5 Minute JournalClub

Key ASH Presentations
Issue 4, 2011

ABVD versus Stanford V in Hodgkin Lymphoma

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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 from a plethora of ongoing clinical trials 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 and other cancer clinicians in the formulation of optimal clinical management strategies for hematologic cancer.

LEARNING OBJECTIVE

- Apply the results of the Phase III trial comparing ABVD to Stanford V to the initial management of Hodgkin lymphoma.

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Consulting Agreements: Allos Therapeutics, Celgene Corporation, Millennium, The Takeda Oncology Company; Paid Research: Allos Therapeutics, Genzyme Corporation.

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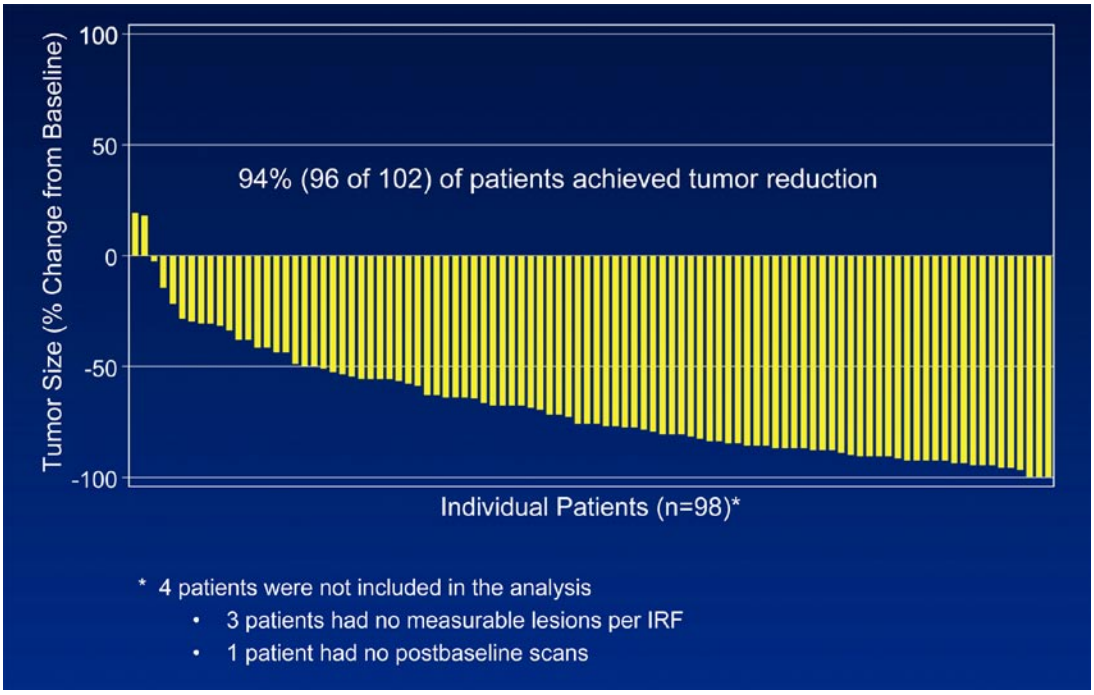
Click here for papers on Hodgkin lymphoma.

When one queries lymphoma investigators about the key data sets from the December ASH meeting, at the top of almost every list is a stunning **report** in which 102 patients with Hodgkin lymphoma (HL) and disease progression after a median of 3.5 prior chemotherapy treatments and an autologous stem cell transplant were treated with brentuximab vedotin. "B vedotin" is an immune conjugate, with an antibody against CD30 hooked to an antitubulin agent (monomethyl auristatin E) that is similar to vinblastine.

Like the trastuzumab/maytansine conjugate T-DM1 in breast cancer, B vedotin is thought to deliver the cytotoxic to or into the tumor cell, but the exact mechanism of antitumor effect has yet to be defined. Of great interest, unlike its breast cancer cousin, the naked antibody in B vedotin is not active in heavily pretreated HL.

In this pivotal Phase II, single-arm trial, more than 90 percent of patients had tumor responses (check out the waterfall plot), with 34 percent complete and 40 percent partial remissions. The agent was well tolerated with apparently reversible peripheral neuropathy identified as the only important toxicity. It should come as no surprise that this fascinating agent is quickly tracking through the FDA and being incorporated into ongoing and emerging clinical trials, including as consolidation after transplant and up front with ABVD.



Three other ASH presentations on HL are also profiled in our slide sets:

1. The long-awaited **Phase III ECOG/Intergroup trial** in locally extensive or bulky advanced HL randomizing between ABVD and Stanford V.

Many were disappointed to see that there was no major efficacy difference between the two arms, and in the US, ABVD remains the standard. In this trial, only patients with bulky mediastinal disease received radiation therapy with ABVD as opposed to essentially a multimodality approach with Stanford V.

2. **A German study** evaluating PET scanning in patients with advanced-stage HL and a residual mass on CAT scan greater than 2.5 cm after BEACOPP.

