Brentuximab vedotin

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Brentuximab vedotin is an anti-CD30 antibody-drug conjugate with proven efficacy in patients with CD30+ malignancies, including classical Hodgkin lymphoma and anaplastic large cell lymphoma. Promising activity has also been seen in other lymphomas that express CD30. Because of its acceptable toxicity profile and significant clinical efficacy, single-agent brentuximab vedotin is an approved treatment for relapsed patients with these diseases. Brentuximab vedotin has safely been combined with chemotherapy and is now being compared with standard treatments in randomized trials. (*Blood*. 2014;124(22):3197-3200)

**Introduction**

Delivery of cytotoxic agents specifically to malignant cells has always been a goal of cancer therapy. With the development of monoclonal antibodies for clinical use, this goal has become a reality, and antibody-drug conjugates are now part of standard therapy in diseases such as lymphoma and breast cancer. Brentuximab vedotin, which targets CD30, has contributed to the success of antibody-drug conjugates and has demonstrated significant clinical activity in classical Hodgkin lymphoma and other CD30+ lymphoproliferative diseases.

**CD30 as a therapeutic target**

CD30 is a membrane glycoprotein and a member of the tumor necrosis factor (TNF) receptor family, and signaling through CD30 can have pleiotropic effects, depending on the type and activation state of the cell. The cytoplasmic CD30 domain interacts with multiple members of the TNF receptor-associated factor family and is capable of inducing apoptosis through the c-Jun N-terminal kinase (JNK) n38. It also mediates cell activation via nuclear factor kappa B as well as effector functions via Fas-associated protein with death domain (FADD).1,2

The ligand for CD30 is CD30L (CD153), a type 2 membrane protein with structural homology to TNF-α, TNF-β, and CD40 ligand. Signaling mediated by CD30 promotes cell proliferation and survival but can also induce antiproliferative responses and trigger cell death. Whether CD30 activation results in proliferation of cells or reduced viability depends on the cell type receiving the signal and the environment in which the signal is delivered.3

CD30 is usually not typically expressed in most human tissue under normal physiologic conditions. However, expression can be seen in thymocytes during thymus development, and there is also expression on pancreatic exocrine cells, as well as on decidual cells in the uterus and endometrium during pregnancy. CD30 can also be transiently upregulated on activated T cells, and CD30L may cause proliferation of T cells in the presence of T-cell receptor engagement. With subsequent activation of T cells, CD30 expression can be sustained. This suggests a potential role for CD30 in regulating memory T cells.5

CD30L may promote the proliferation of neoplastic cells. CD30 is highly expressed by Reed-Sternberg cells in Hodgkin lymphoma and on anaplastic large cell lymphoma (ALCL) cells. CD30 can also be expressed at variable levels on many other subtypes of non-Hodgkin lymphoma. CD30 signaling in malignant lymphoma cells plays a pathophysiological role in maintaining their growth and survival.5,6 In Hodgkin lymphoma, CD30L enhances cytokine production, particularly interleukin-6 and TNF-α, and CD30L upregulates intercellular adhesion molecule-1 expression on Reed-Sternberg cells.7 CD30 signaling also induces nuclear factor kappa B activation resulting in expression of antiapoptotic genes, including cFLIP, XIAP, and bclxl in Reed-Sternberg cells, thereby promoting their growth and survival.5,9

**Preclinical data**

Monoclonal antibodies targeting CD30 have shown activity both in vitro and in clinical trials in Hodgkin lymphoma and ALCL. In models of Hodgkin lymphoma, the chimeric monoclonal antibody cAC10 was shown to promote arrest of tumor cell growth and to cause DNA fragmentation.10 Crosslinking cAC10 suppressed proliferation in a variety of Hodgkin and ALCL cell lines. Despite cAC10 providing a survival advantage in mouse models of both Hodgkin lymphoma and ALCL, cAC10 had only modest clinical activity in early-phase trials in patients with these diseases.11,12

