5 Minute JournalClub

POST-ASH Issue 4, 2013

Brentuximab Vedotin and CHP as Front-Line Therapy in ALCL and NK/T-Cell 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

- Appraise recent clinical research findings on the use of PET scans after initial chemotherapy to identify patients with early-stage Hodgkin lymphoma who can avoid additional radiation therapy, and apply this information in the management of patients' disease.
- Recall emerging clinical research data with combined proteasome and histone deacetylase inhibition in patients with peripheral T-cell or NK/T-cell lymphoma.
- Evaluate the benefits and risks of novel therapeutic approaches under evaluation with brentuximab vedotin as front-line or later-line therapy in advanced and relapsed/refractory Hodgkin and T-cell lymphomas.
- Consider patient characteristics associated with long-term responses to single-agent romidepsin in the care of patients with relapsed/refractory peripheral T-cell lymphoma.

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This activity is supported by educational grants from Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Seattle Genetics and Teva Oncology.

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 2013
Expiration date: March 2014

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POST-ASH Issue 4, 2013

Will brentuximab vedotin increase the cure rate of advanced Hodgkin lymphoma?... and more

To go directly to slides and commentary for this issue, **click here**.

Vincent T DeVita Jr, MD
NCI Director 1980-88

On a crisp autumn afternoon in 1990, I timidly entered the office of the Physician-in-Chief of Memorial Sloan-Kettering Cancer Center and former NCI Director Dr Vincent DeVita. My journey to the Big Apple was for our nascent breast cancer audio series (on cassette tapes!) and specifically focused on Dr DeVita's perspectives on the controversial "NCI Clinical Alert" he helped launch, defining the duration of adjuvant tamoxifen (discussed in our **recent breast cancer email**). Throughout the interview, Dr DeVita nibbled from a jar of chocolate-covered coffee beans, which seemed to further stimulate the conversation, and he became particularly animated when discussing his vision for combination chemotherapy exemplified by his prototypical MOPP regimen in Hodgkin lymphoma (HL) — or Hodgkin's disease, as it was known then. He then went on to describe for our listeners the principles of tumor cell kinetics and noncross-resistant combination regimens that spawned an entire generation of oncologic research.

A lot has happened since that fall day, and while tens of thousands of people have been cured of HL and other cancers with chemotherapy, for most patients in the advanced setting treatment has been palliative in nature and marred by toxicities. In that regard, most investigators, including the one who now occupies Dr DeVita's august Memorial office and title (Dr José Baselga), have concentrated their efforts on developing novel targeted agents designed to make cytotoxics obsolete. Unfortunately, we are not there yet and chemotherapy remains a mainstay in our treatment armamentarium, and at ASH we saw this dynamic play out as both new agents and tried-and-true chemotherapy grabbed headlines in HL and T-cell lymphomas:

1. Chemotherapy without radiation therapy (RT) in early-stage HL

According to another Memorial maven, Dr Andy Zelenetz, the ASH presentation of the much-awaited UK RAPID trial may set a new standard in this disease — specifically for patients with Stage IA and IIA HL or mediastinal bulky disease who have a negative PET scan after 3 cycles of ABVD. In RAPID, at 4 years more than 90% of patients were progression free with or without involved-field RT and, based in part on these findings, investigators are continuing to carefully consider treatment without RT in early PET-negative cases, particularly for younger women at risk for delayed secondary breast cancers.

2. Brentuximab vedotin (BV) as part of up-front treatment of advanced HL

Dr DeVita must be pleasantly surprised at the advent of antibody-drug conjugates (ADC) like BV and the just-approved (in metastatic breast cancer) T-DM1 (ado-trastuzumab emtansine) — agents that can deliver cytotoxics inside tumor cells with minimal normal cell kill. Although BV was approved only 18 months ago, ASH was a reminder that this ADC is here to stay for the long term. Phase II trials of BV in the relapsed/refractory (RR) HL setting revealed a 75% response rate (34% CR) and have helped foster attempts, including a randomized Phase II trial first reported at last year's ASH, to integrate this anti-CD30 ADC into up-front treatment of advanced HL. As part of last year's report, ABVD combined with BV yielded an unacceptable pulmonary toxicity rate. However, this was not seen with BV and AVD (ABVD without the bleomycin), and efficacy findings were encouraging enough to spawn a major ongoing multicenter Phase III trial comparing ABVD to BV + AVD. In this ASH update of the Phase II study, 24 of 26 patients had negative FDG-PET scans after 2 cycles of BV + AVD, which was well tolerated other than mostly reversible peripheral neuropathy.