Ninety-two percent of patients with negative PETs were disease-free at three years without radiation therapy. Whether this can be extrapolated to ABVD is being debated.

3. **An Italian study** of interim PET scanning after two cycles of ABVD in patients with both early and advanced disease.

Patients with PET positivity did poorly and should be considered for immediate referral to a tertiary center for clinical trial consideration.

It is worth remembering that while most of the 8,000 patients diagnosed with HL annually in the US are cured, approximately 1,500 (mostly those presenting with advanced disease) are not. Fortunately, for the first time maybe ever there are a number of promising agents in development, including B vedotin, lenalidomide, panobinostat and everolimus, offering new hope that some of these mostly younger patients can be salvaged.

Next up on ASH *5-Minute Journal Club*: Another major paper on B vedotin — this time in anaplastic large cell lymphoma — and other new data in T-cell lymphomas.

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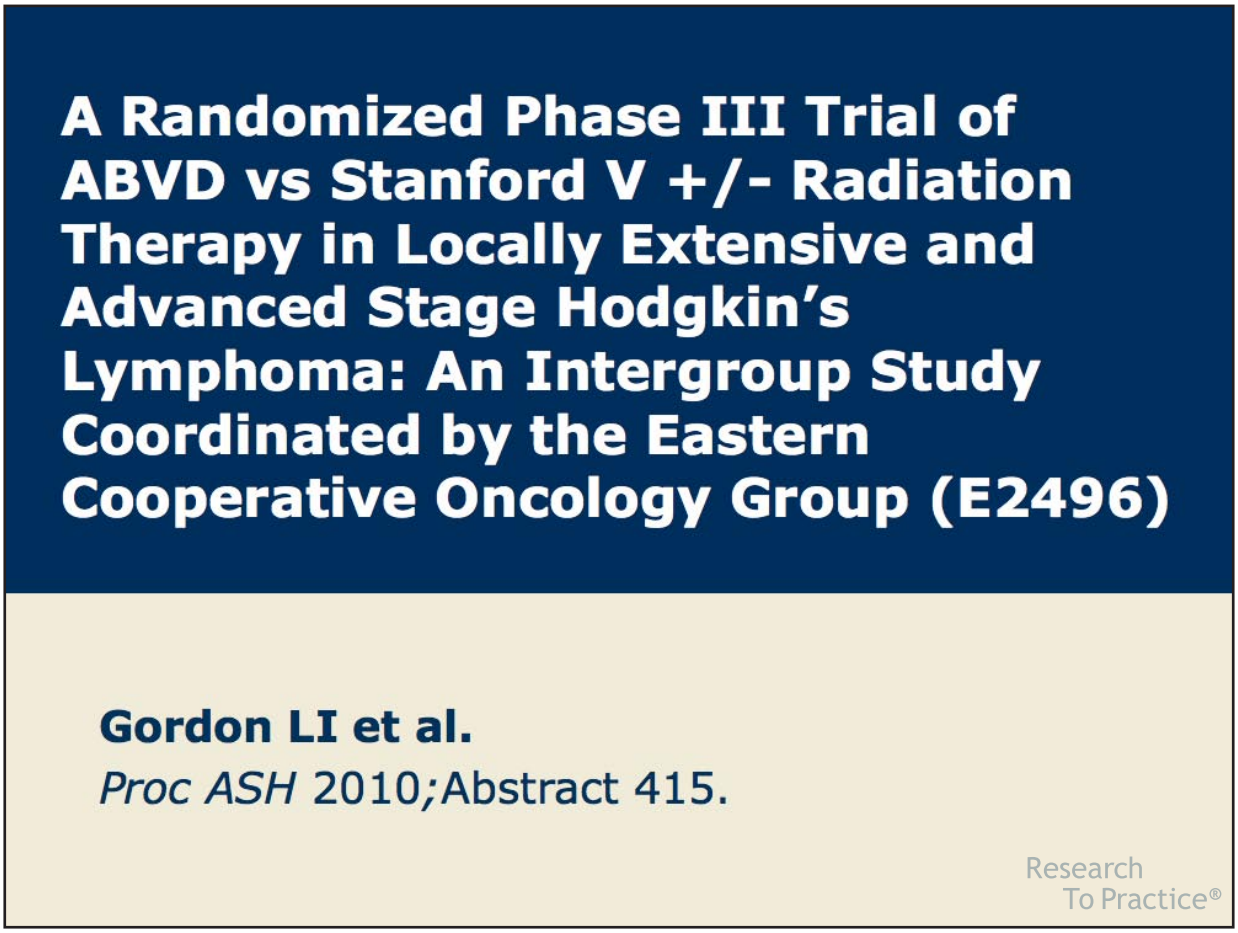
ABVD versus Stanford V in Hodgkin Lymphoma

