

FRESH FROM THE PIPELINE

Brentuximab vedotin

Anas Younes, Uma Yasothan and Peter Kirkpatrick

In August 2011 brentuximab vedotin (Adcetris; Seattle Genetics), a CD30-specific antibody–drug conjugate, was approved by the US Food and Drug Administration (FDA) for the treatment of patients with Hodgkin's lymphoma and patients with systemic anaplastic large cell lymphoma (ALCL).

Monoclonal antibodies (mAbs) directed against antigens expressed on cancer cells have become a widely explored class of therapeutics in oncology, with several demonstrating substantial clinical success, such as the CD20-specific mAb rituximab (Rituxan/MabThera; Biogen Idec/Genentech/Roche) for the treatment of non-Hodgkin's lymphoma. However, as the activity of mAbs has often not been sufficient to produce a lasting treatment benefit, various strategies have been investigated to increase their potency, including the development of antibody–drug conjugates (ADCs)¹.

ADC technology is based on the principle that linking a cytotoxic drug to a mAb that is specific for an antigen that is more highly expressed on cancer cells could allow high doses of the cytotoxic drug to be specifically delivered to cancer cells, largely sparing normal tissues¹. However, harnessing this principle has been challenging, with various first-generation ADCs not showing sufficient activity¹. Furthermore, although the pioneering ADC — gemtuzumab ozogamicin (Mylotarg; Pfizer), a CD33-specific mAb conjugated to calicheamicin — was approved by the FDA in 2000 for the treatment of acute myeloid leukaemia, it was voluntarily withdrawn in 2010 when post-marketing studies indicated that the ADC did not improve survival and had greater toxicity than chemotherapy alone.

Research on ADCs has revealed several factors that affect the likelihood of success¹. First, the selected antigen should allow substantial tumour selectivity¹. Second, as only a small amount of the ADC will reach the target cells, the cytotoxic drug should be highly potent¹. Third, linker technologies are needed that result in the stability of the ADC in circulation while leading to efficient release of the cytotoxic drug following its internalization into target cells or localization in the tumour¹. Based on an improved understanding of such

factors, several second-generation ADCs have been evaluated in clinical trials in various cancers¹, and brentuximab vedotin is the first to be approved.

Basis of discovery

CD30, which is a member of the tumour necrosis factor receptor superfamily, is highly expressed on the surface of tumour cells in Hodgkin's lymphoma and ALCL^{2–4}. Furthermore, its normal expression is limited largely to activated immune cells, and CD30 was therefore considered to be a promising target antigen for mAb-based anticancer therapies^{2–4}. However, although human CD30-specific mAbs such as the chimeric mAb cAC10 showed anticancer activity in preclinical studies³, their activity in clinical trials was limited.

To enhance the potency of CD30-specific mAbs, an ADC known as cAC10-vcMMAE (and subsequently as SGN-35 and brentuximab vedotin) was generated^{4,5}. This was based on technology developed to link mAbs to the potent cytotoxic drug monomethyl auristatin E (MMAE) — a synthetic analogue of the marine natural product dolastatin 10 that inhibits tubulin polymerization — using a stable dipeptide linker that is selectively cleaved by lysosomal enzymes after internalization^{4,5}.

Drug properties

Brentuximab vedotin is a CD30-directed ADC that consists of three components: the chimeric immunoglobulin G1 mAb cAC10, which is specific for human CD30; the microtubule-disrupting agent MMAE; and a protease-cleavable covalent linker that attaches cAC10 to MMAE^{4–6}. The mAb is produced in Chinese hamster ovary cells, and the small-molecule components are chemically synthesized. Brentuximab vedotin is produced by chemical conjugation of the mAb and small-molecule components, and ~four molecules of MMAE are attached to each antibody⁶.

In preclinical studies, binding of brentuximab vedotin to cells was followed by internalization of the ADC–CD30 complex, and release of MMAE via proteolytic cleavage, leading to G2/M phase growth arrest and apoptotic cell death^{4,5}. Brentuximab vedotin showed potent activity in mouse xenograft models of Hodgkin's lymphoma and ALCL^{4,5}.

Clinical data

In a Phase I open-label trial involving 45 patients with relapsed or refractory CD30-positive haematological cancers — primarily Hodgkin's lymphoma or ALCL — patients were treated with escalating doses (from 0.1 mg per kg to 3.6 mg per kg) of brentuximab vedotin, administered by intravenous infusion every 3 weeks⁷. Objective responses were observed in 17 patients, including 11 complete remissions⁷. Dose-limiting toxicities included neutropenia and hyperglycaemia, and the dose to be used in Phase II trials was determined to be 1.8 mg per kg every 3 weeks⁷.

The efficacy of brentuximab vedotin in Hodgkin's lymphoma was evaluated in an open-label, single-arm Phase II trial involving 102 patients who had relapsed after autologous stem cell transplant (ASCT)⁶. The overall response rate, determined by clinical and radiographic measures, was ~73% (with 32% of patients showing a complete response and 40% showing a partial response), with a median duration of response of 6.7 months⁶.

The efficacy of brentuximab vedotin in patients with relapsed systemic ALCL was evaluated in an open-label, single-arm Phase II trial involving 58 patients, 72% of whom were anaplastic lymphoma kinase-negative⁶. The overall response rate, determined by clinical and radiographic measures, was 86% (with 57% of patients showing a complete response and 29% showing a partial response), with a median duration of response of 12.6 months⁶.

