Brentuximab vedotin in Hodgkin lymphoma and systemic anaplastic large-cell lymphoma

The FDA approval of this novel antibody-drug conjugate is based on durable responses, with no data yet showing improved survival.

See related Commentary on page 3

Brentuximab vedotin was recently granted accelerated approval by the Food and Drug Administration for two indications: the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplantation (ASCT) or after failure of at least two multiagent chemotherapy regimens in patients who are not candidates for ASCT; and for the treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one multiagent chemotherapy regimen.[1] Both indications are based on response rate, with no data currently being available to demonstrate improved outcomes or survival.

Brentuximab vedotin is a CD30-directed antibody-drug conjugate.[2] CD30 is a defining marker of Hodgkin lymphoma and is also expressed on anaplastic large cell lymphoma cells. Its expression on a relatively small population of activated B and T cells and a small proportion of eosinophils makes it a rational drug target. Brentuximab vedotin comprises the anti-CD30 monoclonal antibody brentuximab and the antitubulin agent monomethyl auristatin E (MMAE; vedotin). After binding to CD30, the conjugate is internalized and transported to lysosomes, with vedotin being released into the cell; it binds to tubulin, resulting in breakdown of microtubules, gap 2 phase and mitosis cell cycle arrest, and apoptosis.

The approval of brentuximab vedotin was based on findings in two open-label, single-group phase II trials.[1] In both of those studies, brentuximab vedotin was administered intravenously at a dose of 1.8 mg/kg over 30 minutes once every 3 weeks. The study in Hodgkin lymphoma included 102 patients with a median age of 31 years (range, 15–77 years), of whom 53% were women and 87% were white. The patients had received a median of five previous therapies, including ASCT. Objective response occurred in 73% of patients, with median response duration of 6.7 months. Complete response occurred in 32% of patients, with a median response duration of 20.5 months and some responses were ongoing at the time of the analysis (range, 1.4–21.9 + months). Partial response occurred in 40% of patients, with a median duration of 3.5 months (range, 1.3–18.7 months).

What's new, what's important

Brentuximab vedotin is a CD30-directed antibody-drug conjugate approved for Hodgkin lymphoma after failure of autologous stem-cell transplant (ASCT), Hodgkin lymphoma patients who are not candidates for ASCT after failure of at least two multiagent chemotherapy regimens, and for systemic anaplastic large-cell lymphoma (sALCL) after failure of at least one multiagent chemotherapy regimen.

The recommended dose is 1.8 mg/kg, administered as an IV infusion over 30 minutes every 3 weeks. This is the first antibody-drug conjugate approved by the Food and Drug Administration for CD30-positive Hodgkin lymphoma. The approval is based on response rate, which is impressive even in the refractory setting. The side effects, which include hematologic and neurological, are predictable with this combination. Among the most common are neutropenia, peripheral sensory neuropathy, fatigue, upper respiratory tract infection, nausea, diarrhea, anemia, pyrexia, thrombocytopenia, rash, abdominal pain, cough, and vomiting.

The approval of brentuximab vedotin is an encouraging development for patients with refractory Hodgkin lymphoma, and we hope to see the approval of other drugs from this class of antibody-drug conjugates. Ongoing studies will give us a better idea about how to position brentuximab vedotin in the treatment of Hodgkin lymphoma, especially in regard to long-term side effects and improved outcomes or survival.

—Jame Abraham, MD

Report prepared by Matt Stenger, MS.

Commun Oncol 2012;9:5-7
doi:10.1016/j.cmonc.2011.12.007

How I treat patients with Hodgkin lymphoma

Treatment strategies for patients with Hodgkin lymphoma are evolving. The standard approach to those with early-stage disease had been involved-field radiation therapy (IFRT) and 6 cycles of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) for patients with advanced-stage disease. With those approaches, about 90% of patients with limited disease were cured, as were between 60% and 75% of those with advanced-stage disease. However, most of the patients who are not cured with initial treatment eventually die from the disease. Those who are cured often suffer from the long-term sequelae of treatment-related toxicities from both the radiation and the chemotherapy drugs. As such, treatment paradigms that alter therapy for patients with a likelihood of a poor outcome or limit therapy for those with a more favorable outcome are evolving.

A number of pretreatment characteristics have been suggested as prognostic factors, including age, disease stage, erythrocyte sedimentation rate, sex, serum albumin, and the number of involved nodal sites. However, it has been suggested that surveillance with fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) scanning might be the most powerful tool for predicting recurrence and that it has the potential to change our approach to treatment. A posttreatment scan is predictive of outcome, with a negative predictive value of 95%, but a positive predictive value of only 80% because of false-positive results. Currently, researchers in a number of national and international studies are looking at a risk-adapted approach based on an interim PET scan (after 2 cycles of chemotherapy). A negative scan carries a 95% negative predictive value. However, the predictive value of a positive scan is highly variable among reported studies.

For patients with limited-stage disease (stages I or II, not bulky disease), I administer 2 cycles of ABVD and repeat a PET scan just before the start of cycle 3. Then, if the scan is negative, I stop after 4 total cycles of chemotherapy. If the scan is positive, I continue with the full 6 cycles. Ongoing clinical trials are investigating whether changing therapy on the basis of the scan results improves outcome, and it remains unproven at this time. Trials are also looking at delivering even fewer cycles based on PET results to reduce long-term complications of the treatment.

