



POST-ASH Issue 6, 2014

Phase I/II Study of Brentuximab Vedotin in Pediatric Patients with Relapsed or Refractory HL or Systemic Anaplastic Large Cell Lymphoma

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on targeted therapies for Hodgkin lymphoma from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Evaluate the benefits and risks of brentuximab vedotin after long-term follow-up of patients with relapsed or refractory Hodgkin lymphoma.
- Assess the efficacy and safety of brentuximab vedotin in investigational settings, such as for elderly and pediatric patients with Hodgkin lymphoma or as salvage therapy prior to stem cell transplant.
- Appraise recent clinical trial data on the use of panobinostat in combination with chemotherapy for relapsed or refractory Hodgkin lymphoma.
- Recall the clinical features, treatment, survival outcomes and prognosis of gray zone lymphoma.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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This activity is supported by educational grants from Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc, Seattle Genetics and Spectrum Pharmaceuticals Inc.

Hardware/Software Requirements:

A high-speed Internet connection

A monitor set to 1280 x 1024 pixels or more

Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later

Adobe Flash Player 10.2 plug-in or later

Adobe Acrobat Reader

(Optional) Sound card and speakers for audio

Last review date: March 2014

Expiration date: March 2015

To go directly to slides and commentary for this issue, [click here](#).

One of the best ways to allow experienced clinical investigators to illustrate their perspectives on the translation of research to clinical care is to ask them to present and discuss patients from their practices, and this month in Miami and New York we will do just that by hosting daylong CME symposia structured around 32 cases managed by 10 invited researchers ([Join us! Click here](#)). In reviewing the first faculty slide set submitted for the Miami meeting by Dr Craig Moskowitz, I was immediately drawn to his selection of a case of a 72-year-old woman with classical Hodgkin lymphoma (cHL) who had significant comorbidities requiring a plethora of medications. The dilemma of this important cHL subset — which is estimated to comprise up to 35% of cHL patients — is that the natural history of the disease seems somewhat more aggressive, yet poor health and reduced baseline renal function often mean that even modified chemotherapy regimens may not be delivered at close to full doses.

Dr Moskowitz includes in his talk a slide illustrating the design of a single-arm Phase II trial in older patients evaluating the antibody-drug conjugate brentuximab vedotin (bv) followed by scaled back chemotherapy (AVD [doxorubicin/vinblastine/dacarbazine]) and then bv consolidation. This is not the first time we have heard about this intriguing study, as last summer at our lymphoma think tank Dr Andrew Evens presented an 87-year-old woman who had entered the trial but unfortunately had major problems with the chemotherapy during the first cycle, including sepsis and congestive heart failure.

