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Where Does Brentuximab Vedotin Fit into the Management of Patients with Hodgkin Lymphoma?

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Abstract Brentuximab vedotin is an antibody-drug conjugate that targets CD30 and links monomethyl auristatin E, a microtubule disrupting agent, to an anti-CD30 monoclonal antibody. A phase II study of brentuximab vedotin in relapsed/refractory classical Hodgkin lymphoma (cHL) showed an impressive overall response rate of 75 % with 34 % complete responses, and median remission duration of 20 months in complete responders. In addition, brentuximab vedotin has very modest toxicity in heavily pretreated patients, with reversible peripheral neuropathy being the most common side effect. Brentuximab vedotin received accelerated FDA approval in August 2011 for use as a salvage therapy in cHL following failure of at least two prior therapies. Brentuximab vedotin is the treatment of choice for patients relapsing after stem cell transplant and for patients refractory to standard salvage regimens pre-transplant. Because of high single-agent activity and limited side effects, brentuximab vedotin has emerged as an ideal drug to test in combination therapy for cHL. Current trials are examining the use of brentuximab vedotin in frontline combination regimens, as salvage therapy prior to stem cell transplant, and as adjuvant treatment post-transplant. Such studies will help clarify the optimal use of brentuximab vedotin in the treatment paradigm for Hodgkin lymphoma.

Keywords Brentuximab vedotin · Classical Hodgkin lymphoma · CD30 · Antibody drug conjugate · Neuropathy · stem cell transplantation

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Introduction

While the prognosis of classical Hodgkin lymphoma (cHL) has improved significantly over the recent decades, 15–30 % of patients do not achieve long-term remission with conventional chemotherapy or combined modality therapy. Autologous stem cell transplant (ASCT) can salvage approximately 50 % of relapsed or refractory patients [1]. For patients who relapse after ASCT, prognosis is poor with a median overall survival (OS) of 2.4 years [2]. Achievement of durable complete remissions with standard chemotherapy agents in multiply relapsed cHL is rare. Brentuximab vedotin, an antibody-drug conjugate that targets CD30, has changed the clinical landscape for patients with refractory/recurrent cHL. Recent clinical trials have shown excellent and occasionally durable responses in a heavily pretreated patient population [3•, 4•]. Brentuximab vedotin received accelerated Food and Drug Administration (FDA) approval in August 2011 for cHL relapsing after either ASCT or two multi-agent chemotherapy regimens in patients ineligible for ASCT. This article will summarize both efficacy and safety data from the key clinical trials leading to FDA approval and describe ongoing clinical trials designed to potentially expand the indications for brentuximab vedotin in cHL. It will also highlight and address practical concerns regarding the incorporation of brentuximab vedotin into the management of patients with cHL.

Targeting CD30

In malignancy, CD30 expression is seen on the surface of Hodgkin Reed-Sternberg cells, anaplastic large cell lymphoma (ALCL), and certain B-cell and mature T-cell non-Hodgkin lymphomas (NHLs). In cHL, Reed-Sternberg cells constitute only a small fraction (0.1–10 %) of the nodal

infiltrate. Reed-Sternberg cells attract inflammatory cells to the nodal microenvironment by secreting survival factors. Theoretically, ablation of Reed-Sternberg cells could prompt nodal regression. Since normal CD30 expression is highly restricted to activated B and T cells, targeting CD30-expressing Reed-Sternberg cells is an attractive treatment strategy for cHL.

SGN-30, a chimeric mouse anti-human CD30 antibody, preceded brentuximab vedotin in development. In phase I and II studies of SGN-30 in refractory/relapsed cHL or CD30+ NHL, no objective responses occurred in 59 patients with relapsed cHL [5, 6]. A phase I/II study of SGN-30 in combination with GVD (gemcitabine, vinorelbine, Doxil®) was closed prematurely due to unexpected pulmonary toxicity in patients receiving combination therapy [7]. Furthermore, the response rates in the combination group were not improved over those receiving GVD alone, although the study was underpowered for this comparison due to early closure.

Since the unconjugated chimeric anti-CD30 antibody showed minimal efficacy, Seattle Genetics developed an antibody drug conjugate in an effort to improve response rates while still taking advantage of the favorable target characteristics of CD30. Brentuximab vedotin (SGN-35, ADCETRIS™) is an antibody-drug conjugate which uses a protease-cleavable linker to couple monomethyl auristatin E (MMAE), a microtubule disrupting agent, to SGN-30. Brentuximab vedotin binds to CD30 on the surface of the malignant cell and the brentuximab vedotin-CD30 complex traffics to the lysosome where MMAE is released. MMAE binds to tubulin, resulting in breakdown of the microtubules, and ultimately leads to cell cycle arrest and apoptosis (Fig. 1).

