

ADVANCES IN LLM: Brentuximab Vedotin in Relapsed/Refractory Hodgkin Lymphoma

Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol*. 2012;30:2183-2189.

Background

Although the majority of patients with Hodgkin lymphoma attain a complete response with initial combination chemotherapy and/or radiotherapy, 20–40% of patients with newly diagnosed, advanced-stage Hodgkin lymphoma are refractory to initial therapy or relapse following a response.^{1,2} The optimal second-line treatment approach for these patients is high-dose chemotherapy followed by autologous stem cell transplantation (SCT).³ However, autologous SCT induces durable long-term remission in approximately half of patients. For the remaining patients, outcomes are poor, with a median survival of 28 months.⁴ The lack of effective therapies for this relatively young population has been a key unmet need in cancer therapy.

Hodgkin lymphoma is characterized by the presence of Reed-Sternberg cells that express CD30, a tumor necrosis factor superfamily member. Expression of CD30 on normal cells is limited to a small proportion of activated lymphocytes and eosinophils. The highly restricted expression pattern of CD30 makes it an attractive therapeutic target in Hodgkin lymphoma and other CD30-positive malignancies, such as systemic anaplastic large-cell lymphoma (ALCL).

The antibody-drug conjugate (ADC) brentuximab vedotin (Adcetris, Seattle Genetics) was developed to selectively deliver cytotoxic therapy to CD30-expressing cells. Brentuximab vedotin consists of an anti-CD30 antibody conjugated to the potent antimicrotubule agent monomethyl auristatin E (MMAE) via a protease cleavable linker. Binding of brentuximab vedotin to CD30 triggers internalization of the ADC-CD30 complex. In the lysosomal compartment, MMAE is proteolytically cleaved, enabling it to bind tubulin. The binding of MMAE to tubulin disrupts the microtubule network, prevents cell cycle progression, and causes cell death.⁵

Brentuximab vedotin was initially evaluated in a phase I study in 45 patients with relapsed or refractory

CD30-positive lymphomas.⁶ In that study, brentuximab vedotin demonstrated significant antitumor activity and was fairly well tolerated, with primary adverse events including fatigue, pyrexia, diarrhea, nausea, neutropenia, and peripheral neuropathy. The study identified the maximum tolerated dose as 1.8 mg/kg administered intravenously every 3 weeks; this dosing schedule was selected for further study.

Based on the promising activity and acceptable safety profile in the phase I study, 2 pivotal phase II studies were undertaken to further evaluate the efficacy and safety of brentuximab vedotin: one in patients with Hodgkin lymphoma and the other in patients with systemic ALCL. Both studies showed high response rates and acceptable toxicity, resulting in the FDA approval of brentuximab vedotin for both indications in 2011. The pivotal trial in Hodgkin lymphoma is described here.^{7,8}

Study Description

This prospective, open-label, multicenter phase II study was conducted in the United States, Canada, and Europe. The study enrolled 102 patients with relapsed or refractory Hodgkin lymphoma after high-dose chemotherapy and autologous SCT. Inclusion criteria included documented CD30-positive, measurable disease (≥ 1.5 cm by CT; PET-positive); an Eastern Cooperative Oncology Group (ECOG) performance status of less than 2; and adequate hematologic, renal, and liver function. Exclusion criteria included pregnancy and previous receipt of an allogeneic SCT.

A total of 102 patients were enrolled. Nearly half (47%) were male, 87% were white, and the median age was 31 years (range, 15–77 years). Patients had received a median of 3.5 prior chemotherapy regimens (range, 1–13 regimens). Seventy-two patients (71%) had primary refractory disease, defined as failure to obtain a complete remission with frontline therapy or relapse within 3 months of frontline therapy. Forty-three patients (42%) were refrac-

tory to their last therapy, defined as a best response of stable or progressive disease to the most recent therapy.

As per eligibility criteria, all patients had received prior autologous SCT; the median time to relapse after SCT was 6.7 months (range, 0–131 months), with 71% of relapses occurring within a year of transplant. At baseline, 59% of patients had an ECOG performance status of 1, and 34% had B symptoms.

The study treatment consisted of brentuximab vedotin administered at 1.8 mg/kg over a 30-minute intravenous infusion, once every 3 weeks for up to 16 infusions. The primary endpoint, overall response rate (ORR) as assessed by an independent review facility (IRF), was 75%, with 34% of patients attaining complete remission (CR). The median duration of any response was 6.7 months, and the median duration of CR was 20.5 months. Another 22% had stable disease, for a disease control rate of 97%. The investigators' analysis yielded similar outcomes, including an ORR of 72% (33% CR) and a disease control rate of 99%. Tumor size reductions were observed in 94% of evaluable patients.

The median times to response and CR were 5.7 weeks and 12 weeks, respectively, reflecting the approximate time until the first follow-up CT and PET assessments, respectively. However, responses were also observed later, up to 56 weeks after initiation of therapy.