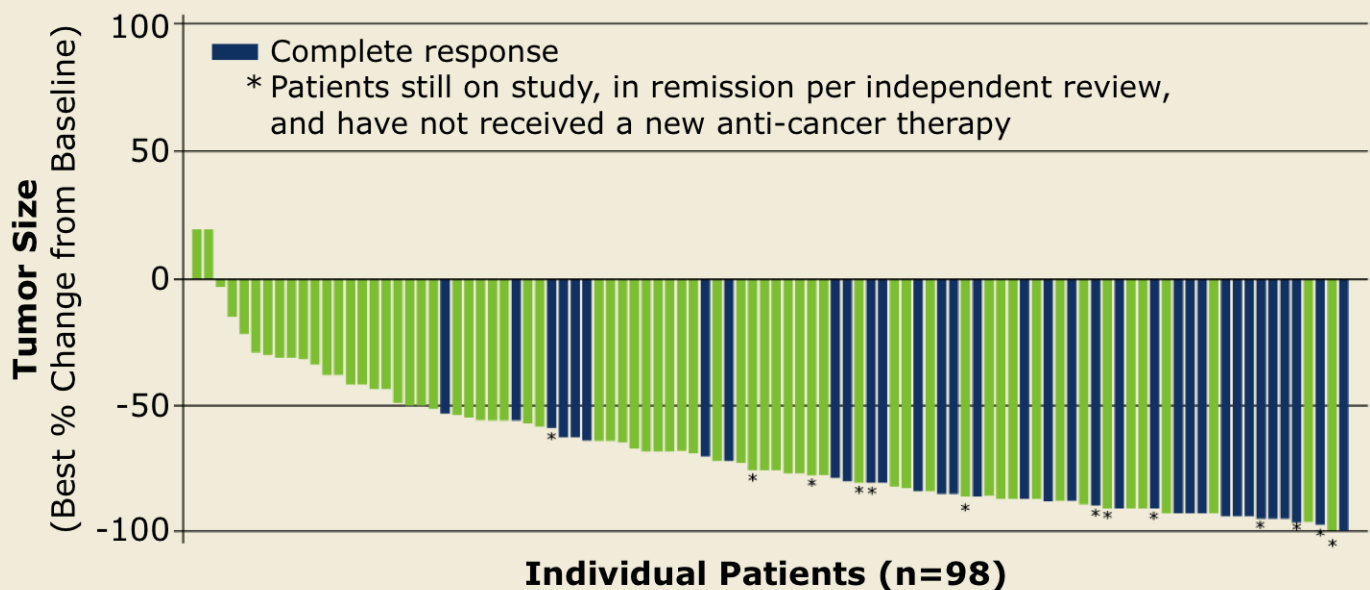
For precisely this reason many clinicians have for some time expressed great interest in taking things even further and eliminating chemotherapy altogether for the “frail elderly” population, and at ASH we got a first glimpse that this in fact may be quite possible. Specifically, preliminary data were presented from 11 of the projected 50 patients aged 60 and older enrolled on [an ongoing Phase II study](#) of bv up front. The results were impressive, as 7 patients achieved a complete response (CR) and 2 had a partial response. Among these, the 2 that got my attention were a 92-year-old woman with Stage IV disease and PS 1 and an 88-year-old man with Stage II disease and PS 2, both of whom had CRs. It is worth noting that the durability of these responses in this very early data set has not yet been established, and it could be, as is being tested in the trial discussed at the think tank, that integration of some form of chemotherapy will be optimal.

The challenge of the frail elderly patient permeates all corners of oncology, and oncologists frequently inquire about the potential up front role of agents like T-DM1 in HER2-positive breast cancer or ibrutinib in CLL and mantle-cell lymphoma as less toxic alternatives when even “gentle” forms of chemotherapy like paclitaxel and bendamustine pose a significant risk. I will be curious to find out in Miami what happened with Dr Moskowitz’s 72-year-old patient and to hear his thoughts and those of the other faculty members on how this compelling issue plays out in their practices as well as their perspectives on new HL data sets presented in New Orleans, including those profiled below:

- **More follow-up of bv in relapsed/refractory (RR) HL**

The **3-year update** from the pivotal Phase II study revealed a median overall survival of 40.5 months with 14 of the 76 patients who had objective responses still in remission, suggesting that a fraction of these patients may be cured. Perhaps even more impressive, the waterfall plot (see below) illustrates that all but 2 of the 98 patients experienced decreases in tumor size, and 34 patients (35%) achieved CR.

Responses in a Phase II Trial of Brentuximab Vedotin in Relapsed/Refractory Hodgkin Lymphoma



- Patients received a median of 9 cycles (range, 1–16) of B-vedotin
- Those who achieved an objective response received more cycles of therapy

With permission from Gopal AK et al. *Proc ASH* 2013;Abstract 4382.

On the flip side of the coin, while bv is generally better tolerated than conventional chemotherapy, toxicities are a reality, and almost half of the patients in this study experienced some form of neuropathy (only 9% being Grade 3 or 4). In a related matter, an interesting ASH poster described **8 cases of pancreatitis** in patients receiving bv, including 2 who died of that complication. Although this rare but

concerning side effect has been reported with other tubulin drugs, it is of interest that CD30 is present on normal pancreatic cells, but it is not clear if this is of clinical significance with regard to this phenomenon. Regardless, many investigators caution that a baseline serum amylase and lipase should be obtained and that abdominal discomfort be investigated thoroughly.