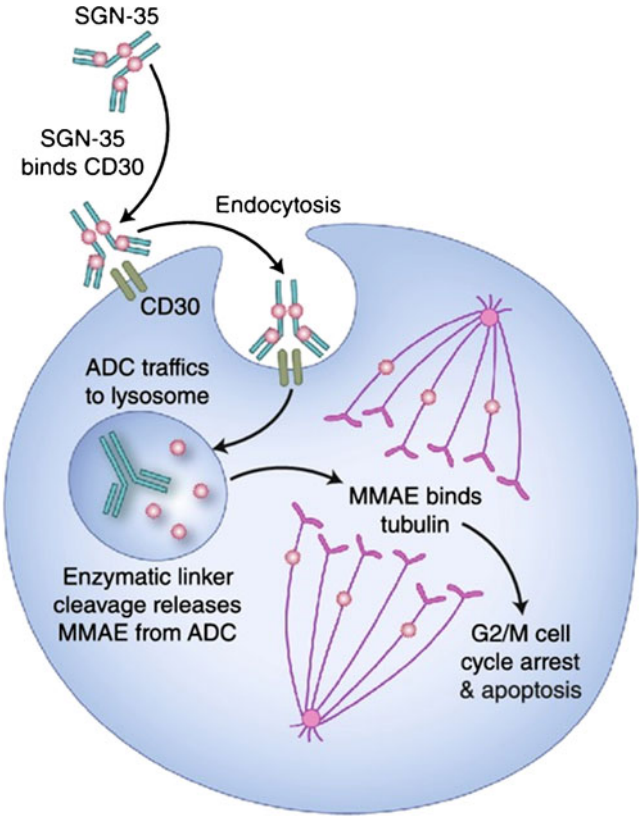

Fig. 1 Mechanism of brentuximab vedotin

Phase I–II Clinical Studies of Single-Agent Brentuximab Vedotin

Phase I

In a phase I multicenter study, 45 patients with CD30+ lymphomas were treated with escalating doses of brentuximab vedotin [3•]. Brentuximab vedotin was administered at 0.1–3.6 mg/kg intravenously every 3 weeks. Forty-two of the 45 patients had cHL. Patients had received a median of 3 prior treatments with 73 % having a prior ASCT. At the highest dose of 3.6 mg/kg, the only patient treated had a dose-limiting toxicity (DLT) of febrile neutropenia with sepsis, multi-organ failure, and subsequent death. At the 2.7 mg/kg dose, 2 of 12 patients suffered 3 DLTs which included hyperglycemia, prostatitis, and febrile neutropenia. Subsequently, 1.8 mg/kg every 3 weeks was determined to be the maximum tolerated dose (MTD).

Across all dosing cohorts, the most common adverse events included fatigue (36 %), pyrexia (33 %), diarrhea (22 %), nausea (22 %), neutropenia (22 %), and peripheral neuropathy (22 %). The majority of these were grade 1 or 2. Of the 16 patients who developed peripheral neuropathy, 13 were treated at the 1.8 or 2.7 mg/kg doses, and the median time to onset was 9 weeks. Patients typically presented with sensory findings such as numbness and tingling in the hands or feet. Two of 40 patients who were tested for an anti-therapeutic antibody were found to have low titer positivity, and both of these patients had stable disease as their best response. Because of the low incidence of anti-therapeutic antibody, no conclusions can be drawn about the potential effect on safety or efficacy of the drug.

Objective responses were noted in 15 of the 42 cHL patients, including nine complete remissions (CR) (Table 1). Thirty-four of 42 evaluable patients had tumor regression. A 50 % objective response rate was seen at both the 1.2 mg/kg and 1.8 mg/kg (MTD) doses. The duration of objective response was 17.3 months for the 17 responding patients, including two patients with ALCL.