The management of patients with limited-stage, bulky disease is controversial. The standard would be 4–6 cycles of chemotherapy, followed by IFRT. Whether or not the radiation is necessary is the subject of an ongoing CALGB risk-adapted study. Again, if a patient has a negative PET scan after 2 cycles, I deliver 6 cycles of ABVD without the radiation. If the scan is positive, then radiation is recommended; however, in that setting it may not be adequate to overcome drug resistance.

I treat patients with advanced-stage disease with 6 cycles of ABVD and no radiation, even to sites of previous bulky disease. If there is a concern of pulmonary dysfunction, then I omit the bleomycin without much concern for a reduction in efficacy. The German Hodgkin Study Group has shown clearly that patients with a negative PET after treatment for advanced-stage disease despite having a residual tumor mass do not require additional radiation therapy.

Patients with relapsed or refractory disease are currently treated with a regimen such as ICE (ifosfamide, carboplatin, etoposide) or DHAP (cytosine arabinoside, cisplatin, dexamethasone) and, if they are chemosensitive, then they are referred for autologous stem cell transplantation or allogeneic bone marrow transplant. If transplant is not successful or if the patient is not considered a suitable candidate for transplant, then we are fortunate to now have brentuximab vedotin as an effective treatment. Other drugs being studied in this setting include bendamustine, lenalidomide, and everolimus.

Thus, with the high cure rate in Hodgkin lymphoma, the goals of treatment have changed to individualized therapy: maximizing efficacy in high-risk patients and reducing toxicity in low-risk patients. Participation in one of the several important risk-adapted trials will help us towards that goal.

—Bruce D. Cheson, MD
Division of Hematology-Oncology, Georgetown University Hospital Lombardi Comprehensive Cancer Center, Washington, DC

The study in systemic anaplastic large cell lymphoma included 58 patients who had either relapsed after their most recent previous therapy (50%) or who had disease refractory to their most recent previous therapy. The patients in this study had a median age of 52 years (range, 14–76 years), 57% were men, and 83% were white. They had received a median of two previous therapies, with 26% of the patients having received previous ASCT; 72% were anaplastic lymphoma kinase (ALK)-negative. Objective response occurred in 86% of patients, with a median duration of response of 12.6 months (range, 0.1–15.9+ months). Complete response occurred in 57% of patients, with a median duration of response of 13.2 months (range, 0.7–15.9+ months), and partial response occurred in 29%, with a median duration of 2.1 months (range, 0.1–15.8+ months). Some complete and partial responses were ongoing at the time of analysis.

Adverse effects with brentuximab vedotin are primarily hematologic, neurologic, and constitutional. In the study in Hodgkin lymphoma, the most common adverse events (>20%) irrespective of causality attribution to the study drug were neutropenia, peripheral sensory neuropathy, fatigue, upper respiratory tract infection, nausea, diarrhea, anemia, pyrexia, thrombocytopenia, rash, abdominal pain, cough, and vomiting. The most common grade 3 or 4 adverse events were neutropenia, anemia, thrombocyto-

penia, and peripheral sensory neuropathy. In the trial in systemic anaplastic large cell lymphoma, the most frequent adverse events (>20%) were neutropenia, peripheral sensory neuropathy, anemia, fatigue, nausea, pyrexia, rash, diarrhea, and pain. The most common grade 3 or 4 adverse events were neutropenia, thrombocytopenia, peripheral sensory neuropathy, and pain.

Overall, serious adverse events occurred in 31% of patients. The most common in Hodgkin lymphoma patients were peripheral motor neuropathy (4%), abdominal pain (3%), and pulmonary embolism, pneumonitis, pneumothorax, pyelonephritis, and pyrexia (2% each). The most common in systemic anaplastic large cell lymphoma patients were septic shock, supraventricular arrhythmia, pain in extremities, and urinary tract infection (3% each). Progressive multifocal leukoencephalopathy, Stevens-Johnson syndrome, and tumor lysis syndrome occurred in one patient each. Adverse events led to treatment discontinuation in 21% of patients, with the most common reasons being peripheral sensory neuropathy (8%) and peripheral motor neuropathy (3%). Adverse events resulting in dose modification in greater than 5% of patients consisted of neutropenia (14%) and peripheral sensory neuropathy (11%). Two cases of anaphylaxis were seen in phase I trials of brentuximab vedotin. There were no grade 3 or 4 infusion-related reactions in the phase II trials; grade 1 or 2 reactions were observed in 12% of patients, most commonly chills, nausea, dyspnea, pruritus, pyrexia, and cough.

Brentuximab vedotin carries warnings and precautions for peripheral neuropathy, infusion reactions, neutropenia, tumor lysis syndrome, Stevens-Johnson syndrome, progressive multifocal leukoencephalopathy (a fatal case of the latter occurred in one patient who received four chemotherapy regimens before brentuximab vedotin treatment), and use in pregnancy.

References

1. ADCETRIS™ (brentuximab vedotin) for injection prescribing information. Seattle Genetics Inc. August 2011. Available at: http://www.seagen.com/pdf/ADCETRIS_US_PI.pdf. Accessed October 31, 2011.

2. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N Engl J Med*. 2010;363(19):1812-1821.