In New Orleans we were also treated to [a fascinating report](#) from Memorial Sloan-Kettering on the use of bv prior to autotransplant. This Phase II study demonstrated that in 11 of 42 patients (26%), bv resulted in FDG PET-negative scans, allowing patients to proceed to transplant without more chemotherapy. This appealing strategy seems likely to be considered for nonprotocol therapy in the future. Finally, [a Phase I/II study](#) reported encouraging response and tolerability findings using bv in 16 pediatric patients with HL.

- **Phase I study of panobinostat combined with ICE (ifosfamide/carboplatin/etoposide) in RR cHL**

The subject of novel agents in HL was addressed at ASH in [a brilliant review lecture by Dr Anas Younes](#). In addition to other monoclonal antibodies and antibody-drug conjugates, he highlighted histone deacetylase inhibitors and agents targeting the PI3 kinase pathways as ones to look out for. In that regard, in New Orleans we saw [data from a Phase I study](#) evaluating panobinostat combined with ICE. The regimen resulted in CR in 15 of 21 (71%) patients, and all were able to have stem cells harvested successfully, with 17 responding patients going on to autotransplant without additional treatment except mobilization chemotherapy. Toxicity was considered “acceptable” and included fatigue, GI complaints and myelosuppression, but of course Phase III testing will be needed to determine the potential additional benefit of this regimen.

- **Gray zone lymphoma case series**

Dr Evens and colleagues [reported a retrospective analysis](#) of 96 patients diagnosed with this difficult-to-classify B-cell lymphoma that commonly has features intermediate between primary mediastinal diffuse large B-cell lymphoma (DLBCL) and cHL. This important paper identified a subset of these patients who present without mediastinal involvement and have distinct characteristics. Patients in this series received various forms of chemotherapy and, in most cases, rituximab, and overall the outcomes seem less favorable than with either DLBCL or cHL. At a median follow-up of 25 months, 2-year progression-free survival is 41% and overall survival is 84%, suggesting that much more research is needed to optimize the care of these patients.

- **Reduced-intensity conditioning for allotransplant for RR HL in the “bv era”**

Allotransplant is thought to have the potential to eradicate HL via a graft-versus-host effect, and [this retrospective report](#) of 27 patients suggested better outcomes among patients who had received prior bv. The findings, while preliminary, appear to have renewed interest in allotransplant for HL.

Next, on the final issue of our ASH review series, we visit perhaps the most exciting corner of the field — chimeric antigen receptor T-cell therapy, as discussed by an investigator in the middle of it all, Dr David Porter.

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Phase I/II Study of Brentuximab Vedotin in Pediatric Patients with Relapsed or Refractory HL or Systemic Anaplastic Large Cell Lymphoma

Presentation discussed in this issue

Locatelli F et al. **Phase 1/2 study of brentuximab vedotin in pediatric patients with relapsed or refractory (R/R) Hodgkin lymphoma (HL) or systemic anaplastic large-cell lymphoma (sALCL): Preliminary Phase 2 data for brentuximab vedotin 1.8 mg/kg in the HL study arm.** *Proc ASH 2013*; [Abstract 4378](#).

Slides from a presentation at ASH 2013 and transcribed comments from a recent interview with Christopher Flowers, MD, MS (2/24/14)

Phase 1/2 Study of Brentuximab Vedotin in Pediatric Patients with Relapsed or Refractory (R/R) Hodgkin Lymphoma (HL) or Systemic Anaplastic Large-Cell Lymphoma (sALCL): Preliminary Phase 2 Data for Brentuximab Vedotin 1.8 mg/kg in the HL Study Arm

Locatelli F et al.

Proc ASH 2013; Abstract 4378.