A phase I study utilizing weekly dosing of brentuximab vedotin was also completed [8]. Doses ranged from 0.4 to 1.4 mg/kg and were given on days 1, 8, and 15 of a 28-day cycle. Forty-four patients were enrolled—38 with cHL, five with systemic ALCL, and one with peripheral T-cell lymphoma not otherwise specified. The overall response rate was 59 % with 34 % CRs (Table 1). The MTD was 1.2 mg/kg. Sixty-six percent of patients had peripheral sensory neuropathy (14 %

Table 1 Efficacy and neurotoxicity for phase I and phase II studies

	Phase I, weekly [8] n=44 (38 with cHL)	Phase I, every 3 week [3•] n=45 (42 with cHL)	Phase II, every 3 week [4•] n=102 (all with cHL)
Dosing	0.4–1.4 mg/kg	0.1–3.6 mg/kg	1.8 mg/kg
ORR	59 %	38 % [a]	75 %
CR	34 %	24 % [b]	34 %
Tumor regression	85 %	86 %	94 %
Median PFS (all)			5.6 months
Median PFS for CR			21.7 months
Peripheral neuropathy			
Any grade	73 %	22 %	56 %
Grade 3/4	14 %	0 %	11 %

[a] 50 % at 1.8 mg/kg dose

[b] Includes two patients with ALCL

with grade 3). In comparison to the every 3 week schedule, the weekly schedule showed similar response rates, but increased neurotoxicity. Therefore, this schedule has not been pursued further for single agent use.

Phase II

In a multinational, open-label, phase II study, 102 patients with relapsed/refractory cHL were treated with brentuximab vedotin at 1.8 mg/kg every 3 weeks for a maximum of 16 cycles for stable disease or better response [4•]. Seventy-one percent of patients had primary refractory disease and 42 % were refractory to their most recent treatment. The median number of prior chemotherapy regimens was 3.5, all patients had failed ASCT, and 71 % had relapsed≤1 year from ASCT. The objective response (OR) rate was 75 % with a median progression-free survival (PFS) of 5.6 months (Table 1). In the 34 % of patients who achieved a CR, the median PFS was 21.7 months (Fig. 2). The median time to OR and CR was 5.7 and 12 weeks, respectively. At a median follow-up of 18.5 months, 31 of the 102 patients were free of documented progressive disease.

Patients received a median of nine cycles of treatment. Grade 3 and 4 adverse events included neutropenia (14 % with grade 3 and 6 % with grade 4), peripheral sensory neuropathy (8 %, grade 3), fatigue (2 %), pyrexia (2 %), and diarrhea (1 %). Grade 1–2 neuropathy occurred in 48 % of patients. The median time to onset of peripheral neuropathy was 12 weeks for any grade, 27 weeks for grade 2, and 38 weeks for grade 3. Of patients experiencing neuropathy, 80 % had improvement after dose decrease or discontinuation including 50 % with complete resolution of symptoms.

Historically, single-agent treatments such as vinblastine, vinorelbine, or gemcitabine showed OR rates of 20–60 % with CR rates ranging from 10 % to 15 % [9–12]. Though one must exercise caution in comparing outcomes across studies, brentuximab vedotin showed a superior OR rate of 75 % with 34 % CRs in a heavily pretreated patient population and was associated with an acceptable toxicity profile, including minimal myelosuppression. Based on these results, brentuximab vedotin should be the first therapy administered to patients relapsing after stem cell transplant. Brentuximab vedotin is also a rational choice in pre-transplant patients who do not respond to a standard salvage regimen such as ICE (ifosfamide, carboplatin, etoposide) or ESHAP (etoposide, solumedrol, cytarabine, cisplatin) with the goal of proceeding to transplant in eligible, responding patients.

Brentuximab Vedotin Re-treatment

Re-treatment with brentuximab vedotin can result in repeat response. In a case series described by Bartlett et al., seven patients with CD30+ malignancies (6 with cHL) had eight retreatment experiences [13]. In 4 of 7 of these patients, 1–3 chemotherapy regimens were given between brentuximab vedotin treatments. At retreatment, objective responses occurred in 6 of 8 patients (2 CR, 4 PR). All patients had tumor regression. Time to objective response was 5–13 weeks with response durations of more than 52 weeks reported. Toxicity

