engineering have paved the way for new applications, including the development of novel immunotherapeutic agents called antibody-drug conjugates (ADCs). ADCs are composed of a cytotoxic agent and a monoclonal antibody directed against a specific antigen. BV was the first ADC to be developed for clinical use.

BV (SGN-35)

Chemistry and Mechanism of Action

BV is an ADC composed by an anti-human CD30 antibody and four molecules of monomethyl auristatin E (MMAE), an antimicrotubule agent with high antitumoural potency. BV specifically binds to CD30+ cells and is internalised, triggering the release of MMAE into the cytoplasm, which in turn, inhibits tubulin polymerisation occurring in the G2/M Phase of the mitosis and induces

targeted apoptosis.[21] MMAE has also been found to accumulate in the extracellular compartment, thus pursuing its cytotoxic effects on surrounding cells.[22]

Pivotal Phase II Clinical Studies

Following promising Phase I studies, two single-arm, single-agent, multicentre Phase II studies were conducted. Heavily pretreated patients with either refractory or relapsing HL[23] and sALCL[24] received a single dose of 1.8 mg/kg of BV every 3 weeks for up to 16 cycles. The first Phase II study[23] enrolled 102 patients with relapsed HL after autologous stem cell transplantation (ASCT), while the second study[24] aimed to evaluate the efficacy of BV in 58 patients with refractory or relapsing sALCL. Both studies demonstrated remarkable efficacy for BV with an overall response rate (ORR) of 75% and 86% in HL and sALCL, respectively. CR was achieved in 34% of HL patients and in 57% of sALCL patients for median durations of 20.5 and 13.2 months. Tumour reductions were observed in 94% and 97% of HL and sALCL patients, respectively. In the subgroup of ALK-negative sALCL patients, BV showed similar results with an ORR of 88% and complete remission in 52% of patients.[24]

The most frequent adverse events were peripheral sensory neuropathy, nausea, fatigue, pyrexia, diarrhoea, rash, constipation, and neutropaenia. Most patients who developed peripheral sensory neuropathy showed partial or complete resolution of their symptoms after dose reductions or treatment discontinuation. However, some patients developed persistent neuropathy; this should be taken closely into account when BV is used to treat potentially curable cases of lymphoma, particularly when combined with other neurotoxic drugs. Adverse events led to treatment discontinuation in 20% and 24% of HL and sALCL patients, respectively. No drug-related deaths were reported.[23,24]

Overall, BV showed important antitumoural efficacy with a good risk-to-benefit ratio, which led to accelerated approval by the US FDA in 2011 and conditional approval by the EMA in 2012 for the following indications: HL after failure of ASCT; HL in patients who are not ASCT candidates after failure of at least two multi-agent chemotherapy regimens; and sALCL after failure of at least one multi-agent chemotherapy regimen. Follow-up data on the outcomes for the continuous complete responders from both studies were recently presented at the American Society of Hematology meeting in 2013. After a median observation time of about 3 years, 51 HL patients were alive at last follow-up (including 14 who had a sustained response) were still in remission, and did not start a new treatment cycle.[25] After a median observation time of 33.4 months for the Phase II sALCL, 64% were still alive at last follow-up for an estimated 3-year survival rate of 63%. Patients who had achieved a CR with BV therapy had a higher OS than patients who did not; the median OS for patients with a CR had not yet been reached at the time of analysis.[26]

BV was also evaluated in a range of CD30+ hematological malignancies, such as cutaneous T cell lymphoma,[27,28] other peripheral T cell CD30+ lymphomas,[29] and in diffuse large B cell lymphoma.[30] In January 2012, the FDA issued a revision of the product package insert, with a boxed warning about the risk of progressive multifocal leukoencephalopathy (ML), a potentially fatal brain infection, which has also been associated with the monoclonal anti-CD20 antibody rituximab. To date, three cases of ML with BV have been reported. As BV is contraindicated with concomitant bleomycin due to increased pulmonary toxicity, patients undergoing BV therapy should be closely monitored for symptoms of ML and pulmonary toxicity. Also, recent safety updates have raised caution that BV may be associated with the development of acute pancreatitis.