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Background

- Brentuximab vedotin (BV) is an antibody-drug conjugate (ADC) containing an anti-CD30 monoclonal antibody.
- Pivotal Phase II studies have reported that BV is effective in Hodgkin lymphoma (HL) and sALCL with a manageable toxicity profile (*JCO* 2012;30:2183; *JCO* 2012;30:2190).
 - These studies led to its FDA approval for use in adult patients with relapsed or refractory (R/R) HL and R/R sALCL in 2011.
- Data from studies of BV in children with these lymphomas are currently limited but promising.
- **Study objective:** To report the preliminary efficacy, safety and pharmacokinetic (PK) findings from the Phase II study of BV in pediatric patients with R/R HL.

Locatelli F et al. *Proc ASH* 2013;Abstract 4378.

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Ongoing Phase I/II Trial Design

NCT01492088

Target accrual (n = 42)

R/R HL or R/R sALCL
Age 5 to <18 years
No prior anti-CD30 antibody

BV
1.8 mg/kg (IV), q3wk*
up to 16 cycles

* The Phase I portion established the recommended Phase II dose (RP2D) as 1.8 mg/kg every 3 weeks

- **Phase II primary endpoint:** Overall response rate (ORR) at RP2D
- **Phase II secondary endpoints include:** Overall and progression-free survival, PK characterization, safety and determination of immunogenicity of BV

Locatelli F et al. *Proc ASH* 2013;Abstract 4378.

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Patient Characteristics

Patients with R/R HL	n = 16
Median relative dose intensity	100%
Median age (range)	15 years (8-18)
Male	56%
Ann Arbor stage at initial diagnosis	
Stage I	0%
Stage II	44%
Stage III	6%
Stage IV	44%
Not specified	6%
With B symptoms at baseline	50%

- The median dose of BV received was 435.5 mg (range, 128-2,036)

Locatelli F et al. *Proc ASH* 2013;Abstract 4378.

Response in Patients with R/R HL

Best response	n = 15*
ORR	47%
Complete response	33%
Partial response	13%

* Patients with available data at cutoff

- Responses were evaluated after 2 cycles of therapy
- The median duration of treatment was 114.5 days (range, 41-357)

Locatelli F et al. *Proc ASH* 2013;Abstract 4378.

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Secondary Endpoints: Patients with R/R HL

Clinical outcome	
Median time to progression (n = 15)	4.8 months
Median time to response (n = 15)	2.7 months
Median duration of response (n = 7)	Not estimable
Median event-free survival (n = 16)	2.1 months
Median progression-free survival (n = 16)	2.8 months

Locatelli F et al. *Proc ASH* 2013;Abstract 4378.

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Study Outcomes in R/R HL

- At data cutoff (October 8, 2013), patients (n = 16) had received a median of 4.5 cycles of BV.
- Patients discontinued treatment (n = 14):
 - Due to progressive disease (n = 8)
 - Due to adverse events (AEs) (n = 3)
 - Due to hematopoietic stem cell transplant (n = 1)
 - Due to unspecified reasons (n = 2)

Locatelli F et al. *Proc ASH* 2013;Abstract 4378.

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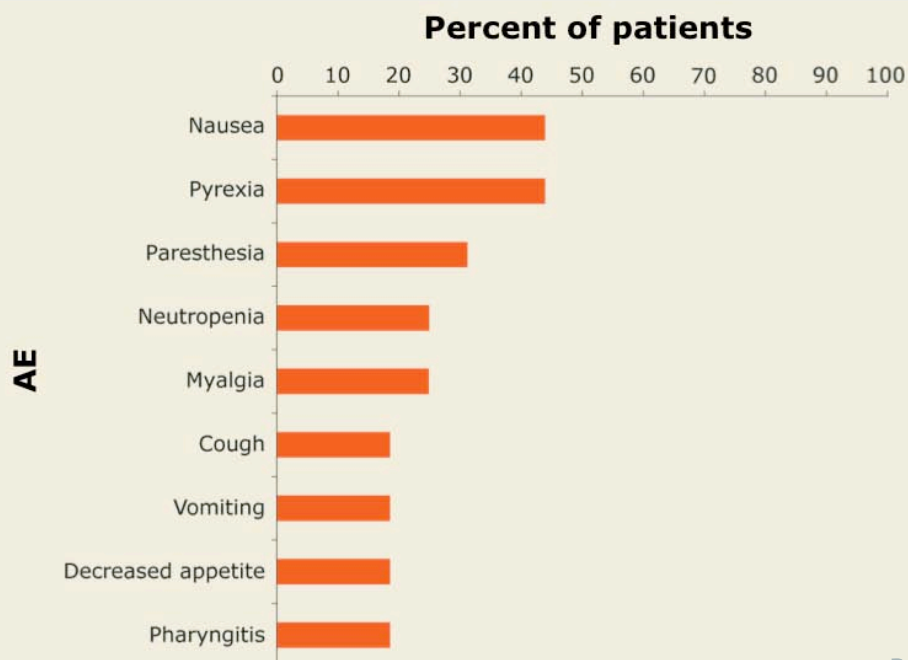
PK Analysis (R/R HL)

