5 Minute JournalClub

POST-ASH Issue 6, 2014

Phase II Trial of Front-Line Brentuximab Vedotin for Patients Aged ≥60 Years with Hodgkin 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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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

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POST-ASH Issue 6, 2014

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.

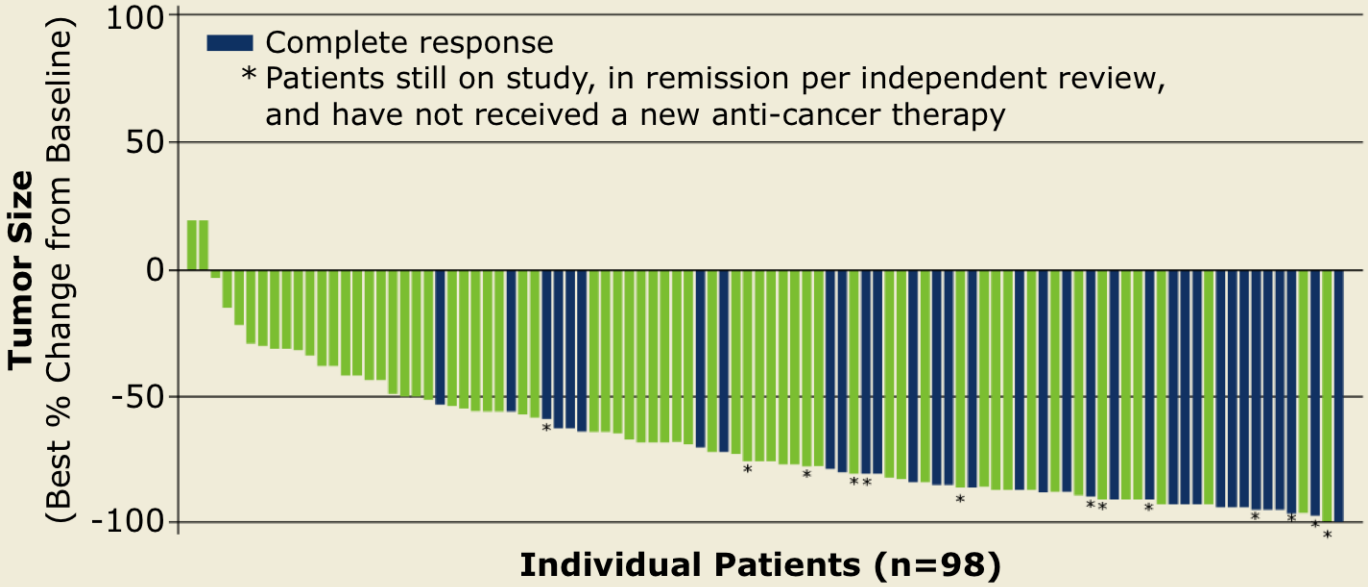
For precisely this reason many clinicians have for some time expressed great interest in taking things even further and eliminating chemotherapy altogether for the "frail elderly" population, and at ASH we got a first glimpse that this in fact may be quite possible. Specifically, preliminary data were 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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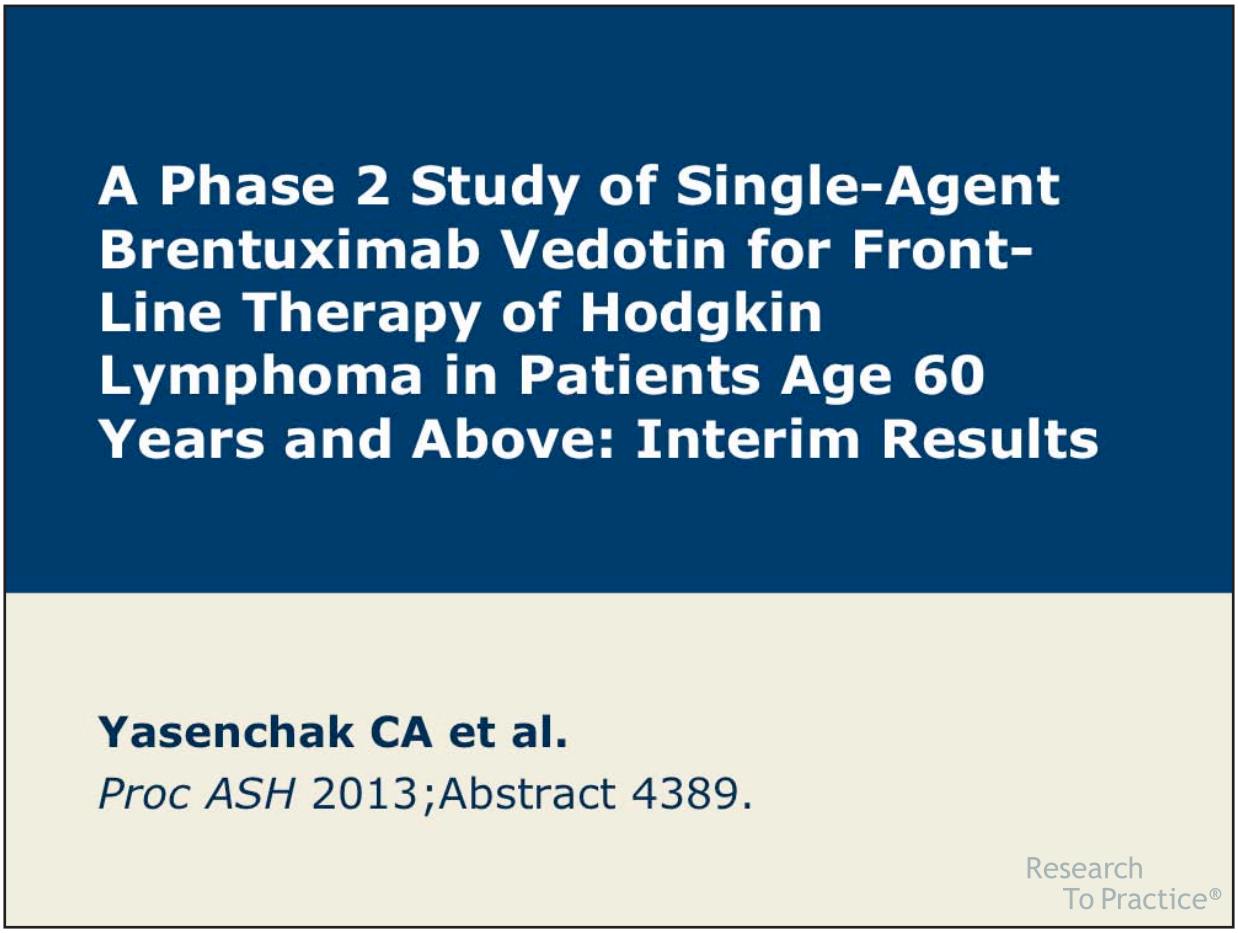
Phase II Trial of Front-Line Brentuximab Vedotin for Patients Aged ≥60 Years with Hodgkin Lymphoma

