5 Minute JournalClub

Key ASH Presentations
Issue 5, 2011

Activity and Safety of Brentuximab Vedotin (SGN-35) in Relapsed/ Refractory Systemic Anaplastic Large Cell Lymphoma (sALCL)

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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

- Describe the efficacy and safety of brentuximab vedotin (SGN-35) in patients with relapsed or refractory sALCL.

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Steven M Horwitz, MD
Assistant Attending
Lymphoma Service, Division of Hematologic Oncology
Memorial Sloan-Kettering Cancer Center
New York, New York

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 T-cell lymphomas.

Although there are seemingly a multitude of different subtypes, peripheral T-cell lymphomas (PTCL) comprise only about 10 percent of all NHL cases. The related variants of cutaneous T-cell lymphoma (CTCL) are even less common. Nonetheless, in recent years an extraordinary effort by clinical and laboratory investigators has greatly expanded our understanding of the complex biology of these cancers and defined a number of new targets for intervention. In this issue of *5-Minute Journal Club* we profile a handful of new reports in a field that has become a model for research in uncommon, potentially lethal diseases.

1. PTCL papers

Molecularly heterogeneous and with relatively poor long-term outcomes with anthracycline-based chemotherapy, PTCL NOS (not otherwise specified) has been in need of more effective therapies for quite some time. Fortunately, several important advances are beginning to change this discouraging situation. Most recently at ASH, Bertrand Coiffier presented findings from a Phase II trial of 131 patients with PTCL treated with the histone deacetylase (HDAC) inhibitor romidepsin demonstrating a 26 percent objective response rate, with half of these CRs. This report and others have generated enthusiasm that this agent — already approved in CTCL — has important clinical activity in PTCL as well.

A second ASH data set focused on another recently FDA-approved agent for T-cell lymphoma, the targeted antifolate pralatrexate. At ASH we saw the subanalysis from the Phase II PROPEL trial specifically focused on patients with disease progression despite prior treatment with ICE (ifosfamide, carboplatin and etoposide). Eight of 20 patients (40 percent) treated with pralatrexate had an objective tumor response. One of the most common side effects observed with this agent in the trial was mucositis, but weekly scheduling and the concomitant use of folate and vitamin B12 can help mitigate this problem.

2. Anaplastic large cell lymphoma (ALCL)

This intriguing disease has a very different outlook depending on ALK status, as ALK-positive ALCL responds well to anthracycline-based chemotherapy but the ALK-negative variant does not. The good news at ASH relates to the anti-CD30 immune conjugate brentuximab vedotin. As in the related Hodgkin lymphoma (HL) presentation described in a recent issue of this series, the waterfall plot from the **Phase II study in ALCL** was impressive as 56 of the 58 patients (97 percent) with mostly ALK-negative tumors

treated on the trial experienced reductions in tumor size. The CR rate was 53 percent, the PR rate was 33 percent and at the point of follow-up the median response duration had not been reached. Unlike HL, in which minimal activity has been observed with the "naked antibody," in ALCL it has a substantial antitumor effect. However, the exact mechanism of action of the immune conjugate remains to be defined. Because B vedotin is relatively well tolerated, discussions are ongoing about trials evaluating maintenance treatment.

3. CTCL papers

In an interesting poster, Madeleine Duvic reported on a series of 20 patients with CD25-positive CTCL who were re-treated with denileukin diftitox (DD) — a bioengineered protein combining interleukin-2 and diphtheria toxin — after having responded to this agent earlier on a clinical trial and then relapsing. In this series, eight patients (40 percent) experienced an objective response, an important observation suggesting that the presence of anti-DD neutralizing antibodies generated during prior treatment does not preclude further response. Adverse events were mild to moderate, and there were no instances of the much-dreaded capillary leak syndrome that is now uncommon with the preemptive use of corticosteroids.

Finally, Steve Horwitz reported a study employing a dose deescalation design to attempt to find an active but lower dose/regimen of pralatrexate in CTCL that would allow for continuous or maintenance treatment of this generally indolent disease. Steve's findings show that using 15 mg/m^2 for three out of four weeks was effective and worthy of additional study.

Next up on this ASH highlights series: New agents and regimens in mantle-cell and diffuse large B-cell lymphoma.