- Serum concentrations of BV, the microtubule-disrupting monomethyl auristatin E (MMAE) component of BV and total therapeutic antibody were determined.
- PK analysis demonstrated that:
 - Serum BV and therapeutic antibody concentrations peaked just after infusion.
 - The plasma MMAE concentration peaked 2 days after each infusion of BV, as expected with ADCs.
 - Over the treatment period, BV was detectable in blood prior to the next infusion.
 - Thus, patients remain exposed to BV from cycle to cycle.

Locatelli F et al. *Proc ASH* 2013;Abstract 4378.

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Most Common AEs of All Grades (≥3 Patients with R/R HL)



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Serious AEs (SAEs) in R/R HL

SAEs	Patient ID	Intensity	Cycle, day
Hepatotoxicity* [†] Febrile neutropenia*	1	Grade 3 Grade 3	C1, D13 C1, D14
Supraventricular tachycardia	2	Grade 2	C2, D2
Cardiac arrest [†]	3	Grade 5	C2, D4
Pneumonia*	4	Grade 3	C2, D12
Pyrexia Pyrexia Vomiting	5	Grade 3 Grade 2 Grade 1	C2, D20 C3, D3 C3, D3
Anaphylactic reaction*	6	Grade 3	C6, D1

* BV-related SAE

[†] SAE resulting in BV discontinuation

Locatelli F et al. *Proc ASH* 2013;Abstract 4378.

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Author Conclusions

- For the majority of the pediatric patients with R/R HL, treatment-emergent AEs ranged from mild to moderate.
- The most common treatment-emergent AEs ($\geq 5/16$ patients) were nausea, pyrexia and paresthesia.
- Four Grade ≥ 3 SAEs considered to be treatment-related events were observed (n = 3):
 - Hepatotoxicity (n = 1)
 - Febrile neutropenia (n = 1)
 - Pneumonia (n = 1)
 - Anaphylactic reaction (n = 1)

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Author Conclusions (Continued)

- Three patients discontinued treatment due to AEs:
 - Hepatotoxicity (Grade 3)
 - Peripheral neuropathy (Grade 3)
 - Cardiac arrest (Grade 5)
- BV was detectable in the blood just prior to the next infusion. Therefore, patients remained exposed to treatment from cycle to cycle.
- BV demonstrated activity in this patient population.
 - Complete response: 33%
 - Partial response: 13%
- The Phase II part of the study is ongoing to determine the ORR with BV in 15 response-evaluable pediatric patients with R/R sALCL, including ≥ 10 patients in first relapse.

Locatelli F et al. *Proc ASH* 2013;Abstract 4378.

Investigator Commentary: Phase I/II Study of BV in Pediatric Patients with R/R HL or sALCL: Preliminary Phase II Data for BV in HL

HL in pediatric patients exists along the continuum with young adults and adults. This is a logical extension of BV into this population of patients. In this trial, 16 patients with R/R HL with a median age of 15 years were enrolled. About half of the patients were male and half were female, as can be expected for HL in the pediatric population.

The ORR was 47% with a complete response rate of 33%, and 13% of the patients achieved a partial response. These results are quite meaningful.

Interview with Christopher Flowers, MD, MS, February 24, 2014