Presentation discussed in this issue

Yasenchak C et al. **A Phase 2 study of single-agent brentuximab vedotin for front-line therapy of Hodgkin lymphoma in patients age 60 years and above: Interim results.** *Proc ASH* 2013;**Abstract 4389**.

Slides from a presentation at ASH 2013 and transcribed comments from a recent interview with Andrew M Evens, DO, MSc (2/12/14)



Background

- Patients who are aged ≥60 years with Hodgkin lymphoma have disproportionately inferior outcomes compared to younger patients.
- Comorbidities in older patients are associated with higher rates of treatment-related toxicities and can prevent delivery of the standard intensity and/or duration of chemotherapy (*Blood* 2012;119:692).
- A retrospective analysis of patients aged ≥60 years with relapsed/refractory CD30+ lymphomas across 7 single-agent brentuximab vedotin studies showed antitumor activity and durable responses consistent with those observed in younger patients (*Leuk Lymphoma* 2013;[Epub ahead of print]).
- **Study objective:** To conduct an interim analysis of efficacy and safety of front-line brentuximab vedotin monotherapy for patients with HL who are ≥60 years of age.

Yasenchak CA et al. *Proc ASH* 2013;Abstract 4389.

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Ongoing Phase II Trial Design

NCT01716806

Target accrual (n = 50)*
Classical HL (Stages I-IV)
Previously untreated
Age ≥60 years
ECOG PS ≤3
Ineligible for or declined conventional chemotherapy

→ **Brentuximab vedotin**
1.8 mg/kg (IV)
Every 3 weeks

Patients achieving stable disease (SD) or better can receive up to 16 cycles of treatment, after which therapy can be continued for those experiencing clinical benefit.

* To date, 13 patients have been enrolled

- **Primary endpoint:** Objective response rate (ORR)
- Response assessments are performed at cycles 2, 4, 8, 12 and at the end of treatment (EOT)
  - This includes PET scans at cycles 2, 8 and EOT

Yasenchak CA et al. *Proc ASH* 2013;Abstract 4389; www.clinicaltrials.gov, accessed February 2014.