Exploratory analyses demonstrated the activity of brentuximab vedotin across patient subgroups, regardless of age, sex, race, baseline tumor size, and response to prior therapy. After a median follow-up of 19 months, the estimated median progression-free survival (PFS) in an intent-to-treat analysis was 5.6 months overall and 21.7 months among patients who attained a CR. The median overall survival (OS) was 22.4 months, and the estimated 12-month OS was 89%. Efficacy outcomes are summarized in Table 1.

Five patients who attained a CR with brentuximab vedotin proceeded directly to an allogeneic SCT prior to any evidence of disease progression. The median PFS among these patients was 21.1 months, compared with 21.7 months among the 30 patients in CR who did not receive a subsequent allogeneic SCT.

Of the 102 patients enrolled in the study, 57 patients had received systemic therapy upon relapse after autologous SCT. The median PFS associated with this last prior therapy was 4.1 months; among the same patients, the median PFS associated with brentuximab vedotin was 7.8 months. This prespecified, investigator-assessed analysis indicated a significant 59% reduction in the risk of progression or death with brentuximab vedotin compared with the most recent prior therapy (hazard ratio, 0.41; $P < .001$).

All patients enrolled on the study received at least 1 dose of study drug and were included in the safety analysis. Overall, patients received a median of 9 cycles (range,

Table 1. Efficacy Outcomes With Brentuximab Vedotin in Relapsed/Refractory Hodgkin Lymphoma After Autologous Stem Cell Transplant

Parameter	All Patients (N=102)
Objective Response Rate	75%
Complete Response	34%
Partial Response	40%
Stable Disease	22%
Median Duration of Response	
Any Response	6.7 months
Complete Response	20.5 months
Median Progression-Free Survival	5.6 months
Median Overall Survival	22.4 months

Data from Younes et al. *J Clin Oncol*. 2012;30:2183-2189.⁸

Table 2. Most Common Adverse Events Reported in Patients With Relapsed/Refractory Hodgkin Lymphoma Receiving Brentuximab Vedotin

Adverse Event	Any Grade*	Grade 3†	Grade 4†
Peripheral Sensory Neuropathy	42%	8%	0%
Nausea	35%	0%	0%
Fatigue	34%	2%	0%
Neutropenia	19%	14%	6%
Diarrhea	18%	1%	0%
Pyrexia	14%	2%	0%
Vomiting	13%	0%	0%
Arthralgia	12%	0%	0%
Pruritus	12%	0%	0%
Myalgia	11%	0%	0%
Peripheral Motor Neuropathy	11%	1%	0%
Alopecia	10%	0%	0%

Data from Younes et al. *J Clin Oncol*. 2012;30:2183-2189.⁸

*Limited to drug-related events observed in at least 10% of patients.

†Any event, independent of relationship to study drug.

1–16) and a median dose-intensity of 96%. The most common treatment-related adverse events were peripheral neuropathy, nausea, fatigue, neutropenia, and diarrhea (Table 2). The most common grade 3/4 adverse events were neutropenia (20%), peripheral sensory neuropathy (8%), thrombocytopenia (8%), and anemia (6%). No

patients died within 30 days of receiving brentuximab vedotin, and there were no treatment-related deaths.

Adverse events led to treatment discontinuation in 20% of patients, primarily due to peripheral sensory neuropathy (6%) and peripheral motor neuropathy (3%). Nearly half of patients (47%) required at least 1 dose delay, although only 8% of all doses were delayed. Dose delays were most often due to neutropenia (16%) and peripheral sensory neuropathy (13%). Peripheral neuropathy manifested primarily as grade 1/2 numbness and tingling of the fingers and toes. It appeared to be reversible, with symptoms improving to at least some degree in 80% of patients and fully resolving in 50% of patients.

Clinical Relevance

In this pivotal, multicenter phase II trial, brentuximab vedotin was associated with an objective response rate of 75% and a CR rate of 34% in patients with relapsed/refractory Hodgkin lymphoma after autologous SCT, a patient population typically associated with a very poor prognosis. Many patients attained durable complete remissions, with the median PFS of 22 months in patients in CR. Subgroup analyses did not indicate any group that did not benefit from brentuximab vedotin. Moreover, intrapatient comparisons showed that the median PFS attained with brentuximab vedotin was significantly longer than that attained with the last prior therapy postautologous SCT.

Brentuximab vedotin was fairly well tolerated; the most common adverse event was peripheral neuropathy, which was primarily grade 1/2 and reversible. The investigators noted that peripheral neuropathy was pre-existing in 23% of patients before the study, suggesting

that this population of heavily pretreated patients was predisposed to developing neuropathy.

