5 Minute JournalClub

Key ASH Presentations
Issue 2, 2012

Phase II Study Update of Brentuximab Vedotin in Patients with Relapsed/ Refractory 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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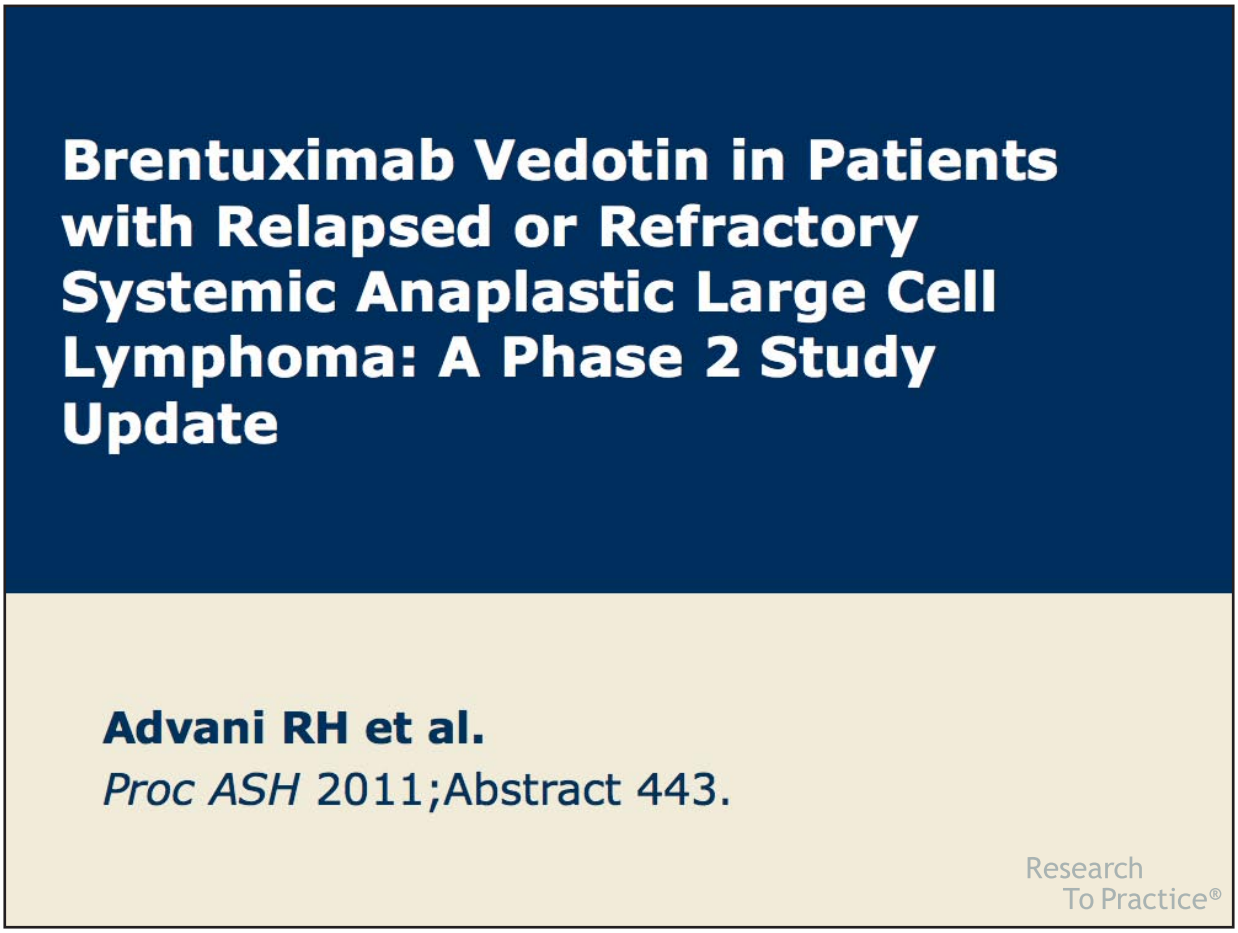
Phase II Study Update of Brentuximab Vedotin in Patients with Relapsed/Refractory Systemic ALCL

Presentation discussed in this issue

Advani RH et al. **Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large cell lymphoma: A Phase 2 study update.** *Proc ASH* 2011;**Abstract 443**.

