5 Minute JournalClub

Key ASH Presentations
Issue 2, 2012

Prolonged Treatment with Brentuximab Vedotin in Patients with Relapsed/Refractory HL or Systemic ALCL

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results and new information lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Consider the inclusion of brentuximab vedotin in the treatment algorithm for relapsed/refractory Hodgkin lymphoma (HL) or systemic anaplastic large cell lymphoma (sALCL).
- Assess the benefit and toxicity resulting from prolonged treatment with brentuximab vedotin in patients with relapsed/refractory HL or sALCL.
- Evaluate the efficacy and toxicity outcomes from studies with brentuximab vedotin in combination with doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) or AVD as front-line therapy for advanced HL.

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To go directly to slides and commentary for this issue, **click here**.

Monoclonal antibodies are an important part of current oncology management, but limitations in efficacy have led to the development of a related class of antitumor agents — so-called immunoconjugates or antibody-drug conjugates (ADCs). These unique therapeutics have become the focus of a plethora of recent and ongoing clinical trials, and in August — following data sets presented at ASH 2010 — for the first time since 2000 when gemtuzumab ozogamicin was approved in AML, we saw the FDA give the green light to another ADC, namely brentuximab vedotin for the management of Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL). Like its sister agent in HER2-positive breast cancer, T-DM1, and other ADCs, B-vedotin has 3 components (**Figure 1**):

Monoclonal Antibody
B-vedotin includes a chimeric IgG1 monoclonal antibody, SGN-30, that targets CD30, an antigen that has limited expression in normal tissues and uniformly high expression in HL (specifically Reed-Sternberg cells), sALCL and select other cancers, including cutaneous and peripheral T-cell lymphomas, where responses were **recently reported**. The "naked" antibody has less antitumor effect than, for example, trastuzumab in HER2-positive breast cancer (in T-DM1).

Cytotoxic Agent
Because of the specificity of delivery, next-generation ADCs have included highly potent smaller cytotoxic agents, in this case the vinblastine-like MMAE that inhibits microtubule polymerization. Hence, its most important clinical toxicity is peripheral neuropathy.

Linker
Investigators get all wide-eyed and excited when they talk about linker molecules used to conjugate ADC components, I guess because of the spectacular technology. B-vedotin includes a dipeptide that is selectively cleaved by lysosomal enzymes after being rapidly internalized into cells. The result is the release of MMAE that causes apoptosis in CD30-positive tumor cells.

Currently, many ADCs are in development targeting a variety of cell types in both myeloid/hematopoietic cancers and carcinomas (**Figure 2**). In this issue of our series we provide slide sets based on presentations from last month's ASH meeting that bring into sharper focus why there is so much excitement about B-vedotin.

1. Abstract 443. More on B-vedotin in sALCL
Memorial's Dr Craig Moskowitz has extensive on- and off-trial experience with this ADC, and in his words, "It approaches a home run in sALCL. It's changed the lives of people with this disease." This ASH paper updates the impressive Phase II study first presented at ASH

2010 in patients with refractory disease, but the real hope is in the up-front setting, where exciting new trials are evaluating a novel "CHOP" in which B-vedotin replaces vincristine.

2. Abstracts 664 and 3091. B-vedotin and reduced-intensity allogeneic stem cell transplant (allo-SCT) in relapsed/refractory HL

These 2 reports detail the courses of a total of 33 patients who received B-vedotin prior to allo-SCT. This strategy had no adverse impact on engraftment, GVHD or survival and provided sufficient disease control for patients to successfully proceed to allo-SCT. Investigators like Dr Moskowitz are currently using B-vedotin extensively as a bridge to transplant, although the appropriate number of doses to deliver is controversial.

3. Abstract 3711. Prolonged treatment with B-vedotin

This retrospective analysis evaluated a subset of 15 patients with HL and sALCL who received B-vedotin until disease progression or unacceptable toxicity. Treatment ranged from 17 to 29 cycles and was well tolerated and not limited by the major side effect, peripheral neuropathy, which was usually reversible and Grade 2 or lower.

4. Abstract 955. Front-line treatment with B-vedotin and either ABVD or AVD in newly diagnosed advanced-stage HL

This Phase I trial from MD Anderson demonstrated excellent responses among 44 patients (97% FDG-PET negativity after 2 treatment cycles). However, concerning adverse effects were seen in the ABVD/B-vedotin arm — specifically a 40% incidence of bleomycin-like pulmonary toxicity that was not observed with AVD/B-vedotin — and the concomitant use of bleomycin and B-vedotin is now contraindicated. A Phase III trial will assess front-line AVD/B-vedotin compared to ABVD.

Up next, having just returned from the GI Cancers Symposium in San Francisco we flip back to solid tumors and some interesting new developments (finally) in colorectal cancer, including perspectives on 2 promising systemic agents: aflibercept and regorafenib.