Baseline Characteristics

Characteristic	n = 13
Median age (range)	75 years (64-92)
Male	54%
With moderate age-related renal insufficiency (CrCl ≥30 and <60 mL/min)	54%

CrCl = creatinine clearance

Yasenchak CA et al. *Proc ASH* 2013;Abstract 4389 (abstract only).

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Responses

Response rate	n = 11
ORR	82%
Complete response (CR)	64%
Partial response (PR)	18%
Patients with interim PET scans after 2 cycles of therapy	**n = 10**
Mean decrease in SUVmax from baseline	83%
Patients with negative scans at cycle 2*	36%

SUVmax = maximum standardized uptake value

* To date, range of duration of response: 0.1+ to 20.6+ weeks

- To date, patients have received a median of 5 cycles of therapy
  - Range: 1-11

Yasenchak CA et al. *Proc ASH* 2013;Abstract 4389 (abstract only).

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Best Response Type by Patient

Patient	Age/sex	Dx Stage*	ECOG PS	Response
1	70 y/F	IV	1	CR†
2	79 y/F	II	1	SD
3	92 y/F	IV	1	CR
4	78 y/M	II	1	CR
5	64 y/M	I	0	CR
6	67 y/M	II	0	PR†
7	88 y/M	II	2	CR†
8	75 y/M	III	1	PR†
9	71 y/F	II	0	CR†
10	74 y/F	II	1	SD†
11	78 y/M	IV	1	CR†

* Disease stage at diagnosis; † Still on treatment

Yasenchak CA et al. *Proc ASH* 2013;Abstract 4389 (abstract only).

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Reasons for Study Discontinuation

- Patients discontinued treatment (n = 4):
  - Due to progressive disease (n = 2)
  - Due to a serious adverse event (n = 1)
    - Grade 3 orthostatic hypotension
  - Due to patient decision (n = 1)

Yasenchak CA et al. *Proc ASH* 2013;Abstract 4389 (abstract only).

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Adverse Events

- Treatment-related adverse events occurring in ≥15% of patients included:
  - Decreased neutrophil count (n = 2)
  - Peripheral sensory neuropathy (n = 2)
  - Pruritus (n = 2)
  - Rash (n = 2)
- Most adverse events were Grade 1 or 2.
- Grade 3 treatment-related adverse events included:
  - Decreased neutrophil count (n = 1)
  - Rash (n = 1)
  - Orthostatic hypotension (n = 1)
- No Grade 4 or 5 adverse events have been observed to date.

Yasenchak CA et al. *Proc ASH* 2013;Abstract 4389 (abstract only).

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Author Conclusions

- In this interim analysis of patients aged ≥60 years with newly diagnosed HL, compelling antitumor activity with single-agent brentuximab vedotin was demonstrated.
- To date, a response rate of 82% has been shown in this historically challenging population of patients who either declined or were ineligible for standard chemotherapy.
- Preliminary safety data demonstrated tolerability in this patient population, and the data are consistent with the current safety profile of brentuximab vedotin.

Yasenchak CA et al. *Proc ASH* 2013;Abstract 4389 (abstract only).

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Investigator Commentary: Interim Analysis of an Ongoing Single-Arm Phase II Trial of Up-Front Brentuximab Vedotin (B-Vedotin) Monotherapy for Patients Aged ≥60 Years with HL

This is an interesting study. The term "elderly" sometimes bears a negative connotation. However, HL is a more malignant, virulent disease in older patients. We know that we find much more mixed cellularity in this setting. With the elderly, we see more Epstein-Barr virus-related and advanced-stage disease than we see in younger patients.

This Phase II study showed a respectable response rate with single-agent B-vedotin without chemotherapy. Usually, responses with B-vedotin in HL are quick, within about 2 cycles. The critical question about this study is, will this be a durable response? Although B-vedotin is a type of chemotherapy, it's more of an antitubulin-like agent. I would argue that the most important agent is an alkylator such as dacarbazine and the second most important therapy is an anthracycline. Therefore, I am not surprised about the initial response rate but the crucial question is, can it be maintained? Will relapses occur because of the lack of an alkylating or chemotherapeutic agent? We will need to see those data. Even so, this would be an attractive treatment strategy for older patients who cannot tolerate any chemotherapy.

Interview with Andrew M Evens, DO, MSc, February 12, 2014