To further enhance the activity of cAC10, the antibody was conjugated by using a valine-citrulline peptide linker to a cytotoxic agent monomethyl auristatin E (MMAE) resulting in an antibody-drug conjugate, cAC10-vcMMAE.13 MMAE is a potent mitotic agent that inhibits cell division by blocking the polymerization of tubulin. The antibody-drug conjugate was stable in human serum but was cleaved by lysosomal proteases after receptor-mediated internalization. Release of MMAE into the CD30-expressing cell induced growth arrest and cell death by inducing apoptosis. Furthermore, the antibody-drug conjugate may have an additional effect on bystander cells because MMAE may diffuse out of the cell, or the agent may be taken up by other phagocytic cells and thereby induce apoptosis of other cells in the tumor microenvironment. This
Initial studies were conducted in CD30⁺ diseases, including Hodgkin lymphoma and ALCL. In an initial phase 1 trial using a schedule of brentuximab vedotin once every 3 weeks, 45 patients with relapsed or refractory Hodgkin lymphoma and ALCL were treated. The maximum tolerated dose (MTD) was 1.8 mg/kg administered once every 3 weeks. Objective responses, including 11 complete responses, were seen in 17 patients. Of the 12 patients who received the MTD, 50% had an objective response, and the median duration of the responses was ~10 months. Most patients benefited from treatment, and tumor regression was observed in 36 (86%) of 42 evaluable patients. A second phase 1 dose-escalation study was performed using brentuximab vedotin on a weekly schedule. Patients received intravenous infusions on days 1, 8, and 15 of a 28-day cycle, and an MTD of 1.2 mg/kg weekly was identified. Clinical benefit was again seen in the majority of patients, and 85% of the patients treated had tumor regression. The overall response rate in this study was 59% (24 of 44 patients), and 34% of the patients had a complete response. The median duration of response in this study was not reached with the median follow-up of 45 weeks.

A subsequent pivotal phase 2 trial was then conducted in patients with relapsed and refractory Hodgkin lymphoma after autologous stem cell transplantation. In all 102 patients were treated with brentuximab vedotin at a dose of 1.8 mg/kg once every 3 weeks. The overall response rate was 75% with a complete response rate of 34%. The median time to objective response was 5.7 weeks (~2 doses of treatment drug) and the median time to complete response was 12 weeks (~4 doses of treatment drug). The median progression-free survival for all patients was 5.6 months, and the median duration of response for those patients in complete remission was 20.3 months. The responses have proved durable, and follow-up beyond 4 years has confirmed that ~25% of patients have remained in remission.

A second phase 2 study was performed in patients with systemic ALCL. In that study, 58 patients were treated with brentuximab vedotin at a dose of 1.8 mg/kg intravenously every 3 weeks. Fifty patients (86%) achieved an objective response, 57% of whom had a complete remission. The median duration of overall response was 12.6 months, and the median duration of complete response was 13.2 months. These studies confirmed the significant activity of brentuximab vedotin in CD30⁺ lymphomas and led to accelerated approval of the drug by the U.S. Food and Drug Administration for use in patients with relapsed/refractory Hodgkin lymphoma after autologous stem cell transplantation or, if the patients were not candidates for transplantation, after at least 2 prior lines of therapy and also for relapsed/refractory systemic ALCL after at least 1 prior line of therapy. It has also received conditional approval for these indications by the Committee for Medicinal Products for Human Use of the European Union.

Subsequent studies have further confirmed the high rate of response in all age groups, including older patients. A retrospective analysis of elderly patients >60 years of age confirmed objective response rates of 56% in Hodgkin lymphoma and 100% in systemic ALCL, suggesting that the use of brentuximab vedotin as a single agent in these diseases in elderly patients may be a feasible option, even as initial treatment. This is being tested in an ongoing trial of single-agent brentuximab vedotin in patients age ≥60 years with newly diagnosed Hodgkin lymphoma, and compelling antitumor activity has been demonstrated. At the time of an interim analysis of 13 patients, a response rate of 82% was reported in this historically challenging population of patients.

Although brentuximab vedotin has been shown to be safe and effective after failure of an autologous stem cell transplantation, studies have assessed whether brentuximab vedotin is safe and effective after allogeneic stem cell transplantation or as a bridge to an allogeneic stem cell transplantation. In an initial study of 25 Hodgkin lymphoma patients with recurrent disease after allogeneic stem cell transplantation, the overall response rate was 50% with a complete response rate of 38%, and the median progression-free survival was 7.8 months. A number of subsequent studies have shown that brentuximab vedotin can be used as a bridge to a reduced-intensity allogeneic stem cell transplantation. In a retrospective analysis of 18 patients, brentuximab vedotin did not appear to adversely affect engraftment, graft-versus-host disease, or survival. Two further studies have shown that brentuximab vedotin followed by an allogeneic stem cell transplantation is an effective salvage regimen in Hodgkin lymphoma, and brentuximab vedotin can serve as a bridge to allogeneic stem cell transplantation.

Subsequent studies have explored the efficacy of brentuximab vedotin in other non-Hodgkin lymphomas that express CD30. A recently reported phase 2 trial evaluated 62 patients with B-cell non-Hodgkin lymphoma, 44 of whom had diffuse large B-cell lymphoma. Of the 43 patients with diffuse large B-cell lymphoma who were evaluable for response, 17 had a response to therapy (40%), 7 (16%) of whom had a complete response to treatment. The median duration of overall response was 36 weeks. Interestingly, there was no correlation between CD30 expression as detected by immunohistochemistry and the response rate in this study. This has led to additional trials using brentuximab vedotin in this disease type.