Additional trials are evaluating brentuximab vedotin in other settings, both in Hodgkin lymphoma and in other CD30-positive malignancies. An ongoing phase I study is evaluating the addition of brentuximab vedotin to combination chemotherapy in previously untreated patients.⁷ A randomized, placebo-controlled, phase III trial is evaluating brentuximab vedotin as post-transplant therapy in patients with high-risk Hodgkin lymphoma following autologous SCT.⁹

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Commentary

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The pivotal phase II study by Younes and colleagues of brentuximab vedotin (Adcetris, Seattle Genetics), an antibody drug conjugate that targets CD30, led to the accelerated approval of this agent by the US Food and Drug Administration (FDA) in August 2011.¹ The FDA-approved indications for brentuximab vedotin include classical Hodgkin lymphoma (cHL) relapsing after either

autologous stem cell transplant (ASCT) or at least 2 multiagent chemotherapy regimens. Encouraging results from a separate phase II study of brentuximab vedotin in relapsed/refractory anaplastic large cell lymphoma (ALCL) also led to FDA approval for this indication.²

In the phase II study for relapsed/refractory cHL following ASCT, 102 patients were treated with brentuximab vedotin at 1.8 mg/kg every 3 weeks for a maximum of 16 cycles.¹ Most patients were heavily pretreated, and 72% of patients were refractory to first-line therapy. The overall response rate to brentuximab vedotin was 75%, with an unprecedented complete remission (CR) rate in this patient population of 34%. Most encouraging was the median remission duration of 21.7 months for the 35 patients achieving a CR compared to 5.1 months for patients with partial response (PR). The most frequent toxicity was mild to moderate peripheral neuropathy related to an off-target effect of free monomethyl auristatin, the microtubule dis-

rupting agent coupled to the anti-CD30 antibody. This is a common side effect of other drugs in this class, such as vincristine and vinblastine, and was reversible in the majority of patients. Importantly, significant myelosuppression was uncommon, making brentuximab an excellent choice for heavily pretreated patients. Based on these results, brentuximab should be the first therapy administered to patients with cHL who relapse after stem cell transplant. Brentuximab is also a rational choice in pretransplant patients who do not respond to standard salvage regimens such as ifosfamide, carboplatin, and etoposide (ICE) or etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP), with the goal of proceeding to transplant in responding patients.

Also encouraging were the results of a small phase II study of brentuximab re-treatment recently presented at the 2012 American Society of Clinical Oncology meeting. Twenty-three patients with prior response to brentuximab were re-treated with brentuximab vedotin at relapse.³ Nine of 15 patients with recurrent cHL and 7 of 8 patients with relapsed ALCL responded to a second course of brentuximab vedotin. Toxicities during re-treatment were mild and similar to those reported in initial therapy trials.

An important question is whether patients who achieve an initial response to brentuximab should be considered for a second stem cell transplant, specifically a reduced intensity conditioning allogeneic stem cell transplant (RIC allo-SCT), if an appropriate donor is available. Given the short remission duration of patients achieving a PR following brentuximab vedotin, this is a very reasonable approach for this subset of patients. However, in the pivotal phase II study, the patients who attained a CR and went on to allo-SCT (n=5) had a similar progression-free survival to those who achieved a CR but did not go on to allo-SCT (n=30). Despite small patient numbers, longer follow-up of both approaches (observation vs RIC allo-SCT), may provide a hint as to whether a subset of patients achieving CR with brentuximab may be cured. Until long-term data are available, either approach is justified.

Additional studies are under way or in development to determine if brentuximab vedotin should be incorporated earlier in the treatment of cHL. A large international phase III study evaluating the efficacy of brentuximab versus placebo as adjuvant therapy after ASCT for high-risk relapsed cHL is currently enrolling.⁴ Because most patients with relapsed cHL following ASCT will eventually succumb to their disease, incorporating brentuximab vedotin into first-line regimens is very attractive and may ultimately result in the highest impact for patients with

cHL. Younes and colleagues presented interim results from a recently completed phase I study looking at brentuximab vedotin combined with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in patients with untreated advanced stage cHL.⁵ Because the incidence of pulmonary toxicity was significantly higher than that reported with ABVD alone, the concomitant use of bleomycin and brentuximab is contraindicated. There were no pulmonary events in a second cohort treated with brentuximab and doxorubicin, vinblastine, and dacarbazine (AVD), and preliminary response rates were encouraging. A pharmaceutical company-sponsored international phase III study comparing ABVD to brentuximab combined with AVD in newly diagnosed advanced stage cHL is in development.

Based on excellent tolerability and impressive response rates, brentuximab vedotin holds considerable promise for patients with relapsed and refractory cHL. Despite very encouraging preliminary results, untested combinations with brentuximab vedotin should not be explored outside the setting of a clinical trial given the potential for unforeseen toxicity as evidenced by an excess number of life-threatening pulmonary events reported when bleomycin and brentuximab were given in combination. Although brentuximab vedotin has a favorable toxicity profile, an FDA-mandated boxed warning indicating a risk of progressive multifocal leukoencephalopathy (PML) was added to the drug label in January 2012, after 3 reported cases in patients receiving brentuximab for multiply relapsed cHL.⁶ Additional follow-up of larger numbers of patients will be needed to clarify any association between brentuximab and PML. In addition, as with many new targeted anticancer agents, the cost of brentuximab vedotin is high, underscoring the importance of continued efforts to precisely define the optimal use and potential benefit of this exciting new agent.

References

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