5 Minute JournalClub

Key ASH Presentations
Issue 2, 2012

Allogeneic Transplant After Brentuximab Vedotin in Patients with Relapsed/Refractory CD30+ Lymphomas

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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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Craig Moskowitz, MD
Clinical Director, Division of Hematologic Oncology
Attending Physician, Lymphoma and Adult BMT Services
Member, Memorial Sloan-Kettering Cancer Center
Professor of Medicine, Weill Medical College of Cornell University
New York, New York

Advisory Committee: Cephalon Inc, Genentech BioOncology, Seattle Genetics; Paid Research: Cephalon Inc, Genentech BioOncology, Lilly USA LLC, Plexxikon Inc, Seattle Genetics.

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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.

Neil Love, MD
Research To Practice
Miami, Florida

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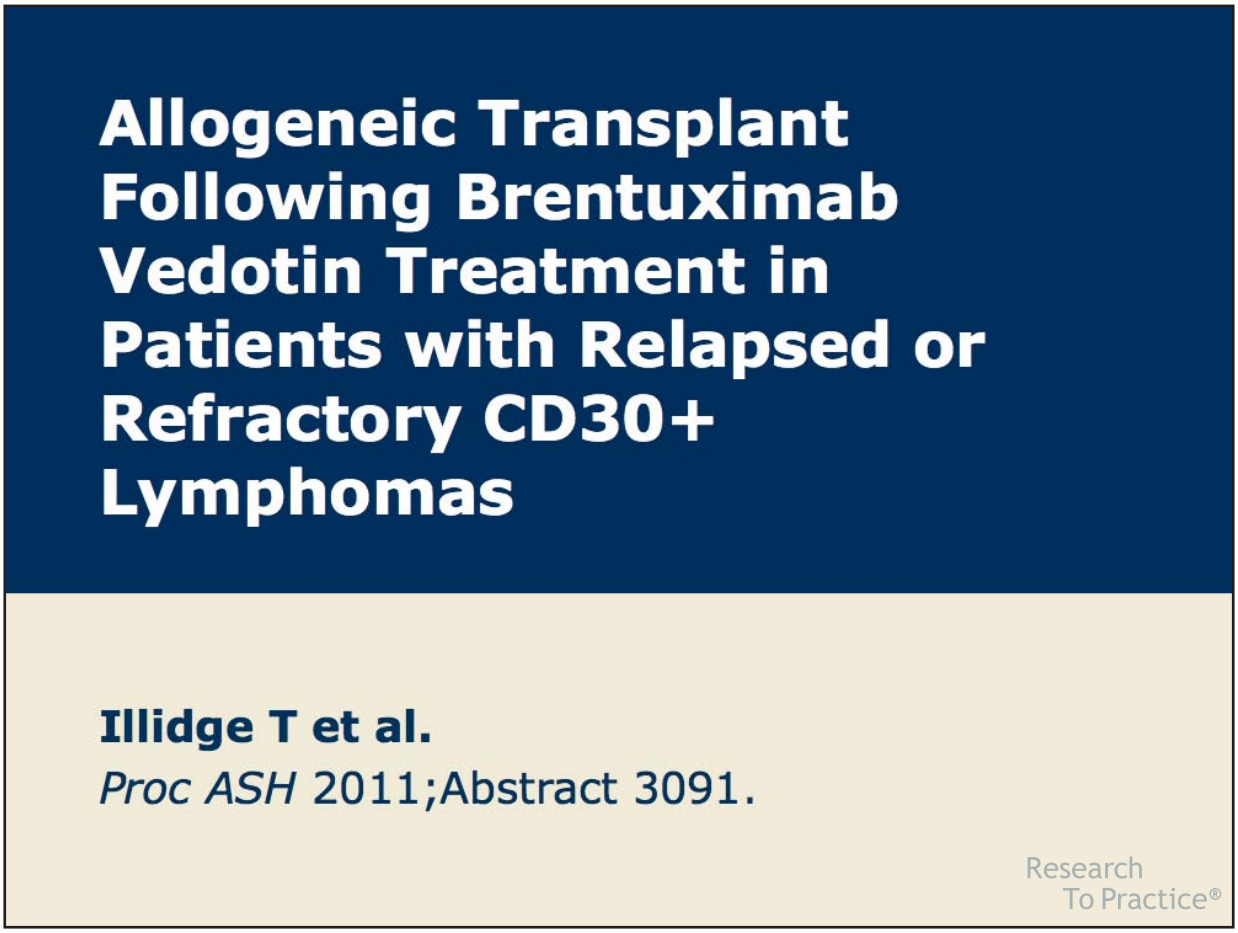
Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

Allogeneic Transplant After Brentuximab Vedotin in Patients with Relapsed/Refractory CD30+ Lymphomas

Presentation discussed in this issue

Illidge T et al. **Allogeneic transplant following brentuximab vedotin treatment in patients with relapsed or refractory CD30+ lymphomas.** *Proc ASH* 2011;**Abstract 3091**.