OPTIMAL STRATEGIES IN RELAPSED/REFRACTORY CD30+ LYMPHOMAS

Standard Management of Relapsed/Refractory HL

Context

In patients with limited-stage HL, first-line chemotherapy (doxorubicin, bleomycin, vinblastine + dacarbazine [ABVD]) plus radiotherapy achieves good clinical results with remission rates ranging from 80-90%.[11] First-line treatment of patients with advanced stage HL with the more intensive BEACOPPesc regimen (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazin, prednisolone) yields superior remission rates and long-term survival, at the expense of more serious toxicity, and also a higher risk of infertility and secondary leukaemia.[31] Nevertheless, a proportion of patients (20-30%

after ABVD and 15-20% after BEACOPPesc) will present refractory or relapsed disease after one or two regimens.[11]

Management of relapsing or refractory HL

The standard management of relapsing or refractory disease (Figure 1) is second-line chemotherapy as induction therapy to ASCT. In about 70% of patients, complete or partial response (PR) is obtained and high-dose chemotherapy (HDC) followed by ASCT can be completed; this therapeutic option is associated to a sustained response in about 50% of patients.[32-34] However, patients who are not eligible for ASCT, or who relapse after two chemotherapy regimens followed by ASCT, seem to benefit from BV.

Outside of clinical studies, real-life data are available from three named patient programmes (NPPs) in Germany, the United Kingdom, and Italy.[35-37] BV showed good ORR (ranging from 60-72%) and CR (ranging from 17%-22%) in heavily pretreated patients.[35,36] Best observed responses were after three-to-four cycles of treatment; consolidation with allogeneic hematopoietic stem cell transplantation (allo-SCT) should be considered early. Clinical outcomes and toxicity profiles were highly similar to those from both pivotal trials,[23,24] suggesting that patients from everyday clinical practices can benefit from the impressive outcomes in the same proportions.

BV as a salvage therapy prior to ASCT in ineligible patients

In the latest National Comprehensive Cancer Network (NCCN) recommendations on HL,[38] the panel advised that BV may be an option in patients who have progressive disease after two chemotherapy regimens, at which point HDC + ASCT is not a recommended option. So far, only a few publications explore the use of BV in transplant-naïve patients with relapsed or refractory HL.

In a retrospective study on a cohort of 24 French patients with relapsing or refractory HL, the ORR was of 66.7% for 45.8% of CRs and 20.8% of PRs. Responding patients underwent a consecutive ASCT or allo-SCT.[39] In another retrospective study of 14 patients, the ORR was 71% with 36% of complete remissions. BV acted as salvage therapy in 36% of patients who subsequently underwent HDC + ASCT. 12-month OS was 69% in the whole cohort.[40] A case series of 20 transplant-naïve patients with relapsed or refractory HL receiving BV reported 6 objective responses and 2 complete remissions, while 3 out of 6 responders underwent ASCT. [41]

Treatment options for patients with multiple relapses

BV retreatment seems to be an option in patients who previously achieved remission with BV. This possibility is most likely due to the persistence of CD30 expression in tumour biopsy immunostaining after BV therapy.[42] Retreatment was evaluated in 21 patients with HL and achieved a response rate of 60% and 30% of CRs (median duration of objective response: 9.2 months) with a similar safety profile[30] as that of the pivotal clinical trials. Retreatment with BV seems to be a good therapeutic option for patients in whom multi-agent chemotherapy side-effects significantly affect QoL.

In patients relapsing after BV treatment, a second ASCT is possible if the previous response to ASCT was sustained for at least 12 months.[43] Prior to ASCT, salvage therapy with chemotherapy or BV may be implemented according to the patient's characteristics. Reduced-intensity allo-SCT is a therapeutic option that can take advantage of the graft versus lymphoma effect and consequently improve clinical outcomes and OS. The role of allo-SCT in relapsed HL remains controversial, but this treatment may represent the only remaining curative option in selected patients. BV can also be used as a bridge therapy to allo-SCT in patients with relapsed or refractory disease following ASCT. This therapeutic option was explored in a retrospective study on 17 patients who had undergone ASCT, and the authors determined that BV provided sufficient disease control prior to allo-SCT.[44] BV was also evaluated after allo-SCT failure in 24 patients; response rates of 50% and 38% of complete remissions were observed.[45]

It should be noted that patients with multiple relapse have a poor prognosis,[46] and the above therapeutic options must be considered and discussed according to the side or late-effects of treatment and the QoL experienced by each patient.[47] If these options are not possible, the patient should be offered enrolment in a clinical trial or palliative chemotherapy.