Neil Love, MD
Research To Practice
Miami, Florida

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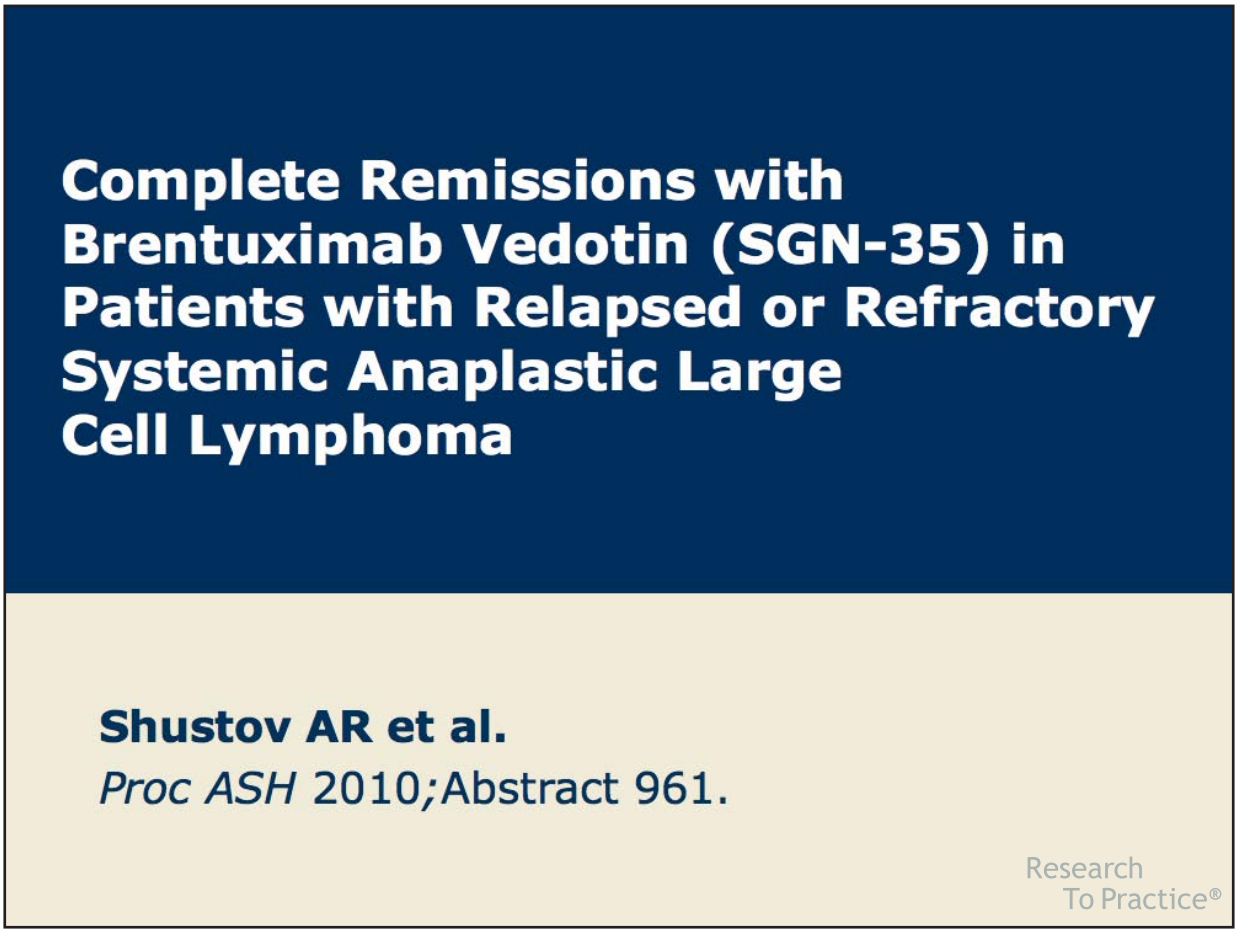
Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

Activity and Safety of Brentuximab Vedotin (SGN-35) in Relapsed/Refractory Systemic Anaplastic Large Cell Lymphoma (sALCL)

Presentation discussed in this issue

Shustov AR et al. **Complete remissions with brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large cell lymphoma.** *Proc ASH* 2010;**Abstract 961**.

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



Background

- Systemic anaplastic large cell lymphoma (sALCL) is a CD30-positive aggressive subtype of peripheral T-cell lymphoma (PTCL).
  - Comprises approximately 2-3% of all cases of non-Hodgkin's lymphoma
- Patients with newly diagnosed high-risk ALK-positive and ALK-negative sALCL have a poor prognosis.
  - Approximately 50% will fail front-line therapy
  - Few salvage therapies exist for relapsed or refractory sALCL
  - Pralatrexate is the only FDA-approved treatment for recurrent PTCL (including sALCL)
- Brentuximab vedotin (SGN-35) is a novel antibody-drug conjugate.
  - Delivers the highly potent antimicrotubule agent monomethyl auristatin E (MMAE) to CD30-positive malignant cells

Shustov AR et al. *Proc ASH* 2010;Abstract 961.