3. BV as part of up-front treatment of systemic anaplastic large cell lymphoma (sALCL) and mature T- and NK-cell lymphomas

As with HL, encouraging findings in the RR setting (86% responses with 57% CR) have led to efforts to combine BV with up-front chemotherapy. At ASH we saw results from 2 arms of a Phase I study evaluating BV combined with CHP (the vincristine was omitted from CHOP to prevent neuropathy) in patients with sALCL or mature T- and NK-cell lymphomas. The regimen was well tolerated and response was observed in all 26 patients in the trial, including 23 CRs. These and other encouraging data have led to an ongoing Phase III trial comparing BV-CHP to CHOP.

4. BV in RR mycosis fungoides (MF)/Sézary syndrome

A small Phase II study reported at ASH evaluated single-agent BV in patients with previously treated MF/Sézary syndrome, and responses occurred in 13 of 19 patients. Importantly, activity was observed with all levels of CD30 expression, although the authors point out significant limitations with conventional immunohistochemical staining

compared to the multispectral image analysis used in this study. Based in part on these findings, a Phase III trial will compare BV to investigator's choice of bexarotene or methotrexate in these patients.

5. Histone deacetylase (HDAC) inhibition in T-cell lymphomas — bortezomib/ panobinostat (BP) and romidepsin

Two reports unveiled in Atlanta further contribute to the growing database on the effectiveness of HDAC inhibitors in T-cell lymphoma. **The first evaluated** the novel BP combination in 11 patients with RR PTCL and NK-cell lymphoma. The results from this effort were encouraging, and the investigators are interested in studying longer-term maintenance with this regimen.

The second important HDAC paper was an update of the pivotal Phase II trial of romidepsin in 130 patients with RR PTCL. Previous data from that study demonstrated a 25% response rate (and led to the FDA approval of this agent in this setting), and the ASH data set is noteworthy in that more follow-up reveals that responses are often durable, lasting on average more than a year, and up to 4 years, further solidifying the role of this agent in these patients.

The shift in research emphasis in HL, T-cell lymphomas and most other corners of oncology away from chemotherapy and toward novel agents clearly is in full swing, and it will be interesting to look back in a quarter of a century when we know whether this strategy delivers or if it repeats the limitations of chemotherapy that crushed the hopes of oncology leaders of the past generation.

Next…Another cancer for which biological treatment has yielded results never dreamed of in the cytotoxic era — multiple myeloma and a series of ASH papers evaluating two exciting novel proteasome inhibitors — the oral investigational compound ixazomib (formerly MLN9708) and the recently approved irreversible agent carfilzomib.

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Brentuximab Vedotin and CHP as Front-Line Therapy in ALCL and NK/T-Cell Lymphomas

Presentation discussed in this issue

Fanale MA et al. **Brentuximab vedotin administered concurrently with multi-agent chemotherapy as frontline treatment of ALCL and other CD30-positive mature T cell and NK cell lymphomas.** *Proc ASH* 2012;**Abstract 60**.

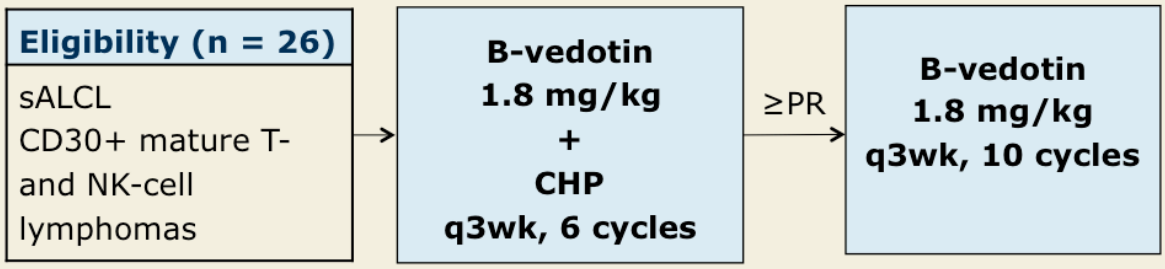
Slides from a presentation at ASH 2012 and transcribed comments from a recent interview with Brad S Kahl, MD (1/17/13)

Background

- CD30 is expressed on systemic anaplastic large cell lymphoma (sALCL) and mature T- and NK-cell lymphomas.
- Front-line anthracycline-containing regimens achieve good response rates, but fewer than half of patients remain disease or progression free after 5 years (*JCO* 2008;26:4124).
- A Phase II pivotal trial of brentuximab vedotin (b-vedotin) in patients with relapsed or refractory sALCL showed an objective response rate of 86% (CR rate 57%) with manageable toxicity (*JCO* 2012;30:2190).
- **Objective:** Evaluate the safety and efficacy of b-vedotin with CHP (CHOP without vincristine) in the front-line treatment of CD30+ mature T-cell and NK-cell neoplasms, including sALCL.