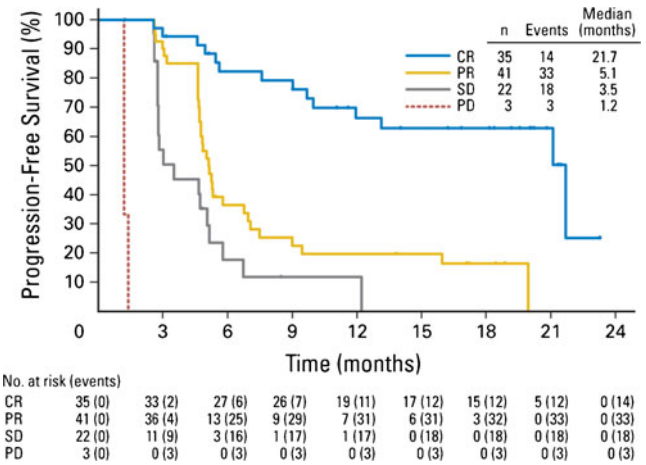

Fig. 2 Progression-free survival by response to brentuximab vedotin. (With permission; figure originally published in *Journal of Clinical Oncology* [4•]. © American Society of Clinical Oncology.)

at retreatment did not differ from that reported in the brentuximab vedotin phase I and II clinical trials.

Duration of Treatment

In the phase II study of brentuximab vedotin in relapsed/refractory cHL, treatment was given every 3 weeks for a maximum of 16 cycles, corresponding to 1 year of therapy, an arbitrary duration. Most initial responses to brentuximab vedotin occur within the first 2–4 cycles [4•]. For the two-thirds of patients who attain a PR as the best response, with persistent FDG-avid disease on PET, continuing therapy as long as response is maintained or until unacceptable toxicity may be reasonable. For patients who achieve a CR early in the treatment course, it is difficult to know whether continuing treatment to 16 cycles is necessary, and whether additional cycles past CR confer benefit in terms of durability of response or survival. Additional studies exploring duration of treatment in complete responders are warranted. Perhaps fewer initial cycles followed by retreatment at relapse would result in similar outcomes and minimize toxicity and cost. However, until more data becomes available, it is reasonable to continue treatment to the maximum of 16 cycles unless there is unacceptable toxicity. For those patients who attained a CR in the phase II trial, the median duration of response was 20.5 months with durable CRs approaching 2 years at the time of this report. Because only early follow-up has been published, we do not know if any patients who attain a CR with brentuximab vedotin are cured. The median PFS for patients who achieved a CR was 21.7 months. Five of the 35 patients in CR subsequently received an allogeneic stem cell transplant (allo-SCT). Their PFS was 21.1 months and did not differ significantly from those patients achieving a CR who did not proceed to allo-SCT (median PFS 21.7 mo).

As neurotoxicity often limits the ability to continue brentuximab vedotin long-term, dose-reductions and increasing dosing intervals may permit additional treatment in a responding patient. Foyil et al. reported a patient with multiply relapsed/refractory ALCL who repeatedly achieved a CR with three separate courses of brentuximab vedotin over 4 years [14]. This patient was initially treated on the phase I trial at the 2.7 mg/kg dose for three cycles. He then underwent an ASCT in CR, but progressed 3 months post-transplant. He received 1 year of retreatment (16 cycles) on a clinical trial, initially at 1.8 mg/kg every 3 weeks for ten cycles and then 1.35 mg/kg with 4 week dosing intervals for the last six cycles due to peripheral neuropathy. He progressed 5 months after completing 16 cycles of brentuximab vedotin and again started treatment with brentuximab vedotin on a clinical trial. Cycles 1–7 were given at 1.8 mg/kg every 3 weeks. Dose was reduced to 1.2 mg/kg for cycle 8 and beyond, and the dosing interval has been incrementally increased over the past 2.5 years, to every 7 weeks at the time of publication. This patient remains in remission with grade 1/2 peripheral sensory neuropathy, now having received a total of 41 cycles of brentuximab vedotin over 4 years. Though this approach cannot be generalized to a broader patient population, a "maintenance dosing" approach is reasonable in patients who relapse after initial brentuximab vedotin, respond to retreatment and for whom no other treatment options are available. A formal treatment extension study is currently gathering outcomes data on patients who remain on prolonged brentuximab vedotin treatment (www.ClinicalTrials.gov #NCT00947856).

Forero-Torres et al. recently presented a retrospective analysis of a subset of patients who received prolonged treatment with brentuximab vedotin in the treatment-extension study [15]. Fifteen patients (ten with cHL, five with ALCL) received >16 cycles of brentuximab vedotin. The median number of treatment cycles was 19 (range 17–29). At the time of analysis, two patients had discontinued treatment, neither due to AEs. Grade 1 or 2 peripheral sensory neuropathy occurred in 73 % of patients and was managed with dose-reductions and dose-delays. For the whole group, median duration of objective response and PFS had not been reached but ranged from 6.5+ to 21.8+ months and 11.8+ to 23+ months, respectively. These data lend support to the safety of continued brentuximab vedotin treatment, although the benefit of continued treatment, particularly in patients with a CR, is unknown.

