



**POST-ASH** Issue 6, 2014

# Reduced-Intensity Conditioning and Allogeneic Transplant for Relapsed/Refractory HL in the Brentuximab Vedotin Era

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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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**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.

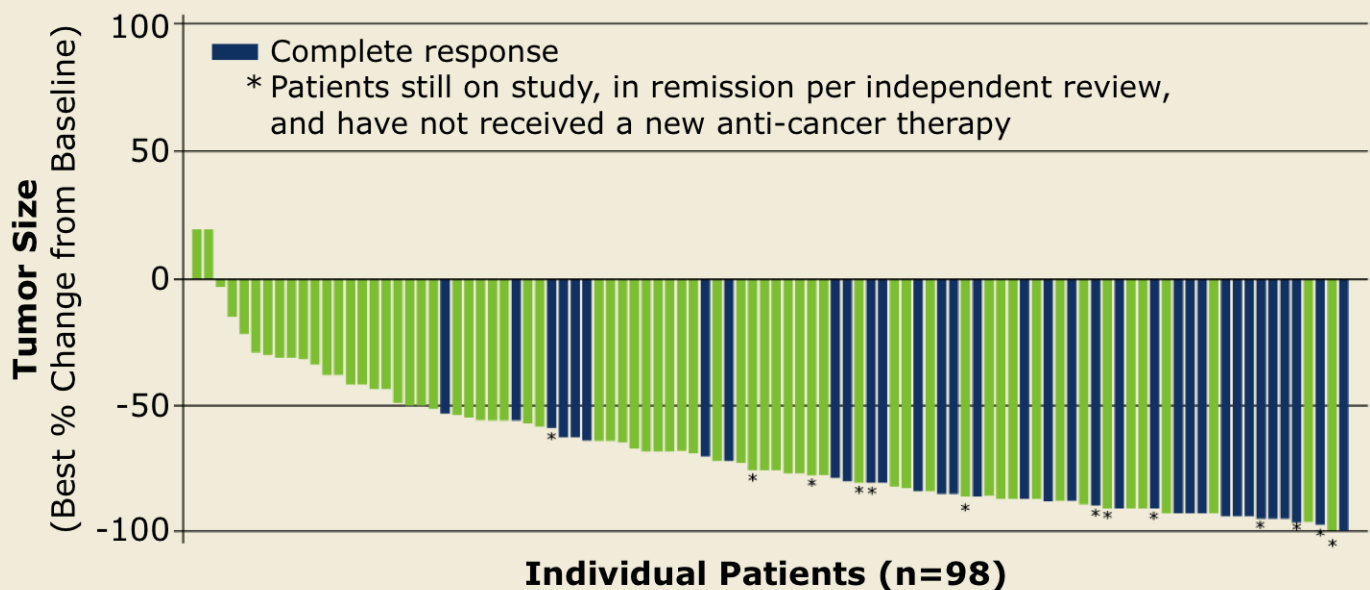
For precisely this reason many clinicians have for some time expressed great interest in taking things even further and eliminating chemotherapy altogether for the “frail elderly” population, and at ASH we got a first glimpse that this in fact may be quite possible. Specifically, preliminary data were 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.

Neil Love, MD

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# **Reduced-Intensity Conditioning and Allogeneic Transplant for Relapsed/Refractory HL in the Brentuximab Vedotin Era**

**Presentation discussed in this issue**

Anderlini P et al. **Reduced-intensity conditioning (RIC) and allogeneic stem cell transplantation (allo-SCT) for relapsed/refractory Hodgkin lymphoma (HL) in the brentuximab vedotin era: Favorable overall and progression-free survival (OS/PFS) with low transplant-related mortality (TRM).** *Proc ASH 2013*; **Abstract 410.**

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

## **Reduced-Intensity Conditioning (RIC) and Allogeneic Stem Cell Transplantation (allo-SCT) for Relapsed/Refractory Hodgkin Lymphoma (HL) in the Brentuximab Vedotin Era: Favorable Overall and Progression-Free Survival (OS/PFS) with Low Transplant-Related Mortality (TRM)**

**Anderlini P et al.**

*Proc ASH 2013*; Abstract 410.