Fanale M et al. *Proc ASH* 2012;Abstract 60.

Phase I Study Design: Arms 2 and 3



- Study had 3 arms:
  - Arm 1: B-vedotin (1.8 mg/kg, q3wk, 2 cycles) followed by CHOP (6 cycles), data previously presented (ESMO 2012)
  - Arm 2: Designed to determine recommended dose of b-vedotin in combination with CHP to be further evaluated in Arm 3
  - The maximum tolerated dose was not exceeded at 1.8 mg/kg q3wk
- **Primary endpoints:** Safety of b-vedotin + CHP and recommended dose of b-vedotin in combination with CHP
- **Secondary endpoint:** Antitumor activity of b-vedotin + CHP

Fanale M et al. *Proc ASH* 2012;Abstract 60.

Best Response by Disease Diagnosis

Response	sALCL (n = 19)	Other diagnoses (n = 7)	Total (n = 26)
ORR*	100%	100%	100%
CR	84%	100%	88%
PR	16%	—	12%
Median PFS	—	—	NR
Median OS	—	—	NR

* At end of cycle 6 or latest assessment for 3 pts who discontinued prior to cycle 6
NR = not reached, pts followed for a median of 9 mo

- 21/26 pts continue to receive single-agent b-vedotin after combination therapy
  - At end of cycle 12, ORR = 92%, CR = 85%
  - At end of cycle 16, ORR = 100%, CR =100%

Fanale M et al. *Proc ASH* 2012;Abstract 60.

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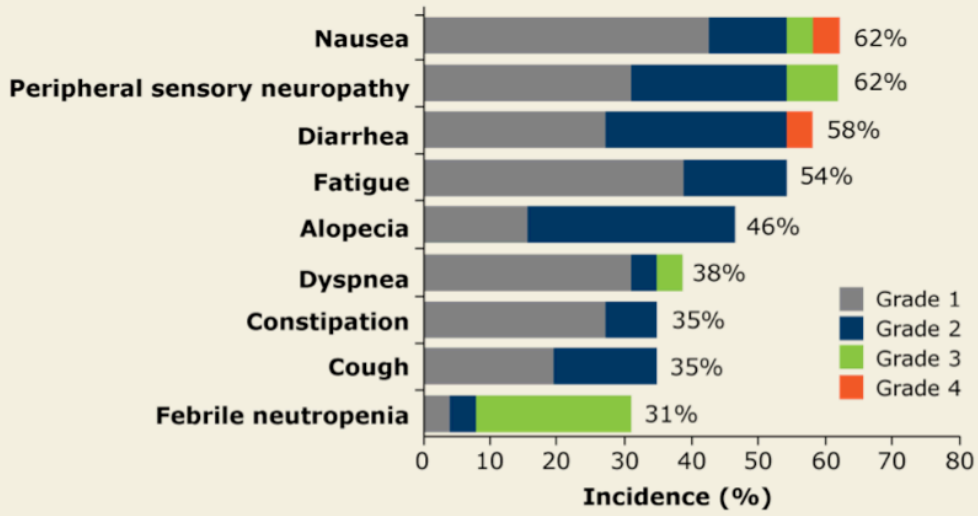
Adverse Events (≥30% of Patients)



Additional Grade ≥3 adverse events occurring in >5% of patients were hyperglycemia, neutropenia, pulmonary embolism and respiratory failure (n = 2 each).

With permission from Fanale M et al. *Proc ASH* 2012;Abstract 60.