Brentuximab Vedotin After ASCT Failure: "Stop" After CR or "Go" for Transplant?

Reduced intensity allogeneic stem cell transplantation (RIC allo-SCT) can induce durable remissions in patients with cHL who relapse after ASCT. However, this salvage treatment option is often limited by the ability to obtain disease control prior to transplantation. Chen et al. presented a retrospective analysis of 16 patients with relapsed/refractory cHL who underwent RIC allo-SCT (six matched related donors, seven matched unrelated donors, three haploidentical donors) after salvage with 2–16 cycles of brentuximab vedotin (Table 2) [16]. Patients had received 2–6 prior lines of treatment, and 14 of 16 patients had a prior ASCT. The best response to brentuximab vedotin was CR in seven patients, PR in seven patients, and SD in two patients. Two patients (one PR and one SD) progressed prior to RIC allo-SCT. At the City of Hope, where 12 of the 16 patients were transplanted, 1-year PFS was 90 % and 1-year OS was 100 %, at a median follow-up of 13.2 months (range 2–20 months). The remaining four patients were transplanted at the Seattle Cancer Care Alliance and are all alive and progression-free at a median follow-up of 7.2 months (range 2.9–19 months). The only patient who relapsed after RIC allo-SCT had progression prior to transplant and 276 days elapsed between brentuximab vedotin and

Table 2 Outcomes of allogeneic transplant following brentuximab vedotin salvage therapy

	Chen et al. [16][a] $n=16$		Illidge et al. [17][b]
	COH $n=12$	FHCRC/SCCA $n=4$	$n=15$ (7 with cHL)
Age range	23–55	25–32	17–61
Prior ASCT (n)	11	3	12
Median number of BV cycles	9.5	7.0	9.0
Best response to BV	5 CR	2 CR	12 CR (5 with cHL)
	7 PR	2 SD	3 PR (2 with cHL)
Disease status at time of allo-SCT	5 CR, 5 PR, 4 PD	2 CR, 1 SD, 1 PD	NR (no PD)
Type of transplant	5 MRD, 7 MUD	3 haplo, 1 MRD	NR
Acute GVHD			
Grade 2	25 %	25 %	NR
Grade 3/4	0 %	0 %	NR
Chronic GVHD	75 %	25 %	NR
Median follow-up (months)	13.2	7.2	16.9
PFS	90 % (1-year)	100 %[c]	21.1 mo (median)
OS	100 % (1-year)	100 %[c]	87 %[cd]

BV brentuximab vedotin; *COH* City of Hope; *FHCRC/SCCA* Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; *GVHD* graft-versus-host disease; *haplo* haploidentical donor; *MRD* matched related donor; *MUD* matched unrelated donor; *NR* not reported

[a]Results reported for each transplant center

[b]Includes four patients with cHL from Chen et al. series

[c]At the time data was reported

[d]All patients with cHL on study are still alive

transplant. No delayed engraftment or increased incidence or CMV/EBV infections were noted. Acute and chronic graft-versus-host disease (GVHD) occurred in 25 % and 63 % of the entire cohort with no grade 3–4 acute GVHD and only one case of extensive chronic GVHD. Illidge et al. also presented a case series of 7 cHL (four patients also included in Chen et al. series [16]) and 8 ALCL patients who received an allo-SCT as their first anti-tumor therapy following brentuximab vedotin (Table 2) [17]. All patients had an objective response (12 CR, 3 PR) to brentuximab vedotin which was maintained at the last assessment prior to allo-SCT. The median duration of follow-up from first dose of brentuximab vedotin was 16.9 months (range 8.2–21.1). Five patients (1/7 with cHL, 4/8 with ALCL) have progressed or died. Four of these five patients had achieved a CR with brentuximab vedotin. The median PFS at the time of analysis was 21.1 months (range 8.2–21.1).