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## Background

- In Hodgkin lymphoma (HL), progressive disease (PD) remains the main cause of treatment failure after reduced-intensity conditioning (RIC) allogeneic stem cell transplantation (allo-SCT).
- Fludarabine (F) and melphalan (M) (FM) as a preparative regimen for RIC allo-SCT in relapsed or refractory (R/R) HL is associated with improved patient outcomes (*Haematologica* 2008;93:257).
- In August 2007, gemcitabine (G), a highly active agent, was added to FM as a RIC regimen for allo-SCT in R/R HL, and the main nonhematologic toxicities were pulmonary, skin related and mucositis (*Leuk Lymphoma* 2012;53:499).
- Subsequently, brentuximab vedotin (BV) was introduced as salvage therapy prior to allo-SCT to maximize response.
- **Study objective:** To augment cytoreduction before transplant and improve overall survival (OS) and progression-free survival (PFS) while reducing PD in R/R HL.

Anderlini P et al. *Proc ASH* 2013;Abstract 410.

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## Study Methods

- Between August 2007 and April 2013, patients with HL who underwent allo-SCT with the G-FM regimen (n = 27)
- Patients who received BV prior to allo-SCT (n = 14)
  - Patients for whom BV was the last therapy prior to allo-SCT (n = 7)
- Patients for whom the donor was an HLA-identical sibling (n = 16)
- Patients for whom the donor was a matched unrelated donor (MUD) (n = 11)

Anderlini P et al. *Proc ASH* 2013;Abstract 410 (abstract only).

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## Study Methods (Continued)

- The conditioning regimen:
  - G: 800 mg/m<sup>2</sup> (IV) x 1
  - F: 33 mg/m<sup>2</sup> (IV) daily x 4
  - M: 70 mg/m<sup>2</sup> (IV) daily x 2
- For patients with a MUD, thymoglobulin (4 mg/kg, IV) was added
- Patients who received peripheral blood progenitor cells (n = 20)
- Patients who received bone marrow transplant (n = 7)

Anderlini P et al. *Proc ASH* 2013;Abstract 410 (abstract only).

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## Patient Characteristics

- All patients had experienced PD on multiple conventional treatments (n = 27)
  - Median age of patients: 31 years (range, 20-46)
  - Median number of prior chemotherapy regimens: 4
  - Radiation therapy: 44%
  - Prior autologous (auto) SCT: 70%
- Disease status at SCT was:
  - CR or undetermined CR (CRu): 63%
  - Partial response: 33%
  - Other: 4%
- Median time to PD after auto-SCT: 5 months (range, 1-68)

Anderlini P et al. *Proc ASH* 2013;Abstract 410 (abstract only).

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## Study Outcomes

- Myeloid recovery was prompt with an absolute neutrophil count of >500/mcL at day 11+ (median)
- Median platelet recovery at 20K/mcL was at day 13+
- In 23 evaluable patients, chimerism studies indicate 100% donor-derived engraftment
- Early deaths (before day 30): n = 3
- Number of cases of graft failure: n = 1
- Cumulative incidence of:
  - Day 100 transplant-related mortality (TRM): 15%
  - Overall TRM: 15%
- Cumulative incidence of acute (Grade 2-4) and chronic graft versus host disease (extensive): 19% versus 39%, respectively

Anderlini P et al. *Proc ASH* 2013;Abstract 410 (abstract only).

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## Responses

Overall response rate (CR/CRu)	BV treated (n = 14)	BV naïve (n = 13)	p-value
Prior to allo-SCT	79%	46%	0.12
After allo-SCT	85%	85%	NSD

NSD = no significant difference

- All 7 patients who received BV as last line of therapy prior to allo-SCT achieved CR/CRu

Anderlini P et al. *Proc ASH* 2013;Abstract 410 (abstract only).