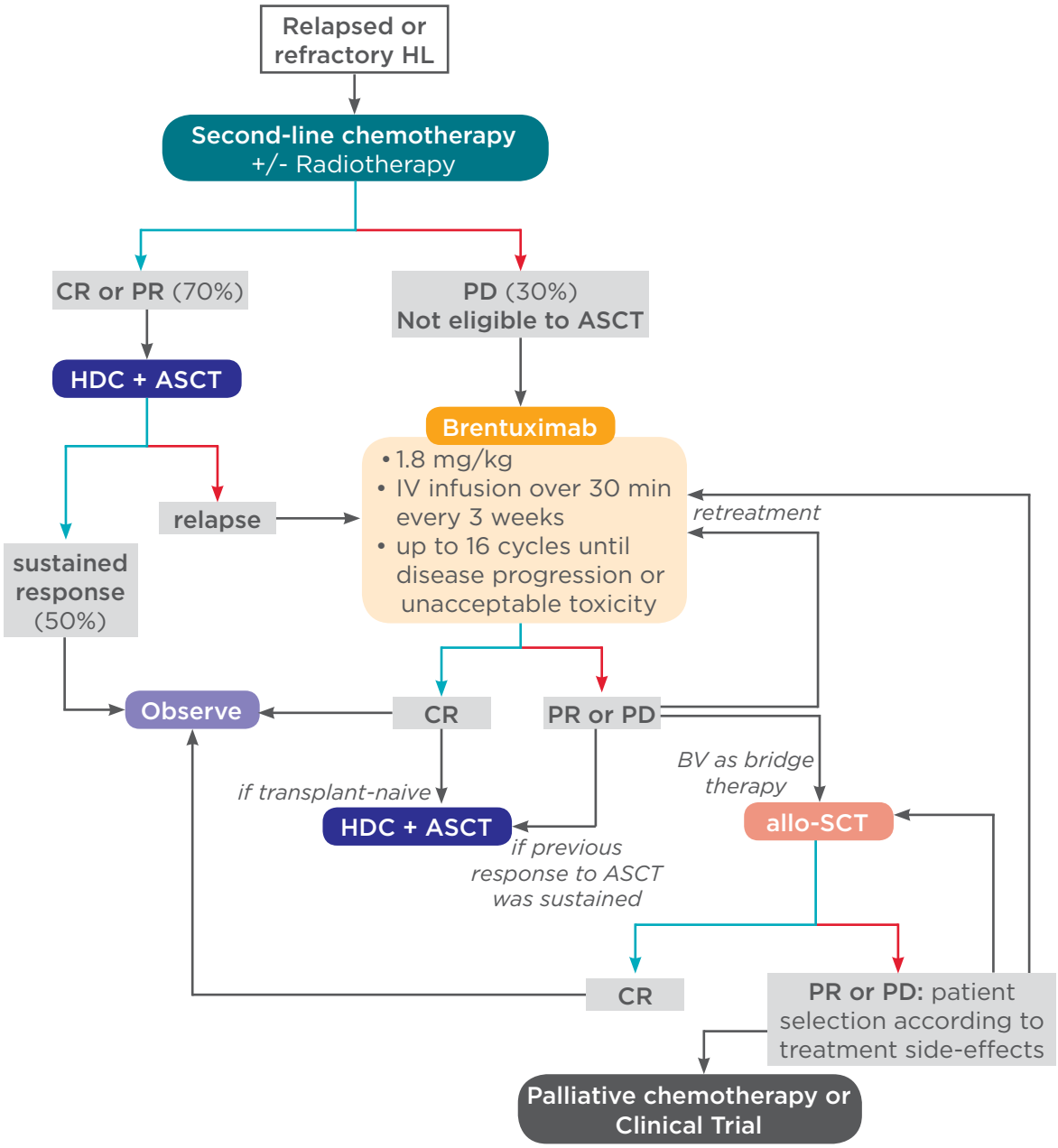

Figure 1: Management of refractory or relapsed HL.

HL: Hodgkin's lymphoma; CR: complete response; PR: partial response; PD: progressive disease; ASCT: autologous stem cell transplantation; HDC: high-dose chemotherapy; IV: intravenous; BV: brentuximab vedotin; allo-SCT: allogeneic stem cell transplantation.

