CURRENT AND FUTURE DEVELOPMENTS IN THE TREATMENT OF CD30⁺ LYMPHOMAS

*Lena Specht,¹ Christian Gisselbrecht²

¹. Departments of Oncology and Haematology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
². Institut d’Hématologie, Hôpital Saint-Louis, Paris, France
*Correspondence to Lena.Specht@regionh.dk

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ABSTRACT

CD30 is a cell membrane protein expressed on the surface of a range of lymphomas, which has important diagnostic, pathogenic, and prognostic roles. The most common CD30⁺ lymphomas are Hodgkin’s lymphoma (HL) and anaplastic large cell lymphoma (ALCL), but other types of lymphoma also express CD30, although less frequently. Attempts to develop a monoclonal antibody therapy that targets CD30 were initially unsuccessful, but recent Phase I and II trials have shown promising results from the use of the immune conjugate brentuximab vedotin in HL and ALCL. Phase III trials are ongoing to evaluate clearly the benefit-risk ratio when compared with standard treatment. The first of these to report preliminary findings, the AETHERA trial, showed improved progression-free survival times in relapsing/refractory HL patients treated with brentuximab vedotin as a consolidation therapy after autologous stem cell transplantation compared with those receiving placebo. Patients with rarer CD30⁺ lymphomas may also benefit from brentuximab vedotin therapy in the future. Moreover, combination treatment with immunomodulatory and cell cycle checkpoint modulators that are currently under development, as well as conventional chemotherapeutic agents, may yield further benefits. To this end, improved methods of CD30 detection and quantitation will improve the delineation of non-HL subtypes in which CD30-targeted therapy may be clinically indicated.

Keywords: CD30⁺ lymphoma, Hodgkin’s lymphoma (HL), immune conjugate, monoclonal antibody (mAb), clinical trial.

BACKGROUND: DISCOVERY, STRUCTURE, FUNCTION, AND DETECTION OF CD30

Until 1982, the neoplastic cells of Hodgkin’s lymphoma (HL) were largely uncharacterised in terms of their surface markers. The establishment of a stable HL cell line led to the discovery of a surface marker that was almost ubiquitous on Reed-Sternberg (RS) cells as well as Hodgkin’s cells, the pathological hallmark of HL.¹ CD30 (also referred to as tumour necrosis factor [TNF] receptor superfamily member 8, Ki-1 antigen, CD30 ligand receptor, and lymphocyte activation antigen CD30) is a member of the TNF receptor superfamily. The protein contains extracellular, transmembrane, and intracellular domains (overall molecular weight: 120 kDa) and there are two isoforms generated by alternative splicing of the gene, which is located at Chr 1p36.22. CD30 is only expressed by activated lymphocytes, both T and B lineages. The extracellular domain can also be cleaved to produce a soluble, cytoplasmic form (85 kDa), which has an undetermined function. Soluble CD30 can be used as a biomarker of disease stage in HL. Indeed, the specificity of CD30 expression to disease states gives it powerful diagnostic²-⁴ and predictive functions,⁵ although this is not current practice in most hospitals at present.
After its initial characterisation in RS cells, CD30 has been shown to be expressed by most human lymphomas, including B and T-cell lymphomas, to variable extents. In addition to its expression by 98% of HL cells, CD30 is ubiquitously expressed by anaplastic large cell lymphoma (ALCL, both kinase-positive and kinase-negative subtypes) and primary cutaneous ALCL. Other CD30+ diseases comprise a variety of less common types of B and T-cell lymphomas, as well as reactive conditions (Table 1). Peripheral T-cell lymphomas (PTCLs) and some B-cell lymphomas, such as diffuse large B-cell lymphoma (DLBCL), can now be subcategorised based upon gene expression profiles that correlate with CD30 expression.

The function of CD30 is 2-fold and depends on which intracellular signal transduction pathways are activated. After binding to its ligand (CD30L, CD153), the protein–ligand complex can activate the TNF receptor-associated factor (TRAF) 2 or TRAF5 pathways. The former leads to activated cell proliferation via interactions with MAPK8/JNK and NF-κB, as seen in aggressive ALCL, while the interaction between CD30 and TRAF5 leads to apoptosis. In HL, TRAF2 and TRAF5 signalling is CD30L-independent, and both protein complexes aggregate in the cytoplasm close to the cell membrane. CD30 has been shown to upregulate the expression of intercellular adhesion molecule-1, most likely via the upregulation of NF-κB. The induction of apoptosis is observed in lymphomatoid papulosis, which is a relatively indolent T-cell cutaneous lymphoma. Driving the choice of signalling pathway towards the TRAF5 pathway is an interesting and unexplored therapeutic option.