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



Background

- Allogeneic stem cell transplantation (allo-SCT) is an available treatment option for relapsed or refractory Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL), though its exact role is unclear.
- Two phase II trials have evaluated brentuximab vedotin (B-vedotin), an anti-CD30 antibody-drug conjugate, in patients with relapsed or refractory CD30+ lymphomas:
  - HL: 75% ORR, 34% CR (*Proc ASCO* 2011;Abstract 8031)
  - sALCL: 86% ORR, 57% CR (*Proc ASCO* 2011;Abstract 8032)
- **Current Study Objective**: To retrospectively characterize the outcome of patients with HL and sALCL who received allo-SCTs after treatment with B-vedotin in the 2 Phase II trials.

Illidge T et al. *Proc ASH* 2011;Abstract 3091.

Baseline Characteristics

- Fifteen patients of 160 total in the 2 Phase II trials received allo-SCT as their first therapy subsequent to treatment with B-vedotin.

Characteristic	N = 15
HL	8
sALCL	7
Refractory to front-line therapy	9 (60%)
Refractory to most recent therapy	4 (27%)
Received a previous ASCT	12 (80%)
Prior chemotherapy regimens, median (range)	3 (2-5)
ALK-positive (sALCL only)	6 (40%)

Illidge T et al. *Proc ASH* 2011;Abstract 3091.

Clinical Responses of Patients Receiving B-Vedotin and Allo-SCT

Response, n (%)	HL n = 7	sALCL n = 8	Total n = 15
Objective responses	7 (100)	8 (100)	15 (100)
Complete remission	5 (71)	7 (88)	12 (80)
Partial remission	2 (29)	1 (12)	3 (20)

Illidge T et al. *Proc ASH* 2011;Abstract 3091.

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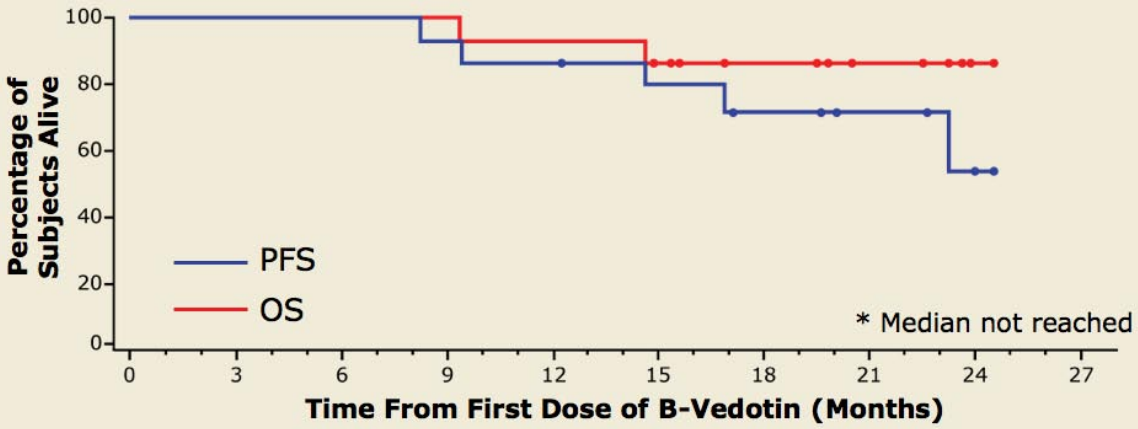
Progression-Free and Overall Survival (Median Follow-Up 19.6 Months)



* Calculated from first dose of B-vedotin

- Five patients (1 with HL, 4 with sALCL) have progressed or died post allo-SCT.
  - Of the 2 deaths (both patients with sALCL who had a CR with B-vedotin), 1 was disease-related and the other due to transplant-related complications.

With permission from Illidge T et al. *Proc ASH* 2011;Abstract 3091.

