5 Minute JournalClub

Key ASH Presentations
Issue 2, 2012

Treatment with Brentuximab Vedotin Prior to Reduced Intensity Allogeneic HCT in Relapsed/ Refractory HL

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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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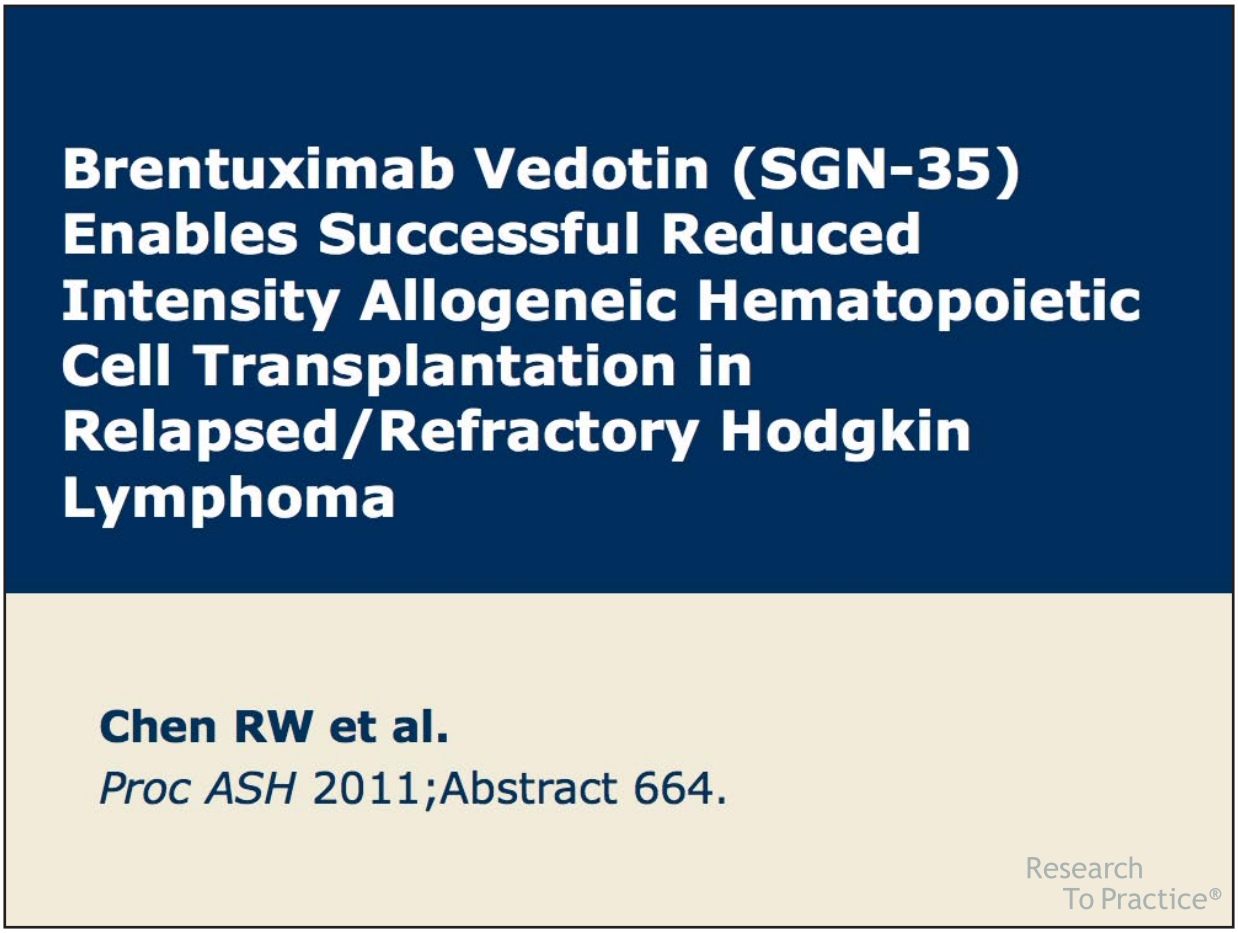
Treatment with Brentuximab Vedotin Prior to Reduced Intensity Allogeneic HCT in Relapsed/Refractory HL

Presentation discussed in this issue

Chen RW et al. **Brentuximab vedotin (SGN-35) enables successful reduced intensity allogeneic hematopoietic cell transplantation in relapsed/refractory Hodgkin lymphoma.** *Proc ASH* 2011;**Abstract 664**.

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



Background

- Reduced intensity allogeneic hematopoietic transplantation (RIC allo-HCT) can induce durable remissions in some patients with relapsed/refractory Hodgkin lymphoma (HL).
- However, its use is limited by lack of disease control prior to transplantation.
- Brentuximab vedotin (B-vedotin), a novel antibody-drug conjugate, has a 75% objective response rate in this patient population (*Proc ASCO* 2011;Abstract 8031).
- **Current Analysis Objective:** To evaluate the efficacy and toxicity of allogeneic transplant after B-vedotin for patients with relapsed/refractory HL.
  - Estimate efficacy of allogeneic transplant after B-vedotin

Chen RW et al. *Proc ASH* 2011;Abstract 664.

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Study Schema

- Patients with relapsed/refractory HL treated at City of Hope National Medical Center (COH) and Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance (FHCRC/SCCA) between October 2008 and October 2011 who received B-vedotin followed by RIC allo-HCT
- Eligibility:
  - PS ≥ 60% by Karnofsky scale
  - No prior allo-HCT but prior autologous transplant allowed
- Methods:
  - Thirty-one patients received B-vedotin and met the inclusion criteria
  - Eighteen of 31 underwent RIC allo-HCT (14 at COH, 4 at FHCRC/SCCA)

Chen RW et al. *Proc ASH* 2011;Abstract 664.