Methods of CD30 Detection and Their Limitations

The expression of CD30 is determined using three techniques: immunohistochemistry (IHC), mostly using antibodies against the extracellular domain; flow cytometry; and enzyme-linked immunosorbent assays for the soluble form. There are broad-ranging technical considerations inherent in making a histological diagnosis of lymphoma, including small numbers of available cells, poor fixation, failure to recognise staining patterns, and inappropriate controls. Indeed, an observational study of laboratories conducting CD30 testing (n=172) found that 77% of sites produced inadequate staining, mostly because of the high rate of false-negative findings. The choice of technique is also dependent on tissue type. For example, flow cytometry is only appropriate for fresh samples, including those from blood or bone marrow aspirates, and solid-tissue biopsies are generally not appropriate. Furthermore, fixation of cells prior to IHC analyses can introduce inaccuracies if delayed or not conducted appropriately. However, a recent study indicated that there is a high degree of correlation between IHC findings and mRNA expression levels providing that adequate controls are used for the IHC (usually tonsil) and that appropriate monoclonal antibodies (mAbs) are used.

Table 1: Summary of CD30+ diseases.

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>Disease</th>
<th>CD30 positivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-neoplastic T and B cells</td>
<td>Reactive conditions, e.g. infectious mononucleosis, HIV, and other viral diseases</td>
<td>Highly variable</td>
</tr>
<tr>
<td>Lymphomas with near-ubiquitous CD30 expression</td>
<td>Hodgkin’s lymphoma</td>
<td>96%</td>
</tr>
<tr>
<td></td>
<td>Anaplastic large cell lymphoma</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Enteropathy-associated T-cell lymphoma</td>
<td>100%</td>
</tr>
<tr>
<td>T-cell lymphomas</td>
<td>Multiple subtypes of peripheral T-cell lymphoma</td>
<td>≈20–50%</td>
</tr>
<tr>
<td></td>
<td>Cutaneous T-cell lymphoma (mycosis fungoides/ Sézary syndrome)</td>
<td>5–33%</td>
</tr>
<tr>
<td></td>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td>0–64%</td>
</tr>
<tr>
<td>B-cell lymphomas</td>
<td>Primary mediastinal large B-cell lymphoma</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>Primary effusion lymphoma</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>Burkitt’s lymphoma</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Diffuse large B-cell lymphoma</td>
<td>≈10%</td>
</tr>
<tr>
<td>Other</td>
<td>Nasopharyngeal carcinoma</td>
<td>≈10%</td>
</tr>
<tr>
<td></td>
<td>Embryonal carcinoma (a form of germ cell tumour)</td>
<td>70%</td>
</tr>
</tbody>
</table>
NOVEL THERAPEUTIC OPTIONS THAT TARGET CD30

One of the most successful recent advances in cancer therapeutics has been the development of targeted strategies against tumour cell-specific surface antigens by mAbs. Prior to the development of mAbs, HL and ALCL were treated with traditional chemotherapeutic agents (e.g. ABVD, BEACOPP, CHOP, CHOEP) and autologous stem cell transplantation (ASCT) for relapses, but, despite leading to a cure in 70–80% of patients with advanced HL, these treatments have previously caused irreversible side effects in some patients and remain far from optimal even now. The cure rates are substantially lower for patients with ALCL, meaning that there is a clear clinical need for new therapies in this area. Furthermore, relapse rates for some CD30+ diseases were high and patients often developed refractory disease for which novel therapeutic options were required. For HL and ALCL, the discovery of CD30 yielded an obvious target as it is overexpressed on the surface of tumour cells in virtually all cases (Table 1).

The cloning and characterisation of CD30 in HL led to the development of the first CD30-targeted mAb in 1992. However, although this monovalent mAb showed reasonable levels of tolerability, the results of Phase I and II trials showed disappointing levels of efficacy. Since 1992, a range of monovalent (CD30-specific), bispecific (CD30 and another target antigen), and radiolabelled (131I-anti-CD30) mAbs have been developed for HL and ALCL. Almost without exception, each strategy failed in Phase I or II trials: antibodies were neutralised by soluble CD30, failed to bind appropriately to CD30 in humans despite being efficacious in animal studies, or failed to blockade CD30 signalling. One initially promising candidate molecule that was shown to be safe and modestly effective in HL and ALCL, SGN-30, subsequently showed unacceptable toxicity when combined with chemotherapy in terms of episodes of pneumonitis, and clinical trials were discontinued. Unacceptable toxicity in terms of haematological effects also ended the development of the 131I-anti-CD30 radiolabelled mAb.