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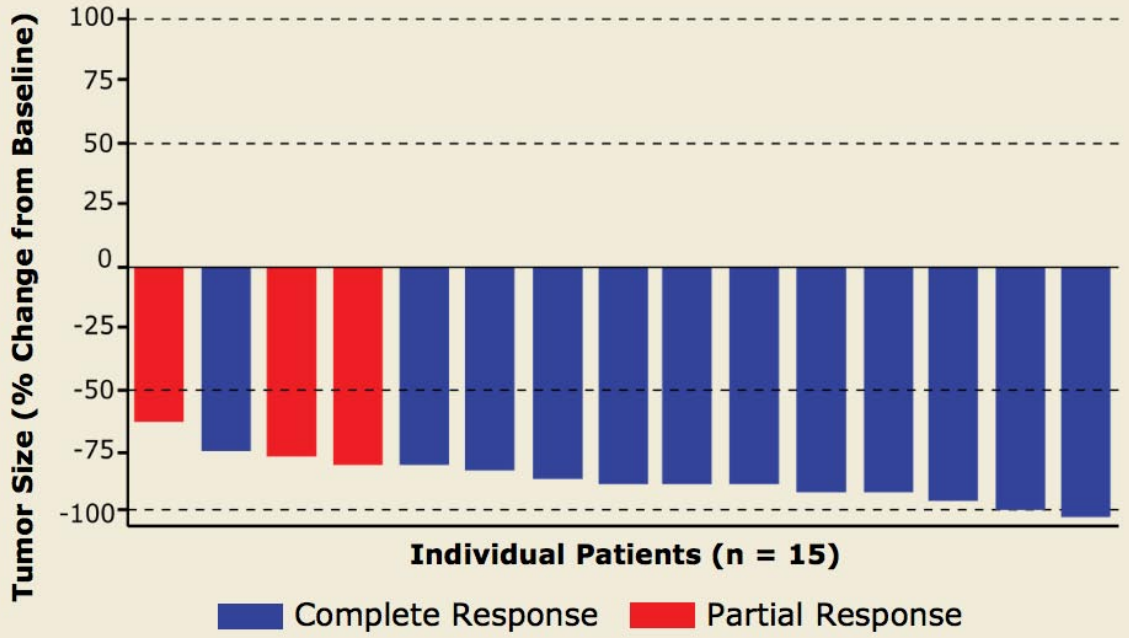
Maximum Tumor Reduction with B-Vedotin Prior to Allo-SCT



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Adverse Events in ≥25% Patients (N = 15)

Adverse event	All grades	Grade 3
Peripheral sensory neuropathy	53%	13%
Pyrexia	53%	—
Diarrhea	47%	7%
Neutropenia	33%	7%
Nausea	33%	—
Chills	27%	—
Dyspnea	27%	7%

Other Grade 3 or 4 events in >2 patients: Anemia (20%) and thrombocytopenia (20%)

Illidge T et al. *Proc ASH* 2011;Abstract 3091.

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Author Conclusions

- Treatment with B-vedotin may be an option for reducing tumor burden to facilitate a consolidative allo-SCT in patients with relapsed or refractory HL or sALCL.
- Despite adverse risk factors, 10 of 15 patients (67%) in this case series remain in remission following treatment with B-vedotin and subsequent allo-SCT.
- After a median duration of follow-up of 19.6 months, the median PFS and OS for patients who received an allo-SCT after B-vedotin treatment has not yet been reached.

Illidge T et al. *Proc ASH* 2011;Abstract 3091.

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Investigator Commentary: Allogeneic Transplant Following B-Vedotin in Relapsed or Refractory CD30+ Lymphomas

In this Phase II trial that I am part of, patients with HL and sALCL who achieved a remission were allowed to be taken off study and taken to transplant. Two out of 3 patients with HL that I have treated have been cured. One patient with sALCL achieved a remission but died because of complications from the transplant. Hence, decisions must be made cautiously.

On the flip side, I treated a 62-year-old patient for whom an autologous transplant failed. She was not likely to receive an allogeneic transplant, so I started B-vedotin for her as part of the open-label study. I will keep her on B-vedotin until she has side effects. Another presentation at ASH showed no added toxicity in patients on extended treatment with B-vedotin. You can envision having a patient who responds to B-vedotin and will not be transplant eligible or does not want a transplant for whom you likely will recommend a treatment strategy by which you will administer this drug indefinitely while adjusting the dose.

Interview with Craig Moskowitz, MD, January 11, 2012

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