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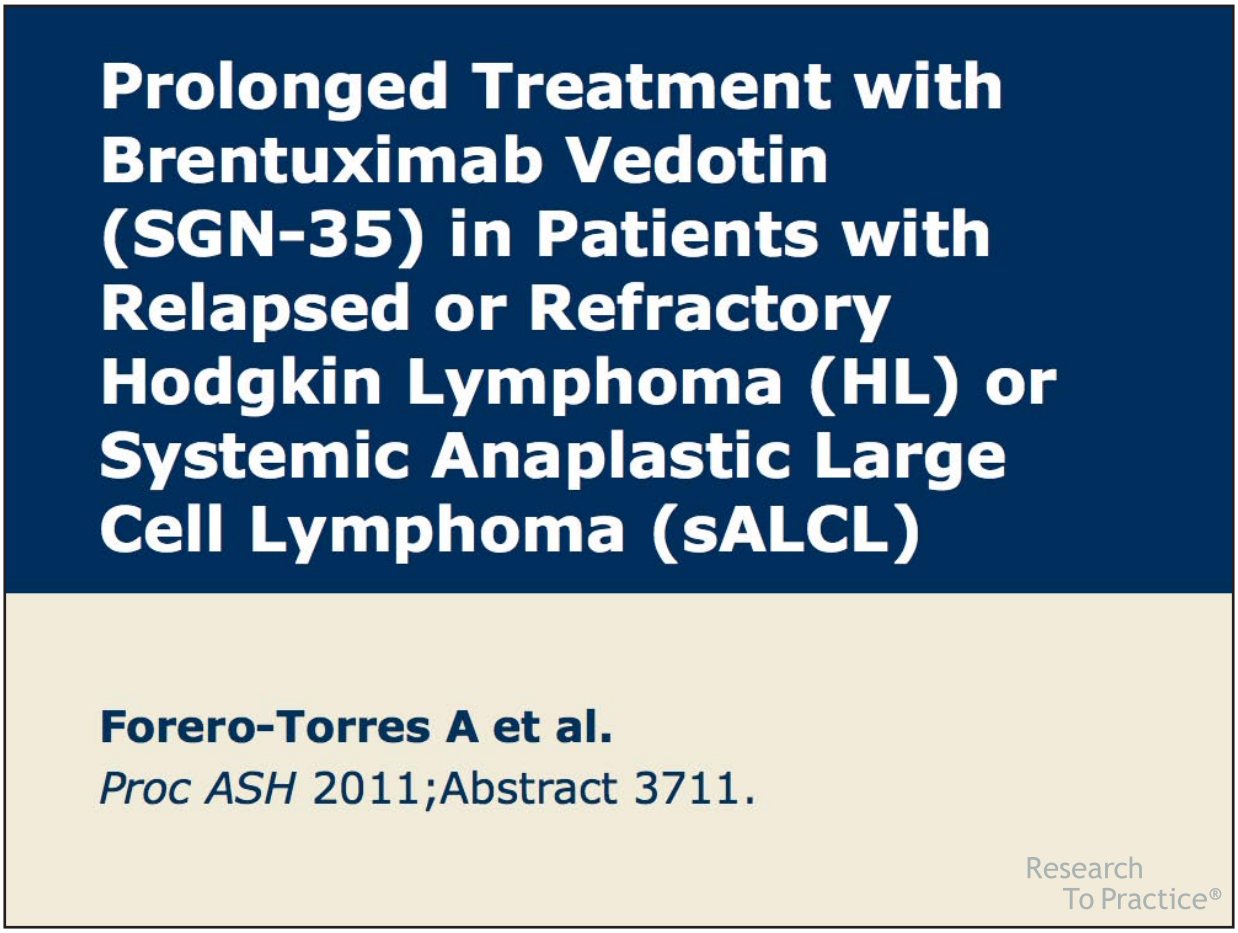
Prolonged Treatment with Brentuximab Vedotin in Patients with Relapsed/Refractory HL or Systemic ALCL

Presentation discussed in this issue

Forero-Torres A 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).** *Proc ASH* 2011;**Abstract 3711**.

Slides from a presentation at ASH 2011 and transcribed comments from a recent interview with Craig Moskowitz, MD (1/11/12)



Background

- Brentuximab vedotin (B-vedotin), an anti-CD30 antibody drug conjugate, induced a high rate of remission in 2 recent trials of patients with relapsed/refractory CD30+ lymphomas.
  - Patients with HL: Complete remission (CR) rate = 34%, median duration of response in patients with CR = 20.5 mo (*Proc ASCO* 2011;Abstract 8031)
  - Patients with sALCL: CR rate = 57%, median duration of response in patients with CR = 13.2 mo (*Proc ASCO* 2011;Abstract 8032)
- In both of these trials, a maximum of 16 cycles of B-vedotin was permitted (a median of 10 cycles for HL and 7 cycles for sALCL).
- **Current Analysis Objective**: To present a retrospective analysis of a subset of patients who received prolonged treatment (>16 cycles) with B-vedotin in a treatment extension study.