There was one exception to these disappointing initial studies and that came with the development of brentuximab vedotin. Brentuximab vedotin is a conjugate of a mAb against CD30 (cAC10) and an antimitotic cytotoxic compound, monomethyl auristatin E (MMAE). The anti-CD30 antibody and MMAE are linked to form a compound that is stable in the plasma and then dissociates once internalised by a tumour cell. Brentuximab vedotin is internalised after binding to CD30, after which MMAE is released into the tumour cell to mediate its anti-tubulin action, leading to G2/M cell cycle arrest and apoptosis. As a result of the disease cell-targeting nature of the CD30 mAb conjugate, the side effect profile of brentuximab vedotin is relatively low, although not negligible in either HL or ALCL, with approximately 20% of patients suffering Grade 1 or 2 side effects. The most common adverse effects in the Phase II trials were fatigue, nausea and vomiting, sensory neuropathy (most of which resolved completely after the cessation of treatment), upper respiratory infection, diarrhoea, anaemia, and thrombocytopaenia. Potentially serious but rare adverse events associated with brentuximab vedotin include pancreatitis and progressive multifocal leukoencephalopathy.

As a result of the encouraging early trial data, the United States Food and Drug Administration (FDA) granted accelerated approval to brentuximab vedotin in 2011 for the treatment of patients with relapsed HL post-ASCT, patients with HL who have failed two standard chemotherapy regimens, patients with ALCL who have failed one multiple agent chemotherapeutic regimen, and those for whom transplantation is not an option. In a subsequent attempt to improve the cure rate in patients with newly diagnosed HL, brentuximab vedotin has been combined with standard chemotherapy in a single Phase I study. The study findings showed that >90% of patients (46/51) achieved a complete response. When bleomycin was removed from the regimen, the risk of pulmonary toxicity was removed with no effect on clinical response rates. The same research group is now conducting a Phase II trial of brentuximab vedotin + AVD in previously untreated unfavourable disease, and have shown no additional toxicity when combined with radiotherapy.

Two Phase III trials are now ongoing to assess brentuximab vedotin + AVD versus the standard ABVD regimen in untreated, advanced HL. The ECHELON-1 study in advanced HL has just finished recruiting patients, but increased levels of neutropenia were found in the experimental arm, which led to the routine prophylactic use of growth factor in all patients who received combined brentuximab vedotin + AVD. Data from this trial are expected in 2018. Furthermore, the
LYSA/FIL/EORTC trial in patients with early unfavourable HL is still recruiting. In this trial, all patients will receive four cycles of either experimental or standard treatment followed by involved site radiotherapy.

For patients with relapsed/refractory HL, Phase II trials have shown an overall response rate (ORR) ranging from 47–75% when brentuximab vedotin is used as a single drug. One study indicated that patients who achieved a complete response displayed an overall survival rate of 73% (95% confidence interval [CI]: 57–88%) and a progression-free survival (PFS) rate of 58% (95% CI: 41–76%). A systematic review of the literature has suggested that brentuximab vedotin can prolong long-term survival in such patients post-ASCT when compared with conventional treatment approaches. Phase I trials are also showing encouraging results for transplant-naïve patients with refractory HL, suggesting that brentuximab vedotin could represent a useful bridge to transplantation. Further studies will be needed to confirm this role, as a study from Turkey has suggested that early transplantation after treatment with brentuximab vedotin is indicated during the early optimal window of opportunity because of declining response rates after six cycles. Encouragingly for patients with either anaplastic lymphoma kinase (ALK)-positive or ALK-negative ALCL, ORRs of 50% and 76% have been observed in two Phase II studies with prolonged durations of response.

The AETHERA trial assessed the use of brentuximab vedotin (1.8 mg/kg every 3 weeks versus best supporting care) as consolidation therapy after ASCT for up to 16 cycles in a randomised, double-blind, multicentre trial. The results of the trial have demonstrated improved 2-year PFS in patients that received brentuximab vedotin versus placebo (63% versus 51%; p<0.001). Brentuximab vedotin post-transplant was approved by the FDA on the basis of this study, with the European Medicines Agency (EMA) currently reviewing a similar application. The ECHELON-2 Phase III trial is designed to test brentuximab vedotin + CHP versus the standard CHOP regimen in patients with newly diagnosed ALCL and CD30+ T-cell lymphomas; its recruitment period is still open.

Beyond HL, the majority of patients with relapsed PTCL have few treatment options. PTCLs comprise a heterogeneous range of aggressive natural killer (NK) and T-cell lymphomas, including ALCL, peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), NK/T-cell lymphomas, angioimmunoblastic T-cell lymphoma (AITL), and cutaneous T cell lymphomas, including mycosis fungoides/Sézary syndrome, amongst others. Many of the lymphoma subtypes that fall under the diagnosis of PTCL have some degree of CD30 positivity, and affected patients have poor outcomes. Between 40–65% of patients with PTCL will relapse after initial multiple agent chemotherapy and no standardised treatment protocols are accepted for these patients, creating a clear unmet clinical need. To date, brentuximab vedotin is only licensed for use in patients with relapsing/refractory HL and systemic ALCL. It is yet to be clarified whether and how patients with other forms of CD30+ lymphoma will benefit from brentuximab vedotin therapy.