These unprecedented findings, with 17 of 19 patients with multiply-relapsed cHL treated with brentuximab vedotin followed by RIC allo-SCT alive and in remission at very early follow-up, need to be validated prospectively with additional patients. In addition to early follow-up, other possible explanations for these remarkable results include improved disease control with brentuximab vedotin prior to transplant compared to traditional salvage regimens, or perhaps better performance status of patients undergoing RIC allo-SCT following brentuximab vedotin compared to other regimens due to a more favorable toxicity profile. However, without longer follow-up of patients who attain a CR with brentuximab vedotin, it is still difficult to know whether to proceed with RIC allo-SCT in this subset, given the significant acute and long-term complications of this therapy. In the phase II study, the patients who attained a CR and went on to allo-SCT ($n=5$) had a similar PFS to those who attained a CR but did not go on to allo-SCT ($n=30$) [4•]. However, one cannot draw conclusions about the benefit, or lack thereof, of transplant in this population because of the very small numbers of patients involved. While the data by Chen et al. and Illidge et al. are encouraging, they are limited by their retrospective nature. Until we attain prospective data to answer the question about management of patients in CR, our current approach is to follow these patients after completion of 16 cycles of brentuximab vedotin. If they relapse, we retreat with brentuximab vedotin and then consider RIC allo-SCT in subsequent remission.

Current Studies and Future Applications

As with many successful salvage therapies in oncology, it is important to know whether incorporation of brentuximab vedotin as an adjuvant therapy following stem cell transplant or using it even earlier in the treatment of cHL can result in improved outcomes. We know that the prognosis of cHL patients who relapse after ASCT is poor. Therefore, focusing efforts on improving durability of remission post-ASCT is rational, and brentuximab vedotin may have a role in this setting. A multicenter, randomized, double-blind, placebo-controlled phase III study, evaluating the efficacy of brentuximab vedotin versus placebo after ASCT, is currently enrolling (www.ClinicalTrials.gov #NCT01100502). Eligible patients will have had an ASCT in the prior 30–45 days and be deemed high-risk for residual HL post-ASCT based on one of the following criteria: history of primary refractory HL, relapsed/progressive HL<12 months from frontline therapy, or extranodal involvement at the time of pre-ASCT relapse. Post-transplant brentuximab vedotin will be given at the standard

dose of 1.8 mg/kg every 3 weeks for 16 cycles. The primary endpoint is PFS.

The phase I and II clinical trials of brentuximab vedotin in cHL primarily enrolled patients with relapsed disease after ASCT; therefore data is limited on the efficacy of brentuximab vedotin as salvage therapy prior to ASCT. Given its impressive response rates, one would expect it to be a good option for disease control prior to ASCT. In practice, this is an excellent choice for patients who fail an aggressive multi-agent salvage regimen (such as ICE or ESHAP) after standard frontline therapy. An important question is whether brentuximab vedotin could replace regimens such as ICE or ESHAP as pre-transplant salvage. A phase II study at the City of Hope for patients with primary refractory or progressive cHL after standard frontline therapy is evaluating single agent brentuximab vedotin as salvage treatment (maximum 4 cycles) prior to ASCT (www.ClinicalTrials.gov #NCT01393717). While the primary endpoint is objective response rate, it will be important to see if brentuximab vedotin salvage therapy pre-ASCT can improve disease outcomes post-ASCT. Investigators at Memorial Sloan-Kettering are also evaluating single agent brentuximab vedotin as initial pre-transplant salvage for relapsed cHL. Brentuximab vedotin is administered at a dose of 1.2 mg/kg on days 1, 8, and 15 of a 28-day cycle for two cycles (www.ClinicalTrials.gov # NCT01508312). Patients with a negative interim PET after two cycles proceed to stem cell collection and ASCT. Those who remain PET-avid receive two cycles of augmented ICE followed by ASCT. Efforts to incorporate brentuximab vedotin into the pre-transplant ICE salvage regimen are also in development.