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## Survival Outcomes at Last Follow-Up

All patients	n = 27	95% CI
OS	69%	41-86
PFS	55%	31-74
Cumulative overall PD incidence	30%	15-61

- Deaths (n = 6)
  - Graft rejection (n = 1); pneumonia (n = 2); respiratory failure (n = 1); PD (n = 2)
- After a median follow-up of 18 months (range, 4-55)
  - Patients alive (n = 21)
- All 7 patients who received BV as last line of therapy prior to allo-SCT are alive

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## FM versus G-FM as a RIC Regimen for Allo-SCT in R/R HL

Variable	FM140 (n = 58)	G-FM140 (n = 27)
Age (range)	32 years (19-59)	31 years (20-46)
Received BV before allo-SCT	0%	52%
Achieved CR/CRu before transplant	24%*	63%
TRM (day 100/overall)	7%/15%	15%/15%
2-year OS	64%	78%
2-year PFS	32%	55%
2-year PD	55%	30%
Median time to PD after allo-SCT	4.5 months	13 months

\* Included 28 patients with <PR before transplant

- Cumulative proportion of patients with CR/CRu surviving and progression free at 18 months:
  - FM140 (57%) versus G-FM140 +/- BV (80%);  $p = 0.2$

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## Adverse Events (AEs) (N = 27)

AE	n (%)
All-grade pulmonary toxicity	9 (33%)
Grade 1-3	6 (22%)
Grade 4-5	3 (11%)
All-grade cutaneous toxicity*	5 (19%)
Grade 1-2	4 (15%)
Grade 3	1 (4%)
All-grade mucositis	13 (48%)
Grade 1-2	12 (44%)
Grade 3	1 (4%)

\* Skin rash, responsive to steroidal therapy

Anderlini P et al. *Proc ASH* 2013;Abstract 410 (abstract only).

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## Author Conclusions

- The G-FM140 regimen continues to show promise in this group of patients with high-risk HL.
- The inclusion of G may affect pulmonary toxicity, but TRM remained low.
- With the current BV-supported approach, the CR rate before transplant may be improved.
  - 18-month PFS in patients who achieved CR/CRu before transplant seems to compare favorably to the FM140 experience in complete responders.
  - 80% versus 57%,  $p = 0.20$
- Although this BV-based transplant strategy needs further evaluation, the role of RIC allo-SCT in HL may need to be reassessed in the BV era.

Anderlini P et al. *Proc ASH* 2013;Abstract 410 (abstract only).

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## **Investigator Commentary: RIC and Allo-SCT for Patients with R/R HL in the Era of BV**

RIC and allo-SCT is an approach that is used in the treatment of lymphomas probably because of the evidence of graft versus lymphoma effect and is a way of eradicating the disease. Although it is an approach that appears to be extraordinarily promising in mantle-cell lymphoma, chronic lymphocytic leukemia and follicular lymphoma, it seems to be less beneficial in HL. The challenge is to try to mitigate the toxicities and maximize the benefit of allo-SCT.

This study involved the use of allo-SCT with a RIC regimen including G-FM in 27 patients with R/R HL. The investigators looked specifically at patients who had received prior BV to see how their responses compared to other patients who underwent allo-SCT. Out of the 27 patients, 14 had received prior BV. All 7 patients who received BV as their last therapy achieved CR/CRu.

**(Continued)**

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This is intriguing evidence that we may have a way of using BV prior to allo-SCT to maximize its efficacy. These data are provocative, but the effectiveness of this approach needs to be confirmed in other studies. These results may help to rejuvenate the use of allo-SCT for HL, for which the graft versus lymphoma benefit does not appear to be quite as great. Perhaps BV will help to extend that benefit.

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

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