A Phase II study regarding the use of brentuximab vedotin in patients with a range of relapsed PTCL diseases, including mature NK/T-cell lymphomas (n=34), AITL (n=15), and PTCL-NOS (n=21), has been reported. Combined complete and partial response rates ranged from 33–54% across these disease subtypes, but it is not clear whether IHC estimates of CD30 positivity correlate with disease response to brentuximab vedotin. A separate Phase II study assessed the use of brentuximab vedotin in patients with two forms of cutaneous T-cell lymphoma, mycosis fungoides/Sézary syndrome. Patients had CD30 expression levels that ranged from 0–100%. Patients with CD30+ levels <5% were less likely to achieve a complete response than those with levels >5%. Brentuximab vedotin is now being tested against standard treatment (methotrexate or bexarotene) in the ALCANZA randomised trial in CD30+ cutaneous T-cell lymphomas. This level of efficacy in the forms of lymphoma with relatively low CD30 expression levels mentioned above gives rise to the hope that brentuximab vedotin could be an effective treatment for patients with a broad range of lymphomas.

With regards to B-cell lymphomas, a Canadian study demonstrated that CD30 is expressed by 25% of DLBCLs and is a favourable prognostic factor. Correspondingly, clinical responses were observed in 44% of relapsed/refractory patients with CD30+ DLBCL (n=49), and also in some patients with other types of B-cell lymphoma. Preclinical studies have indicated that brentuximab vedotin is effective against cell lines and in vivo mouse models of CD30+ primary effusion lymphomas.
lymphoma, a B-cell form of non-HL.\textsuperscript{51} Taken together, these data support further clinical studies of brentuximab vedotin in DLBCL and other rarer forms of B-cell lymphoma. Future work that separates out patients with higher levels of CD30 expression will be required to optimise the subgroups of individuals that will benefit most from brentuximab vedotin therapy.

**AREAS OF ONGOING RESEARCH**

Brentuximab vedotin is one of a series of mAb conjugates to be approved. Preclinical studies are ongoing to develop inotuzumab ozogamicin and polatuzumab vedotin for clinical trials, as well as a raft of others that adopt tumour cell targeting to deliver cytotoxic agents intracellularly. Further data regarding the use of these agents from preclinical studies are eagerly awaited.

Several other therapeutic strategies are coming to the bedside for the treatment of CD30\textsuperscript{+} neoplasms, including immunotherapy via cell checkpoint inhibition, principally by programmed cell death protein-1 (PD-1) blockade, and immunomodulation, via the engagement of cytotoxic immune effector cells against tumour cells. RS cells in classical HL evade immune detection by expressing proteins of the PD-1 pathway. The surface expression of PD-1 proteins enables tumour cells to evade cell killing by CD8\textsuperscript{+} T cells;\textsuperscript{52} accordingly, programmed death ligand-1 (PD-L1) and PD-L2 are overexpressed by RS cells, particularly in the nodular sclerosis form of HL as a consequence of the amplification of Chr 9p24.\textsuperscript{1} Inhibition of PD-1 expression is therefore being investigated as a potential therapeutic strategy. Nivolumab is a mAb targeted to block PD-1, and has been shown to have an acceptable safety profile (22% Grade 3 toxicities) when used in patients with relapsed/refractory HL, including patients that had relapsed after treatment with brentuximab vedotin.\textsuperscript{54} In terms of response rates, of the 23 patients participating in a Phase II study published this year: 3 showed stable disease, 16 had a partial response, and 4 had a complete response; the PFS rate at 24 weeks was 86%.

**SUMMARY AND CONCLUSIONS**

Recent advances in the clinical management and molecular understanding of classical HL and other more common subtypes have yielded novel management options that may be applicable across a wide range of CD30\textsuperscript{+} conditions. The less common subtypes of CD30\textsuperscript{+} lymphomas have been neglected in terms of funding and research interest in the past. Of particular interest is brentuximab vedotin, an antibody conjugate drug against CD30 that targets an antimitotic compound specifically to disease cells. Future studies will be required to assess the use of combination therapies of any of these strategies with brentuximab vedotin, with or without standard chemotherapeutic regimens and before or after ASCT. It will be with advances in the molecular biological understanding of each lymphoma subtype that a truly personalised approach will be developed that is maximally effective with minimal side effects for each patient.

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**REFERENCES**