Study Schema

Accrual = 58 (Closed)

Eligibility
Relapsed or refractory sALCL
Measurable disease ≥1.5 cm FDG-avid
ECOG PS 0-1

→ Brentuximab vedotin, 1.8 mg/kg IV q 3-weeks x (up to) 16 cycles

Primary Endpoint:

Overall objective response rate (ORR) by independent review facility (IRF)

Secondary Endpoints:

Complete remission rate
Duration of response
Progression-free survival (PFS)
Overall survival (OS)
Safety and tolerability

Shustov AR et al. *Proc ASH* 2010;Abstract 961; ClinicalTrials.Gov Identifier NCT00866047.

Efficacy Outcomes (n = 58)

Response	IRF	Investigator
Overall response rate Complete remission Partial remission	86% 53% 33%	81% 59% 22%
Stable disease	3%	9%
Progressive disease	5%	3%

Secondary Endpoints	IRF	Investigator
Median duration of OR	Not reached	36 weeks
Median duration of CR	Not reached	Not reached
Median PFS	Not reached	41 weeks
Median OS	Not reached	

Shustov AR et al. *Proc ASH* 2010;Abstract 961.

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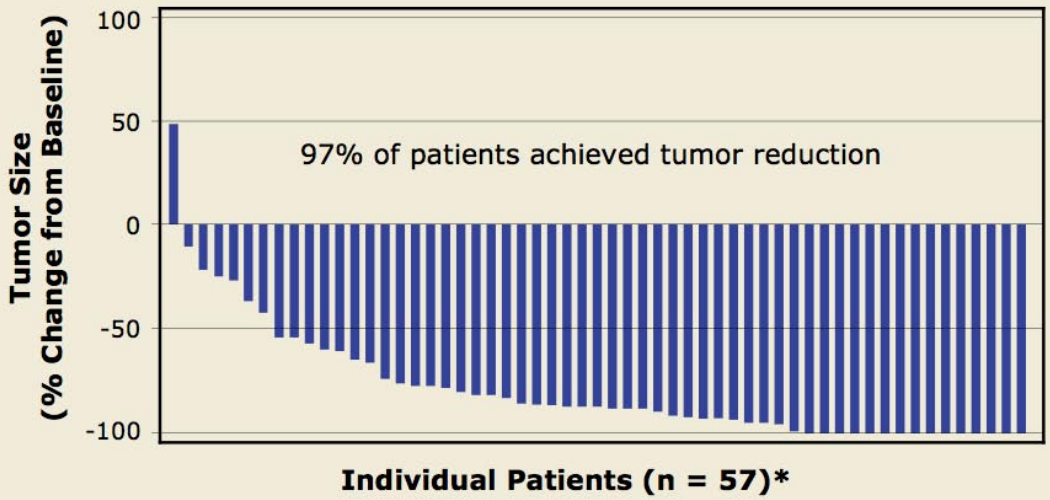
Maximum Tumor Reduction per IRF



* 57 of 58 patients with post-baseline CT assessments

With permission from Shustov AR et al. *Proc ASH* 2010;Abstract 961.

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Select Adverse Events

Treatment-Related Adverse Events (AE)	All Grades*	Grade 3 or 4*
Nausea	38%	Not reported
Peripheral sensory neuropathy	38%	10%†
Fatigue	34%	3%
Pyrexia	33%	Not reported
Diarrhea	29%	Not reported
Rash	21%	Not reported
Neutropenia	21%	21%
Thrombocytopenia	Not reported	14%
Anemia	Not reported	7%†

*All grade AEs occurring in ≥20% of patients and Grade 3/4 AEs occurring in ≥5% of patients
† Grade 3 only

Shustov AR et al. *Proc ASH* 2010;Abstract 961.

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Author Conclusions

- Remission was achieved by 86% of highly refractory systemic ALCL patients.
  - Complete remission rate: 53% (by IRF)
  - Patients achieving tumor reduction = 97%
- Complete remissions observed in ≥50% of patients with ALK-negative and ALK-positive disease.
- Brentuximab vedotin treatment is associated with a manageable adverse event profile.
- Brentuximab vedotin is a promising new agent in the management of systemic ALCL.

Shustov AR et al. *Proc ASH* 2010;Abstract 961.

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Investigator comment on brentuximab vedotin (SGN-35) in relapsed or refractory systemic anaplastic large cell lymphoma (sALCL)

sALCL is one of the subtypes of peripheral T-cell lymphoma (PTCL) and constitutes about 20 percent of PTCLs. This trial essentially shows that in the relapsed/refractory setting, brentuximab as a single agent has good activity with a high response rate. A total of 58 patients received treatment, which does not appear to be a huge number, but for a subset of PTCL, it is a big number.

Activity of other single agents in relapsed T-cell lymphomas is in the range of 20 to 30 percent, so the response rates reported here are very promising in this specific subset of T-cell lymphoma. The drug might become available within the next year for relapsed disease, and ultimately people will consider incorporating brentuximab into earlier lines of therapy. Overall, I believe it is positive and optimistic.

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