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Baseline Characteristics

Characteristic	n = 18 % or median
Best response to B-vedotin	CR (39%), PR (44%), SD (11%), PD (6%)
Disease status at the end of B-vedotin therapy	CR (33%), PR (33%), SD (6%), PD (22%)
Disease status at the time of allo-HCT	CR (33%), PR (44%), SD (11%), PD (11%)
Median time from B-vedotin to allo-HCT	62 days (range: 24-276)

CR = complete response; PR = partial response; SD = stable disease;
PD = progressive disease

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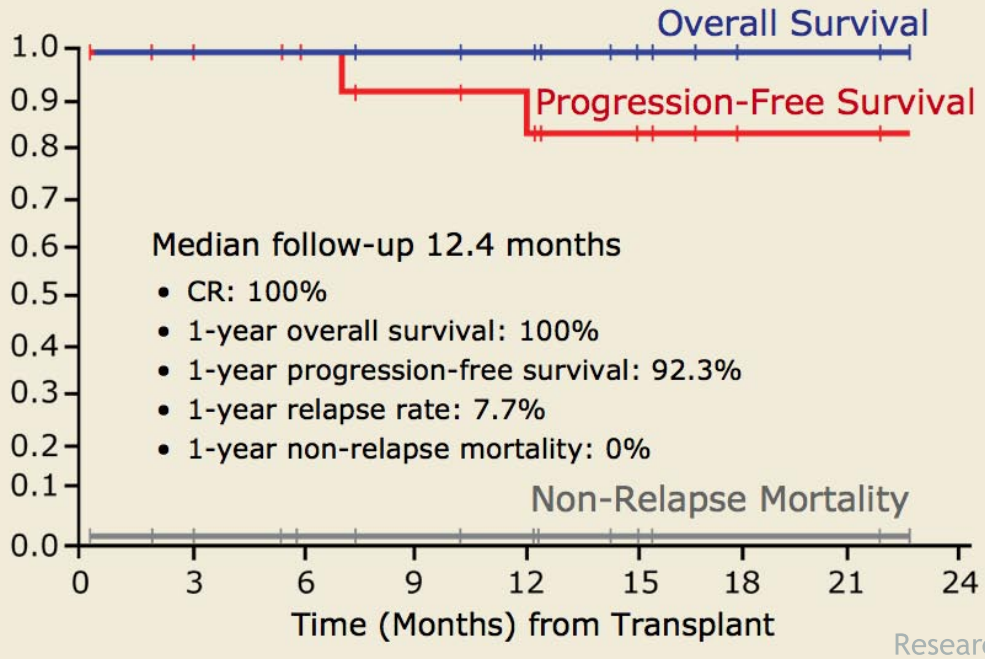
Chen RW et al. *Proc ASH* 2011;Abstract 664.

Survival



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With permission from Chen RW et al. *Proc ASH* 2011;Abstract 664.

Transplant-Related Outcomes

Outcomes	N (%) or median (range)
Engraftment	
Days to ANC ≥ 0.5 x 10^9/L	14 (0-21)
Days to PLT > 20	12.5 (0-21)
% chimerism	>99% (day 30-209)
Acute GVHD	27.8%
Chronic GVHD	56.3%
Infectious disease	27.8%

ANC = absolute neutrophil count; PLT = platelet; GVHD = graft-versus-host disease

Chen RW et al. *Proc ASH* 2011;Abstract 664.

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Bearman Toxicity Table (Patients Treated at COH)

Organ system	Bearman grade	Event incidence (n = 14)
Cardiac toxicity	I	2 (14%)
Central nervous system toxicity	I	1 (7%)
Gastrointestinal toxicity	I/II	6 (43%)
Hepatic toxicity	I/II	7 (50%)
Pulmonary toxicity	I/II	2 (14%)
Renal toxicity	I/II	7 (50%)
Stomatitis	I/II	8 (57%)

Chen RW et al. *Proc ASH* 2011;Abstract 664.

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Author Conclusions

- Addition of B-vedotin prior to allogeneic transplantation does not appear to adversely affect engraftment, GVHD or survival.
- B-vedotin may provide sufficient disease control for selected patients to successfully proceed to allo-SCT.

Chen RW et al. *Proc ASH* 2011;Abstract 664.

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Investigator Commentary: B-Vedotin Enables Successful RIC Allo-HCT in Relapsed/Refractory HL

To examine the impact of B-vedotin on RIC allo-HCT, the authors performed a retrospective analysis of patients with relapsed/refractory HL who received B-vedotin and then went on to receive RIC allo-HCT. Patients at COH have fared well with this approach. Following transplant, most of the patients fared well at a median follow-up of about 1 year. This is exciting because most patients with HL who receive an allo-HCT and survive up to 1 year without being adversely affected by the transplant are probably cured.

The label indication for B-vedotin is for patients for whom an autologous transplant has failed. I personally administer the agent to patients as a bridge to an allo-HCT off study. The number of doses of B-vedotin a patient should receive if the goal is to take the patient to transplant is a matter of debate. You don't have to administer B-vedotin continually. If the patient achieves remission, you can stop treatment. For a young patient who achieves remission with B-vedotin, I believe most doctors would take the patient off the agent and perform a transplant.

Interview with Craig Moskowitz, MD, January 11, 2012

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