Given the high response rate of single-agent brentuximab vedotin and the modest and mostly non-overlapping toxicities, incorporating brentuximab vedotin into first-line regimens is attractive. Higher initial cure rates with chemotherapy alone could obviate the need for radiotherapy in early-stage disease and spare more patients the toxicity of ASCT in advanced-stage disease. Younes et al. presented interim results from an ongoing phase I study looking at frontline therapy with brentuximab vedotin combined with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or AVD (doxorubicin, vinblastine, dacarbazine) in patients with newly diagnosed advanced-stage cHL [18]. Patients received doses of 0.6, 0.9, or 1.2 mg/kg brentuximab vedotin with standard doses of ABVD or 1.2 mg/kg brentuximab vedotin with AVD on days 1 and 15 of a 28-day cycle for up to six cycles. Among the first 44 patients treated, 45 % of patients had stage IV disease, 23 % had an International Prognostic Score (IPS)≥4, and the median age was 32.5 years. No DLTs were observed with either regimen. Grade 3/4 adverse events >10 % included: neutropenia (77 %), febrile neutropenia (11 %), anemia (14 %) and pulmonary toxicity (11 %). Grade 1/2 peripheral sensory neuropathy was observed in 52 % of patients. In the ABVD cohort (n=25), pulmonary AEs that could not be distinguished from bleomycin toxicity led to discontinuation of bleomycin in seven patients, and one patient died of drug-induced pulmonary failure. Because the incidence of pulmonary events was greater than that reported with ABVD, concomitant use of brentuximab vedotin and bleomycin is contraindicated, and the combination is no longer being explored. There have been no pulmonary events reported in 26 patients treated with brentuximab vedotin + AVD. Thirty-six of 37 patients treated with brentuximab vedotin in combination with ABVD or AVD, and with available response data, had a negative interim PET scan by London-Deauville criteria. Given the already favorable prognosis of cHL patients, long-term follow-up will be needed to determine whether incorporation of brentuximab vedotin into frontline therapy leads to better PFS and OS without adverse impact on safety. A phase III pharmaceutical sponsored study is planned to compare frontline treatment with brentuximab vedotin plus AVD versus ABVD alone. In addition, an Alliance-led cooperative group study in development will investigate a reduced number of cycles of brentuximab vedotin + AVD as initial therapy in advanced stage cHL for patients with a negative interim PET scan.

Recommendations and Conclusions

The FDA approval of brentuximab vedotin brings considerable promise for treatment of patients with relapsed/refractory cHL. The tolerability and impressive response rates seen with brentuximab vedotin surpass those of other existing single-agent or combination cytotoxic regimens, and have set a high bar for the development of new salvage therapies for cHL. In a patient with relapse following ASCT, single-agent brentuximab vedotin should be the initial salvage therapy. In this setting, patients who achieve only a PR with the first 4–6 cycles of brentuximab vedotin, as determined by persistent FDG-avid disease on PET scan, should be considered for RIC allo-SCT, as these patients will not achieve durable remissions with brentuximab vedotin alone. For patients achieving a CR with brentuximab vedotin, one option is to continue brentuximab vedotin for a total of 16 cycles followed by observation. At subsequent relapse, re-treat with brentuximab vedotin and consider RIC allo-SCT in repeat responders. Alternatively, based on encouraging data from two small series, it is reasonable to consider RIC allo-SCT as consolidation following the first brentuximab vedotin-induced CR. For patients who are not transplant candidates due to co-morbidities or chemo-refractory disease, brentuximab vedotin should be considered immediately after failure of two prior regimens. In the chemo-refractory cohort, brentuximab vedotin responders should proceed with ASCT as soon as remission is documented. In patients undergoing re-treatment with brentuximab vedotin, modest dose-reductions and/or an increased interval between

doses (4–6 weeks) may allow for prolonged administration and remission with preservation of quality of life.

Important questions are under investigation regarding the utility and feasibility of administering brentuximab vedotin earlier in the course of treatment for cHL, as adjuvant therapy following transplant, or as part of first or second-line regimens. 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 vedotin were given in combination. In addition, off-label use is discouraged until longer-term follow-up is available in larger numbers of patients. While brentuximab vedotin has a generally favorable toxicity profile, an FDA-mandated boxed warning indicating a potential risk of progressive multifocal leukoencephalopathy (PML) was added to the brentuximab vedotin drug label in January 2012, after three reported cases in patients receiving brentuximab vedotin for multiply relapsed cHL [19]. While the relationship between brentuximab vedotin and PML is unclear, vigilance for this toxicity should be incorporated into current and planned clinical trials. Rapid reporting to the FDA of all cases of suspected or documented PML in patients receiving or having received brentuximab vedotin will help clarify any association.

Ideally, quality of life and economic evaluations will be incorporated into current and future studies. Brentuximab vedotin has a significant price tag at approximately $14,500 per dose, excluding the "mark-up" by the prescriber. If clearly defined benefits of diminished toxicity as well as improved progression-free and overall survival rates are shown, these costs will be justified.