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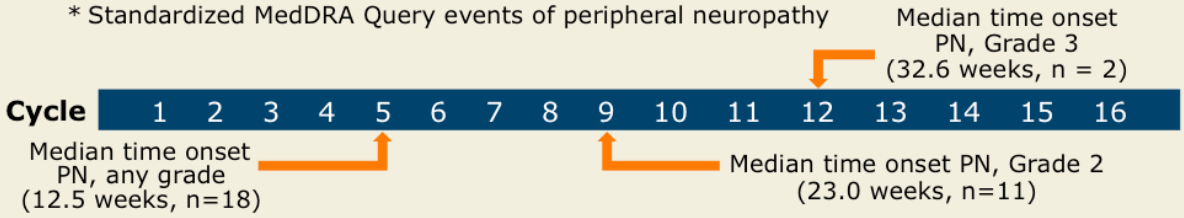
Peripheral Neuropathy (PN)

Preferred term*	Grade 1	Grade 2	Grade 3	Total N = 26
Any event, n (%)	7	9	2	18 (69)
Peripheral sensory neuropathy	8	6	2	16 (62)
Muscular weakness	2	1	—	3 (12)
Peripheral motor neuropathy	—	1	1	2 (8)
Burning sensation	1	—	—	1 (4)
Paresthesia	—	—	1	1 (4)
Peripheral sensorimotor neuropathy	—	1	—	1 (4)
Peroneal nerve palsy	1	—	—	1 (4)

* Standardized MedDRA Query events of peripheral neuropathy



Fanale M et al. *Proc ASH* 2012;Abstract 60.

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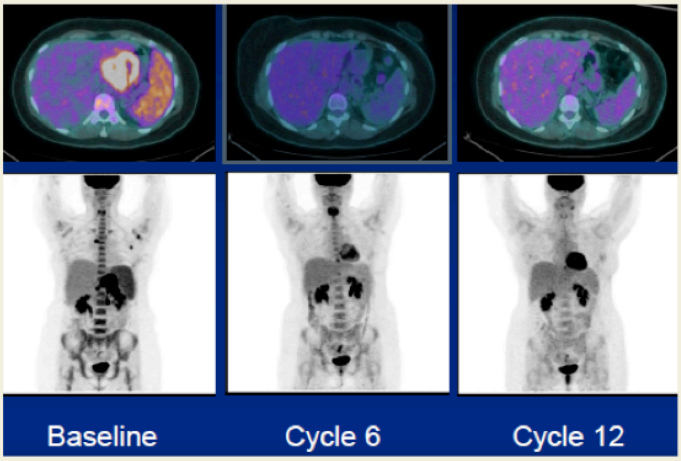
Case Study



- 37-year-old pt, diagnosed with Stage IV PTCL-NOS
- CD30 expression positive by central review
- Received b-vedotin 1.8 mg/kg + CHP (6 cycles), then b-vedotin (9 cycles) alone
- At time of data cutoff, pt continued receiving single-agent b-vedotin

With permission from Fanale M et al. *Proc ASH* 2012;Abstract 60.

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Author Conclusions

- B-vedotin with CHP every 3 weeks exhibited manageable toxicity at the recommended dose of 1.8 mg/kg in patients with CD30+ mature T- and NK-cell neoplasms.
- Combination therapy with b-vedotin demonstrated an objective response rate of 100% (CR rate 88%).
- Adverse events with an incidence greater than 30% included nausea, peripheral sensory neuropathy, diarrhea, fatigue, alopecia, dyspnea, constipation, cough and febrile neutropenia.
- A Phase III study comparing CHOP alone to b-vedotin with CHP in the front-line treatment of CD30+ mature T-cell lymphomas will begin in late 2012 or early 2013.

Fanale M et al. *Proc ASH* 2012;Abstract 60.

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Investigator Commentary: B-Vedotin with Multiagent Chemotherapy as Front-Line Treatment of ALCL and Other CD30-Positive T-Cell and NK-Cell Lymphomas

This was a small Phase I study that evaluated the safety and efficacy of b-vedotin with CHP chemotherapy for patients with ALCL and CD30-positive T-cell lymphomas. B-vedotin is an antibody-drug conjugate that targets CD30 expressed on HL, ALCL and some T-cell lymphomas. It is not currently known how important the degree of CD30 expression is.

The results showed an overall response rate of 100% and a complete response rate of 88%. Though this is a small study, I think these results are incredibly impressive. T-cell lymphomas are a difficult group of cancers to treat. Prior studies with CHOP in T-cell lymphomas have shown overall response rates of around 80% and complete response rates of around 40%. So, even though this a small study, the results are highly encouraging.

A large, international, Phase III study has been initiated for patients with newly diagnosed ALCL or T-cell lymphomas that are CD30-positive. Patients will be randomly assigned to CHOP chemotherapy or CHP with b-vedotin. This trial represents an opportunity to move the field forward for that group of patients.

Interview with Brad S Kahl, MD, January 17, 2013