Toxicity profile

Brentuximab vedotin is typically administered as an outpatient treatment and is generally well tolerated. Infusion-related reactions can be observed, but these are generally manageable with the appropriate premedication. Other common side effects include fatigue, neutropenia, nausea, diarrhea, fever, vomiting, arthralgias, and alopecia. Most of these adverse events, however, are typically low grade.

Peripheral neuropathy is the most clinically significant adverse event and is dose dependent and typically cumulative. Most patients develop sensory neuropathy, but peripheral motor neuropathy has also been observed. Peripheral neuropathy is relatively common, with ~40% of patients developing some degree of peripheral neuropathy; however, ~10% of patients may develop grade 3

Single agent results
Peripheral neuropathy. The median time to onset of any peripheral neuropathy event in the pivotal trial in Hodgkin lymphoma was 12.4 weeks, and the median times to onset of grade 2 and grade 3 peripheral neuropathy were 27.3 and 38.0 weeks, respectively. Complete resolution of all events of peripheral neuropathy occurred in 50% of patients, and the median time to improvement or resolution in this study was 13.2 weeks.

Pulmonary toxicity has also been observed with brentuximab vedotin, particularly when given in combination with other chemotherapy agents. In a phase 1 clinical study combining brentuximab vedotin with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) as first-line treatment for patients with advanced-stage classical Hodgkin lymphoma, pulmonary toxicity was seen in 7 of 19 patients. This led to a formal warning by the US Food and Drug Administration against the use of brentuximab vedotin in combination with bleomycin.

Since the approval of brentuximab vedotin, cases of severe progressive multifocal leukoencephalopathy have been reported. Because of the serious nature of progressive multifocal leukoencephalopathy, a warning highlighting this potential risk has been added to brentuximab vedotin’s drug label. Pancreatitis is another serious and potentially fatal toxicity that treating physicians should be aware of. Recently, a series of 8 patients who developed pancreatitis was reported. Two of these patients died, and this risk was therefore also added to the drug label.

Combination trials

On the basis of the efficacy of brentuximab vedotin as a single agent in Hodgkin lymphoma, a study was done using brentuximab vedotin in combination with ABVD or AVD (ABVD without bleomycin) for up to 6 cycles. The MTD of brentuximab vedotin in combination with this chemotherapy was 1.2 mg/kg. Of note, significant pulmonary toxicity was seen in the study when brentuximab vedotin was given with ABVD. Eleven (44%) of 25 patients had evidence of pulmonary toxicity, and therefore the subsequent cohort of patients was treated without bleomycin. In this second cohort of 25 patients, no significant pulmonary toxicity was seen. The combination of ABVD with brentuximab vedotin was highly effective. Complete responses were seen in 24 (96%) of 25 patients who received brentuximab vedotin with AVD chemotherapy. Similarly, 21(95%) of 22 evaluable patients given brentuximab vedotin and ABVD achieved a complete response. Aside from pulmonary toxicity, the most common grade 3 or higher adverse event seen was neutropenia. On the basis of these encouraging results, a randomized controlled trial of AVD plus brentuximab vedotin compared with ABVD chemotherapy in stage III or IV Hodgkin lymphoma patients is currently enrolling patients.

Similarly, on the basis of the excellent single-agent results seen in relapsed ALCL patients, brentuximab vedotin was combined with multiagent chemotherapy as first-line treatment of newly diagnosed ALCL patients. Patients received brentuximab vedotin in combination with standard-dose cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy or cyclophosphamide, doxorubicin and prednisone without vincristine (CHP). The MTD of brentuximab vedotin in combination with CHOP chemotherapy was 1.8 mg/kg administered every 3 weeks. All treated patients (100%) achieved an objective response, with 23 (88%) of 26 evaluable patients achieving a complete remission. On the basis of these promising results, a randomized trial of brentuximab vedotin with CHP chemotherapy compared with CHOP chemotherapy in the first-line management of patients with CD30+ T-cell non-Hodgkin lymphomas is currently in progress.

In addition, multiple studies are in progress testing brentuximab vedotin in combination with other chemotherapy agents and also in combination with small molecule inhibitors, biological agents, immune checkpoint inhibitors, or radiation therapy. The efficacy of brentuximab vedotin is further being tested in other diseases, including acute myeloid leukemia, germ cell tumors, systemic mastocytosis, and graft-versus-host disease.

Conclusion

Treatment with brentuximab vedotin is currently a standard of care for patients with relapsed or refractory systemic ALCL and for patients with relapsed or refractory Hodgkin lymphoma after autologous stem cell transplantation or at least 2 prior combination chemotherapy regimens. This agent is now being tested in combination with standard chemotherapy in both the first-line and relapsed setting, and the results are very promising. Although the clinical results with this agent to date have been excellent, we will need to wait for results from current randomized trials to determine whether adding brentuximab vedotin to chemotherapy improves patient outcome compared with standard treatment approaches.

Authorship

Contribution: S.M.A. wrote the manuscript.
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