Indications

Brentuximab vedotin has been granted accelerated approval by the FDA for the treatment of patients with Hodgkin's lymphoma and patients with systemic ALCL⁶. In patients with Hodgkin's lymphoma, brentuximab vedotin is indicated for use after the failure of ASCT or after the failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates⁶. In patients with systemic ALCL, it is indicated for use after the failure of at least one prior multi-agent chemotherapy regimen⁶. These indications are based on response rate⁶.

ANALYSIS | CD30-POSITIVE CANCERS

- ▶ Analysing issues in the treatment of CD30-positive cancers is Anas Younes, M.D., Professor of Medicine, Director, Clinical Investigation and Translational Research Department of Lymphoma/Myeloma, MD Anderson Cancer Center, Texas, USA.

Both Hodgkin's lymphoma and ALCL are relatively rare cancers, accounting for ~11,000 newly diagnosed patients, combined, annually in the United States. Importantly, both Hodgkin's lymphoma and ALCL are potentially highly curable types of lymphoma when conventional chemotherapy regimens and radiation therapy are used. However, around one-third of patients are not cured with currently available front-line regimens and require additional therapy. The standard of care for these patients is a second-line treatment to induce a second remission, which can then be consolidated by stem cell transplantation. Such a 'salvage' approach can cure 50% of patients with relapsed and refractory lymphomas. However, patients who relapse after ASCT are considered incurable, and represent an unmet medical need.

Following the recent approval of brentuximab vedotin by the FDA, the majority of these patients in the United States will be treated with brentuximab vedotin, as the drug is highly effective and relatively safe in this setting. In fact, the single-agent activity of brentuximab vedotin in patients with Hodgkin's lymphoma in a post-ASCT setting is

equivalent to that of multi-agent combination chemotherapy⁸, but with a much lower toxicity profile. In addition, the current FDA indication allows treatment with brentuximab vedotin before ASCT, for ALCL after failing one regimen and for Hodgkin's lymphoma after failing two regimens. Although the drug will certainly be used within this indication as a single agent, it is likely to have a higher impact when combined with pre-transplant salvage regimens.

Several other haematological and non-haematological malignancies can express CD30, including primary mediastinal large B cell lymphoma, peripheral T cell lymphoma and germ cell tumours, and it is important to investigate the potential of brentuximab vedotin in such cancers. Phase II trials of brentuximab vedotin in patients with CD30-positive non-Hodgkin's lymphoma (NCT01421667) and CD30-positive non-lymphomatous malignancies (NCT01461538) are ongoing.

The impact of brentuximab vedotin on patients' survival is likely to come from enhancing the efficacy of front-line regimens, such as the ABVD regimen for Hodgkin's lymphoma and the CHOP regimen for ALCL. Phase I studies combining brentuximab vedotin with these regimens are currently being evaluated to ensure the safety of this approach. Depending on the safety of these new regimens, randomized Phase III studies should be conducted to compare the new

brentuximab vedotin-based regimens with standard ABVD or CHOP regimens.

Additional areas to be examined include the potential role of brentuximab vedotin in patients with early-stage Hodgkin's lymphoma, with the goal of reducing treatment-related toxicity, perhaps by eliminating the number of drugs or reducing the number of treatment cycles, and possibly by eliminating the need for radiation therapy. Such trials may be aided by incorporating the use of interim biomarkers, such as fluorodeoxyglucose positron emission tomography or serum thymus and activation-regulated chemokine levels^{9,10}. Finally, because most patients who were treated with single-agent brentuximab vedotin achieved partial remissions, it will be important to determine the mechanisms of resistance for this drug and to develop rationally designed combination regimens that will increase the complete response rate and the remission duration.

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Competing interests statement

The authors declare [competing financial interests](#): see Web version for details.

Box 1 | Market for CD30-targeted therapies

Analysing the market for CD30-targeted therapies is Uma Yasothan, IMS Health, London, UK.

In August 2011, the US Food and Drug Administration approved brentuximab vedotin (Adcetris; Seattle Genetics) for the treatment of patients with Hodgkin's lymphoma and patients with systemic anaplastic large cell lymphoma (ALCL). Brentuximab vedotin is the first drug to be approved for Hodgkin's lymphoma in three decades, and provides a new therapeutic option for patients with refractory disease. The vast majority of patients with Hodgkin's lymphoma are cured by first-line treatment with chemotherapy and/or second-line regimens or ASCT. The size of the target market for potential patients in the refractory disease setting is currently unknown, which makes it challenging to estimate the sales potential of the drug. Systemic ALCL, an aggressive subtype of non-Hodgkin's lymphoma (NHL), is a rare cancer (~3% of all NHL cases) and brentuximab vedotin is the first approved therapy for this malignancy. However, the difficulty in the diagnosis of systemic ALCL, the current approved use of brentuximab vedotin for patients with relapsed and/or refractory systemic ALCL and the poor prognosis of these patients seem likely to translate to a small pool of potential patients for whom the drug might be prescribed at present.

IMS MIDAS 2011 data suggest that Adcetris sales might be off to a better than anticipated start. The product was launched in the United States in the third quarter of 2011 and has already registered sales of US\$6 million in October. Brentuximab vedotin is also being developed for earlier lines of Hodgkin's lymphoma and ALCL treatment, and for other CD30-positive haematological cancers. Approval in the European Union is anticipated in 2012. Analysts' estimated peak sales range from \$70 million in 2012 (Kasimov, C. *et al.* JP Morgan North America Equity Research Report; 8 Sep 2011) to ~\$200 million–288 million by 2015 (Kantor, J. *et al.* RBC Capital Markets Equity Research Report; 4 Nov 2011).