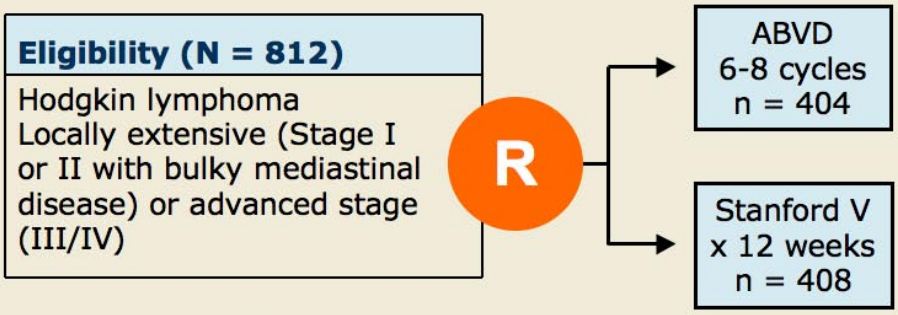
Presentation discussed in this issue

Gordon LI et al. **A randomized Phase III trial of ABVD vs Stanford V +/- radiation therapy in locally extensive and advanced stage Hodgkin's lymphoma: An Intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496).** *Proc ASH* 2010;**Abstract 415**.

Slides from a presentation at ASH 2010 and transcribed comments from a recent interview with Steven M Horwitz, MD (12/29/10)



Study Schema



Primary endpoint:
Failure-free survival: 33% improvement with Stanford V

Radiation therapy (RT, modified IFRT 36 Gy) is administered to patients with bulky mediastinal disease in the ABVD arm.

In the Stanford V arm, RT (modified IFRT 36 Gy) is administered for sites >5 cm or for macroscopic splenic disease.

Gordon LI et al. *Proc ASH* 2010;Abstract 415.

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ABVD and Stanford V Chemotherapy Regimens

- **ABVD Regimen:**
  - Doxorubicin 25 mg/m^2 IV, d1 and d15
  - Bleomycin 10 u/m^2 IV, d1 and d15
  - Vinblastine 6 mg/m^2 IV, d1 and d15
  - Dacarbazine 375 mg/m^2 IV, d1 and d15

- **Stanford V Regimen:**
  - Doxorubicin 25 mg/m^2, q2wks
  - Vinblastine 6 mg/m^2, q2wks
  - Mustard 6 mg/m^2, q4wks
  - Etoposide 60 mg/m^2 x 2, q4wks beginning week 3
  - Vincristine 1.4 mg/m^2, q2wks beginning week 2
  - Bleomycin 5 u/m^2, q2wks beginning week 2
  - Prednisone daily, taper after week 9

Gordon LI et al. *Proc ASH* 2010;Abstract 415.

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Efficacy Outcome

Efficacy Outcome	ABVD (n = 404)	Stanford V (n = 408)	Hazard Ratio	*p*-value
Complete remission (CR + CCR)	72%	69%	—	NS
5-year failure-free survival	73%	71%	—	0.29
5-year overall survival	88%	87%	0.97	0.87

NS = not significant

Gordon LI et al. *Proc ASH* 2010;Abstract 415.

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Adverse Events

Adverse Events	ABVD (n = 404)	Stanford V (n = 408)	*p*-value
Grade 3 or 4 neutropenia	76%	70%	—
Grade 3 lymphopenia	42%	78%	<0.0001
Grade 3 or 4 sensory neuropathy	3%	10%	<0.001
Second primary cancers, n	12	14	NS

NS = not significant

Gordon LI et al. *Proc ASH* 2010;Abstract 415.

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Author Conclusions

- There is no significant difference in responses, failure-free survival or overall survival when ABVD (+ RT for bulky mediastinal disease) is compared to Stanford V (+ RT for nodal sites >5 cm and macroscopic splenic disease).
- There was more Grade 3 lymphopenia and more Grade 3 or 4 sensory neuropathy on Stanford V.
- ABVD (+ RT for bulky mediastinal disease) remains the standard treatment.
  - Stanford V did not meet the objective of 33% improvement in failure-free survival.

Gordon LI et al. *Proc ASH* 2010;Abstract 415.

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Investigator Commentary: ABVD versus Stanford V in the Initial Treatment of Hodgkin Lymphoma

Results of this large US randomized trial of Stanford V have been eagerly awaited. Stanford V is a seven-drug weekly chemotherapy regimen, developed at Stanford, with the advantage that it reduces the cumulative doses of doxorubicin and bleomycin. The disadvantage is that it is a combined-modality program in that in addition to chemotherapy almost everybody undergoes radiation therapy to original sites that are five centimeters or larger and contiguous areas.

The bottom line of the study is that ABVD with radiation therapy for bulky mediastinal disease remains the standard. No difference was recorded in response, failure-free survival and overall survival between Stanford V and ABVD. More sensory neuropathy and lymphopenia occurred with Stanford V. I believe there are certain patients to whom you might still administer Stanford V, if there is a particular concern about lung toxicity or cardiotoxicity from ABVD.

Interview with Steven M Horwitz, MD, December 29, 2010

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