Forero-Torres A et al. *Proc ASH* 2011;Abstract 3711.

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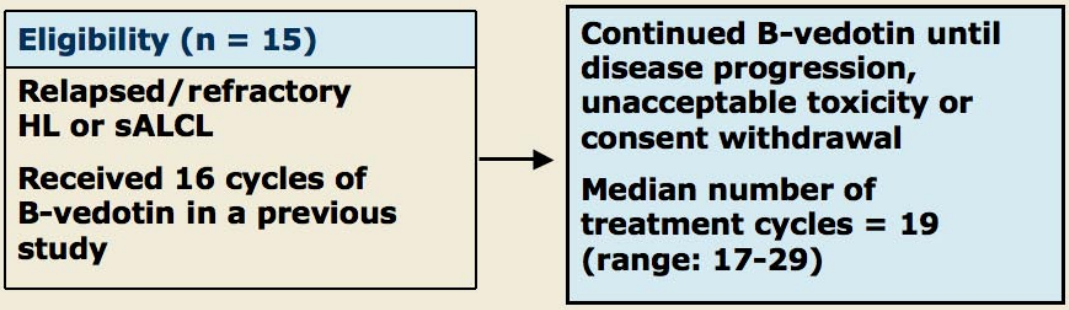
Retrospective Analysis



Forero-Torres A et al. *Proc ASH* 2011;Abstract 3711.

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Baseline Characteristics (Abstract Only)

Characteristic	n = 15
Relapsed/refractory HL	10
Relapsed/refractory sALCL	5
Median age	35 years
Median number of prior therapies	3 (range 1-14)
Failed previous autologous stem cell transplant (SCT)	9*

* Two of these patients also failed allogeneic SCT

Forero-Torres A et al. *Proc ASH* 2011;Abstract 3711.

Best Clinical Responses for Extended B-Vedotin Therapy (Abstract Only)

Response	(n = 15)
CR*	73.3%
Partial remission (PR)	13.3%
Stable disease	13.3%

- Median time from first dose to achievement of CR was 12 weeks (range: 5.4 to 48.9).
- Median duration of objective response has not been reached (range: 6.5+ to 21.8+ months).
- Fourteen patients were alive and free of documented disease progression at time of analysis.
- Median progression-free survival had not been reached (range: 11.8+ to 23.0+ months).

* Includes all patients with sALCL (n = 5)

Forero-Torres A et al. *Proc ASH* 2011;Abstract 3711.

Adverse Events (Abstract Only)

Adverse events (in ≥30% of patients)	All grades (n = 15)
Peripheral sensory neuropathy (PSN)*	73%
Fatigue	53%
Upper respiratory tract infection	53%
Cough	40%
Alopecia	33%
Diarrhea	33%
Neutropenia†	33%
Pyrexia	33%

* Resolved or improved in 7/13 patients with a median time to resolution or improvement of 3.1 weeks (range 0.1-8); no Grade 3 or 4 PSN events observed
† Only adverse event that occurred for the first time after cycle 16 in >1 patient (n = 2)

Forero-Torres A et al. *Proc ASH* 2011;Abstract 3711.

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Author Conclusions

- Patients with relapsed/refractory HL or sALCL exhibited favorable responses to extended treatment with B-vedotin.
- Duration of response (11 CRs and 2 PRs) ranged from 6.5+ to 21.8+ months, with 13 patients still receiving treatment.
- The safety profile of B-vedotin did not change significantly with treatment beyond 16 cycles, with most adverse events being mild.

Forero-Torres A et al. *Proc ASH* 2011;Abstract 3711.

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Investigator Commentary: Prolonged Treatment with Brentuximab Vedotin in Relapsed/Refractory HL or sALCL

This is a retrospective analysis of a subset of patients with HL or sALCL who were treated with B-vedotin until disease progression or unacceptable toxicity. Interestingly, no additional toxicity was observed in patients receiving extended maintenance with B-vedotin. So if you had a patient who was either not eligible for a transplant or who did not want a transplant, you could administer this agent indefinitely. The fear is that the patient could experience chronic severe neuropathy with indefinite use, but that didn't happen. Most patients on the study had Grade 1 or 2 neuropathy.

In my experience with this agent, I've observed little Grade 3 and 4 neuropathy. Grade 2 neuropathy is reversible, so my strategy is to delay treatment for a week. Once it resolves to Grade 1, I reduce the dose and continue.

A Phase III study (AETHERA trial) is currently evaluating the efficacy and safety of B-vedotin in patients at high risk of residual HL following autologous stem cell transplant. I've placed about 15 patients on this study and thus far it's been difficult to discern who is receiving B-vedotin versus placebo.

Interview with Craig Moskowitz, MD, January 11, 2012