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References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1. Majhail NS, Weisdorf DJ, Defor TE, et al. Long-term results of autologous stem cell transplantation for primary refractory or relapsed Hodgkin's lymphoma. Biol Blood Marrow Transplant. 2006;12:1065–72.
2. Crump M. Management of Hodgkin lymphoma in relapse after autologous stem cell transplant. ASH Educ Program Book. 2008;2008:326–33.
3. • Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med. 2010;363:1812–21. *This phase I study demonstrated safety and efficacy of the every 3 week dosing schedule for brentuximab vedotin*.
4. • 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 epub. *This phase II study demonstrated a high response rate for brentuximab vedotin in patients with heavily pretreated Hodgkin lymphoma. It showed highly durable remissions in the group of patients that achieved a complete response to therapy. The results from this study led to accelerated approval for brentuximab vedotin as salvage therapy for Hodgkin lymphoma.*
5. Bartlett NL, Younes A, Carabasi MH, et al. A phase 1 multidose study of SGN-30 immunotherapy in patients with refractory or recurrent CD30+ hematologic malignancies. Blood. 2008;111:1848–54.
6. Forero-Torres A, Leonard JP, Younes A, et al. A Phase II study of SGN-30 (anti-CD30 mAb) in Hodgkin lymphoma or systemic anaplastic large cell lymphoma. Br J Haematol. 2009;146:171–9.
7. Blum KA, Jung SH, Johnson JL, et al. Serious pulmonary toxicity in patients with Hodgkin's lymphoma with SGN-30, gemcitabine, vinorelbine, and liposomal doxorubicin is associated with an FcgammaRIIIa-158 V/F polymorphism. Ann Oncol. 2010;21:2246–54.
8. Fanale MA, Forero-Torres A, Rosenblatt JD, et al. A Phase I weekly dosing study of brentuximab vedotin in patients with relapsed/refractory CD30-positive hematologic malignancies. Clin Cancer Res. 2012;18:248–55.
9. Little R, Wittes RE, Longo DL, Wilson WH. Vinblastine for recurrent Hodgkin's disease following autologous bone marrow transplant. J Clin Oncol. 1998;16:584–8.
10. Rule S, Tighe M, Davies S, Johnson S. Vinorelbine in the treatment of lymphoma. Hematol Oncol. 1998;16:101–5.
11. Venkatesh H, Di Bella N, Flynn TP, et al. Results of a phase II multicenter trial of single-agent gemcitabine in patients with relapsed or chemotherapy-refractory Hodgkin's lymphoma. Clin Lymphoma. 2004;5:110–5.
12. Zinzani PL, Bendandi M, Stefoni V, et al. Value of gemcitabine treatment in heavily pretreated Hodgkin's disease patients. Haematologica. 2000;85:926–9.
13. Bartlett N, Grove L, Kennedy A, et al. Objective responses with brentuximab vedotin (SGN-35) retreatment in CD30-positive hematologic malignancies: a case series, ASCO Annual Meeting Abstracts. 2010;28(15s):8062.
14. Foyil KV, Kennedy DA, Grove LE, et al. Extended retreatment with brentuximab vedotin (SGN-35) maintains complete remission in patient with recurrent systemic anaplastic large-cell lymphoma. Leuk Lymphoma. 2011;53(3):506–7.
15. Forero-Torres A, Berryman RB, Advani RH, et al. Prolonged treatment with brentuximab vedotin (SGN-35) in patients with relapsed or refractory Hodgkin Lymphoma (HL) or Systemic Anaplastic Large Cell Lymphoma (sALCL), ASH Annual Meeting Abstracts. 2011;118:3711
16. Chen R, Forman SJ, Palmer J, et al. Brentuximab vedotin (SGN-35) enables successful reduced intensity allogeneic hematopoietic cell transplantation in relapsed/refractory Hodgkin lymphoma. ASH Annual Meeting Abstracts. 2011;118:664.
17. Illidge T, Bouabdallah R, Chen RW, et al. Allogeneic transplant following brentuximab vedotin treatment in patients with relapsed or refractory CD30+ lymphomas. ASH Annual Meeting Abstracts. 2011;118:3091.
18. Younes A, Connors JM, Park SI, et al. Frontline therapy with brentuximab vedotin combined with ABVD or AVD in patients with newly diagnosed advanced stage Hodgkin lymphoma, ASH Annual Meeting Abstracts. 2011;118:955.
19. Wagner-Johnston ND, Bartlett NL, et al. Progressive multifocal leukoencephalopathy (PML) in a patient with Hodgkin's lymphoma treated with brentuximab vedotin. Leuk Lymphoma. 2012; Mar 16 epub.