INTERVIEW

David J Straus, MD

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DR LOVE: Would you discuss SGN-35, or brentuximab vedotin, and its use in relapsed/refractory Hodgkin lymphoma (HL)?

DR STRAUS: SGN-35 is an immunotoxin — a fusion molecule of a monoclonal antibody directed against CD30, which is expressed on the Reed-Sternberg cells of classic HL. The anti-CD30 monoclonal antibody is attached to auristatin, a mitotic spindle inhibitor. The data presented at ASH 2010 from a Phase II study with this agent were spectacular. The overall response rate was 75 percent, with 34 percent complete responses — and this was in a group of patients with heavily pretreated disease, all of whom had already undergone autologous stem cell transplants (Chen 2010; [2.1]). Approximately 70 percent of the patients had primary refractory disease and did not experience responses to front-line treatment.

Side effects are similar to those of the vinca alkaloids, specifically neuropathy. Sensory neuropathy was observed in 47 percent of patients. Grade III

neuropathy was observed in eight percent, but Grade 1 and Grade 2 fatigue and nausea were also reported.

A companion study was also reported at ASH of SGN-35 in anaplastic large cell lymphoma (ALCL), which is a subgroup of peripheral T-cell lymphoma (PTCL). In this lymphoma, tumor cells also express CD30, which is in common with the Reed-Sternberg cells of HL, although the Reed-Sternberg cells are not T cells. The study reported an impressive overall response rate of approximately 80 percent (Shustov 2010; [2.1]). CD30 is also expressed in some B-cell non-Hodgkin lymphomas, particularly in primary mediastinal diffuse large B-cell lymphomas. They are CD20-positive B-cell lymphomas, but they often express CD30 also, and I believe some data suggest a relationship between this particular non-Hodgkin lymphoma and HL.

2.1

Response and Maximum Tumor Reduction with Brentuximab Vedotin (SGN-35) in Relapsed/Refractory Hodgkin Lymphoma (HL) and Anaplastic Large Cell Lymphoma (ALCL)*

	HL[1] (n = 102)	ALCL[2] (n = 58)
Overall response rate	75%	86%
Complete remission	34%	53%
Partial remission	40%	33%
Maximum tumor reduction (n = 96, 57)	94%	97%

* By independent review facility

[1] Chen R et al. *Proc ASH* 2010;**Abstract 283**; [2] Shustov AR et al. *Proc ASH* 2010;**Abstract 961**.

Tracks 8-9

DR LOVE: What are your thoughts on pralatrexate and romidepsin, which were recently approved for the treatment of advanced T-cell lymphomas?

DR STRAUS: Pralatrexate is newly approved for the treatment of PTCL. It is an antifolate agent with a high affinity for the reduced folate carrier type 1 and is designed to accumulate preferentially in tumor cells. In preclinical studies it is polyglutamated more than agents such as methotrexate, and therefore it is pumped out of the cell less avidly. The PROPEL study reported a 29 percent overall response rate with pralatrexate in relapsed or refractory PTCL, which was enough to obtain approval (O'Connor 2011; [2.2]). Studies are beginning to move pralatrexate into the front-line setting, perhaps with CEOP (NCT01336933).

Romidepsin is an HDAC inhibitor and has an indication in cutaneous T-cell lymphoma (CTCL), with approximately a 30 percent response rate, but I believe it will be approved in PTCL also (Demierre 2009). Romidepsin is administered intravenously, whereas some of the other HDAC inhibitors are oral. This agent can cause fatigue and diarrhea, and in some of the earlier

studies, reports arose of cardiac arrhythmias, although in more recent studies with dose adjustments this has not been a problem. The prospect of having a second agent approved for use in this setting is exciting.

DR LOVE: Outside of a protocol setting, how do you currently use HDAC inhibitors in CTCL?

DR STRAUS: The HDAC inhibitors romidepsin and vorinostat are approved for CTCL that requires systemic treatment, and these are among a longer list of agents that are active in advanced CTCL, including most chemotherapy agents. Almost every class of chemotherapy agent has a 20 to 40 percent response rate in this setting, as do romidepsin and vorinostat. The problem is that, unlike the other non-Hodgkin lymphomas and HL, in which you can treat for some time and expect durable unmaintained remissions, the remissions in CTCL last as long as you're administering treatment. So when you stop treatment, the disease recurs fairly quickly.

DR LOVE: How do side effects factor into the decision to administer the various available agents?

DR STRAUS: The side effects are important because all of the agents have similar activity. Bexarotene tends to be popular because it's an oral agent, as does vorinostat, which is an oral HDAC inhibitor. Denileukin diftitox, which was one of the first immunotoxins to come on the market about 10 years ago, also has a role in this area. ■

2.2

PROPEL Study: Single-Agent Pralatrexate in Relapsed or Refractory Peripheral T-Cell Lymphoma

Efficacy (n = 109)

Complete response	Partial response	Overall response
11%	18%	29%

Grade 3 or 4 adverse events

Thrombocytopenia	32%	Neutropenia	22%
Mucositis	22%	Anemia	18%

O'Connor OA et al. *J Clin Oncol* 2011;29(9):1182-9.

SELECT PUBLICATIONS

Chen R et al. **Results of a pivotal Phase 2 study of brentuximab vedotin (SGN-35) in patients with relapsed or refractory Hodgkin lymphoma.** *Proc ASH* 2010;**Abstract 283**.

Demierre M et al. **Pooled analyses of two international, multicenter clinical studies of romidepsin in 167 patients with cutaneous T-cell lymphoma (CTCL).** *Proc ASCO* 2009;**Abstract 8546**.

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**.