Adapted from Hoppe RT et al.[38]

Standard Management of Relapsed/Refractory sALCL

Context

sALCL has a high remission rate with frontline chemotherapy, which is usually a multi-agent combination (cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]). A long-term study[48] over 8 years revealed an ORR to multi-agent chemotherapy of 86% for ALK-positive patients and 68% for ALK-negative patients, with good survival rates over that same period. The molecular characteristics of ALK-negative sALCL remain obscure.[49] This form is more aggressive[14] with a first-line standard chemotherapy cure rate of only 30%, but the latest studies[14,50,51] on consecutive ASCT have revealed significantly improved outcomes. However, there are few therapeutic options for patients who relapse after first-line therapy, regardless of ALK-status.

Management of relapsing or refractory sALCL

To date, there is no SoC for relapsing or refractory sALCL, and individual patient characteristics must be considered for patient selection towards each of the available therapeutic options. Patients relapsing after first-line therapy could very well benefit from ASCT, but the available data are limited. In a retrospective analysis on 65 patients with peripheral T cell lymphoma (including ALCL),[52] patients undergoing HCT + ASCT or allo-SCT after the first relapse were evaluated in comparison with patients not proceeding to transplant. 4-year OS was 67%, 66%, and 27%, respectively. Crizotinib, an ALK tyrosine kinase inhibitor, is being further investigated in relapsed or refractory ALK-positive sALCL following a Phase I study[53] in which seven out of eight patients achieved complete remission. Several other studies,[54-57] case series or case reports relate the use of crizotinib in relapsed or refractory ALK-positive ALCL.

Over the last few years, several novel agents emerged: pralatrexate (an antifolate), romidepsin (a histone deacetylase inhibitor), and BV; all three products are currently being evaluated in relapsed or refractory sALCL. Pralatrexate and romidepsin are approved by the FDA for the treatment of relapsed or refractory peripheral T cell lymphomas. Pralatrexate showed a 35% response rate in a subset analysis of 17 ALCL patients,[58] while romidepsin therapy achieved an ORR of 25% among 130 refractory T cell lymphoma cases (22 patients had ALK-positive or negative sALCL).[59] BV has shown better response rates and good disease control in patients with CD30+ lymphomas.[24] The drug is being further explored in combination with chemotherapy. In a single centre study, five patients with ALCL who were refractory to at least two chemotherapy regimens received BV therapy. The ORR was of 60% with an identical remission rate.[36]

Treatment options for patients with multiple relapses

As previously discussed in multiple-relapsing HL, a second course of BV is also a possibility in sALCL patients who previously achieved remission with BV. In an open-label, multicentre, Phase II study,[30] retreatment was evaluated in eight patients with sALCL, and achieved a response rate of 88% for 63% of complete remissions (median duration of objective response: 12.3 months).

BV in CD30+ Lymphomas: Ongoing Studies

Clinical studies are currently ongoing to assess the use of BV in a broad range of CD30+ lymphomas.[60,61] A Phase III study that should be completed in 2016 is currently evaluating BV in HL patients at high risk of relapse after ASCT.[62] Another Phase III study is currently ongoing on BV therapy + AVD compared with ABVD therapy in advanced HL.[63] BV is also being assessed in CD30+ mature T and NK cell lymphomas, either in combination with chemotherapy[64] or sequentially.[65] Additionally, further studies are exploring the efficacy and safety of BV in paediatric and adolescent patients with relapsed or refractory HL or sALCL.[66-68]

CONCLUSION AND FUTURE PERSPECTIVES

Overall, the two main CD30+ lymphomas, HL and sALCL, are associated with good first-line remission rates, and patients with relapsed or refractory disease can routinely benefit from multiple or repeated therapeutic options. Nevertheless, significant challenges remain in terms of disease-free survival, long-term remission, and management of chemotherapy-related side-effects in relapsed or refractory disease.

The introduction of novel targeted approaches such as BV expands the therapeutic armamentarium and provides multiple-relapse patients with new perspectives for clinical efficacy without unacceptable loss of QoL. This new drug has impressive anti-tumour activity, but its potential to improve cure rates and long-term OS remains to be seen. Also, as the drug is given in combination with potentially curative first-line or second-line chemotherapy, we need to closely follow the long-term toxicity affecting the patients.

The SoC for these diseases is being refined and will be clarified over time by reliable results from broader-scale Phase II and III clinical trials and by growing clinical experience. Over time, frontline strategies and SoC of CD30+ lymphomas will be targeted in order to improve outcomes for patients with relapsed disease, while allowing clinicians to expand patient selection and provide long-term remission in a wide variety of clinical settings.

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