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



Background

- Systemic anaplastic large cell lymphoma (sALCL) is a CD30-positive aggressive subtype of mature T-cell lymphoma, comprising 2-5% of all NHL cases.
- 76-88% of patients achieve remission with front-line treatment. However, approximately half will experience disease relapse.
- Brentuximab vedotin (B-vedotin), a novel anti-CD30 antibody drug conjugate, selectively induces apoptotic death of $CD30^+$ cells.
- **Current Analysis Objective:** Present updated results from a Phase II, multicenter study evaluating the efficacy and safety of B-vedotin in relapsed/refractory sALCL.

Advani RH et al. *Proc ASH* 2011;Abstract 443.

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Study Schema

Eligibility (N = 58)
Relapsed or refractory systemic ALCL
Measurable disease ≥1.5 cm FDG-avid
ECOG PS 0-1

→ B-vedotin
1.8 mg/kg
q3wk, 1-16 cycles
12-wk follow-ups

After discontinuing treatment, 14 patients received a stem cell transplant (SCT) (7 allogeneic, 7 autologous)

Primary Endpoint: Objective response rate (ORR) by independent review facility (IRF)
Secondary Endpoints: Complete remission rate (CR), duration of response, progression-free survival (PFS), overall survival (OS), safety and tolerability

Advani RH et al. *Proc ASH* 2011;Abstract 443.

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Response Results

Clinical response	(n = 58)
Objective response rate	86%
Complete remission rate	59%
Median duration of response	
Objective response	13.2 mo
Response in patients with CR	Not reached

Advani RH et al. *Proc ASH* 2011;Abstract 443.

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Survival

Progression-free survival	B-vedotin (n = 57)	Hazard ratio*	*p*-value
Median PFS	14.5 mo	0.44	<0.001

PFS in patients with CR by subsequent transplant			
Patients with CR	**Events†**	**Median PFS**	**Median # of cycles received**
No subsequent transplant (n = 20)	9	18.4 mo	13
Subsequent allogeneic SCT (n = 7)	3	16.9 mo	8
Subsequent autologous SCT (n = 7)	1	Not reached	8

Overall survival	(n = 58)
Median OS	Not reached
Estimated OS rate at 1 year	70%
Median observation time from first dose	14.7 mo

* Versus last prior therapy (5.9 mo); † Disease progression or death

Advani RH et al. *Proc ASH* 2011;Abstract 443.

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Select Adverse Events (AEs)

AEs (all grades)	
Peripheral sensory neuropathy (PN)*	45%
Fatigue	28%
Nausea	28%
Diarrhea	19%
Neutropenia	17%
Myalgia	16%
Pyrexia	14%
Vomiting	14%
Upper respiratory tract infection	12%
Rash	10%

* PN managed with dose delays and/or reductions to 1.2 mg/kg
Resolution/improvement in some or all PN events = 79%

Advani RH et al. *Proc ASH* 2011;Abstract 443.

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Author Conclusions

- Durable complete remissions were achieved with B-vedotin in patients with relapsed or refractory sALCL.
- Complete remissions appear durable after completing treatment.
- Adverse events, including peripheral neuropathy, were manageable.
- Based on these results, a Phase I front-line trial is ongoing and a Phase III randomized trial for patients with ALCL and other CD30-positive mature T-cell neoplasms is planned.

Advani RH et al. *Proc ASH* 2011;Abstract 443.

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Investigator Commentary: Phase II Update of B-Vedotin in Patients with Relapsed/Refractory sALCL

This is an update of a previous data set. Most of the patients were heavily pretreated, only a small percent had received a transplant. The fact that most of the patients could not get to transplant suggests their prognosis was not good.

Single agent treatment with B-vedotin resulted in a median duration of response of greater than a year, which is excellent. The median duration of response in patients who had a complete response was not reached. In baseball terms, for sALCL this is approaching a home run. This is amazing — it's changed the lives of patients with this disease.

I believe that once the B-vedotin/CHOP (B-vedotin substituting for vincristine) study is completed, it'll be a "slam dunk" and this will be standard of care for sALCL as primary therapy.

Interview with Craig Moskowitz, MD, January 11, 2012