INTERVIEW

Bruce D Cheson, MD

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Tracks 1-11

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: Would you discuss your approach to considering "watch and wait" versus initiating active treatment for a patient with CLL? Does your approach differ based on cytogenetics?

DR CHESON: My approach is the same regardless of any of the prognostic factors. I have one patient with CLL with deletion 17p whom I have been following for 5 years. It's not the risk factors. It's the eventual symptoms and laboratory findings that will compel us to treat.

Patients can remain on observation for a long time. We sometimes see a rapid increase in the lymphocyte count that will then plateau for months or years, so a single number doesn't compel us to treat. It's the patient who tells us when treatment is indicated.

DR LOVE: How do you manage lymphocytosis in patients responding to ibrutinib?

DR CHESON: Lymphocytosis is a demargination phenomenon. The lymphocyte count can go up several-fold, up to the hundreds of thousands, and even some of my colleagues start to become concerned.

We've seen no correlation between whether it goes up or doesn't and the patient's eventual response. It's simply something that you shouldn't let scare you in and of itself. In fact, we published a paper a couple of years ago after a workshop that I held to make it clear that a number of agents are associated with what appears to be progressive disease — for example, the flare reaction with lenalidomide and this lymphocytosis (Cheson 2014). We are now starting to see it with the checkpoint inhibitors in solid tumors in addition to the lymphomas.

It appears as though the patient's disease is progressing in some areas, but everything else seems like it's improving. So, in these cases, you have to give the patients and the drug the benefit of the doubt, follow them carefully, repeat the appropriate tests and come to a good clinical decision as to whether the patient is experiencing disease progression or not. Lymphocytosis alone is not considered progressive disease in patients who are receiving these agents for CLL.

DR LOVE: Would you also talk more specifically about what you've observed in terms of bleeding or bruising with ibrutinib?

DR CHESON: Bruising and bleeding are a couple of unusual adverse effects of ibrutinib. In most of my patients who have experienced these sorts of complications with ibrutinib, they've been cutaneous. I've seen a couple of nosebleeds. I had a patient who had a conjunctival hemorrhage. I have had 2 patients who were receiving ibrutinib and experienced intracranial hemorrhages. To one of them I had been administering treatment for 20 years, and he died from the bleeding event.

Just because ibrutinib is a pill and is generally well tolerated, you can't assume that everything is going to be easy. You still have to exercise care.

DR LOVE: Is it a relative or absolute contraindication to administer ibrutinib to a patient on anticoagulation?

DR CHESON: If I didn't have alternatives, it would be more difficult. But we have idelalisib, which is also an effective agent. I'm uncomfortable administering a drug that predisposes patients to bleeding when they are already receiving anticoagulants. I don't know what to do with an atrial fibrillation. I have a patient with cutaneous CLL who has had a nice response to ibrutinib but developed atrial fibrillation. It came and went. He didn't have it the last time I saw him, and because he recently received his month's supply, we're going to see what happens in the next month. If he starts fibrillating again, we'll probably switch him to idelalisib.

Track 7

DR LOVE: How have you incorporated bortezomib, lenalidomide and ibrutinib, which are now all approved, into the treatment of relapsed/refractory mantle-cell lymphoma (MCL)?

DR CHESON: I administer ibrutinib first because it has a higher response rate, and then I administer lenalidomide. I've observed some durable responses to lenalidomide in MCL. I have a patient who received lenalidomide after a stem cell transplant failed who has been in remission for 3 years now.

DR LOVE: What are your thoughts on the use of bortezomib as a component of up-front therapy for MCL, specifically the recent data comparing R-CHOP to

bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP) for transplant-ineligible patients with newly diagnosed MCL?

DR CHESON: Those data initially presented by Franco Cavalli at ASCO 2014 and subsequently published in *The New England Journal of Medicine* were interesting and led to bortezomib being approved in this setting (Robak 2015; [4.1]). However, we must consider that the comparator arm was R-CHOP on this trial. If you review the NCCN guidelines, it's the "sick puppy" of all the treatments for MCL, unless it is followed by a stem cell transplant. We have other good options for these patients — BR, R-hyper-CVAD, R-hyper-CVAD/transplant and even R^2 appear to be better.

So again, the comparator is the problem in many of these clinical trials. Once a new regimen becomes available, you have to ask, how did it win? What was the patient population? What was the comparator? And what other options are out there?

4.1

LYM-3002: Results of a Phase III Trial of Bortezomib, Rituximab, Cyclophosphamide, Doxorubicin and Prednisone (VR-CAP) versus R-CHOP for Newly Diagnosed, Transplant-Ineligible Mantle-Cell Lymphoma

Efficacy	VR-CAP	R-CHOP	HR	*p*-value
Median progression-free survival (n = 243, 244)	24.7 mo	14.4 mo	0.63	<0.001
Median overall survival* (n = 243, 244)	NR	56.3 mo	0.80	0.173
Overall response rate (n = 229, 228)	92%	89%	1.03	—
Complete response	53%	42%	1.29	—
Median duration of response (n = 229, 228)	36.5 mo	15.1 mo	—	—

Select adverse events (Grade ≥3)	VR-CAP (n = 240)	R-CHOP (n = 242)
Neutropenia	85%	67%
Thrombocytopenia	57%	6%
Febrile neutropenia	15%	14%
Peripheral neuropathy	8%	4%

Median follow-up: 40 months; * Data not mature
HR = hazard ratio; NR = not reached

Robak T et al; LYM-3002 Investigators. *N Engl J Med* 2015;372(10):944-53.

Tracks 10-11

DR LOVE: What are your thoughts on the results of the Phase III AETHERA trial of brentuximab vedotin for patients with Hodgkin lymphoma (HL) and high risk of disease progression after autologous stem cell transplant (ASCT) presented at ASH 2014 and subsequently published in *The Lancet*?

DR CHESON: We had not yet had many opportunities to use brentuximab vedotin after ASCT, but those results were compelling and will influence my practice. Post-transplant brentuximab vedotin was effective compared to placebo (Moskowitz 2015; [4.2]).

How will this approach fare with more people now using brentuximab vedotin either prior to transplant or as part of initial treatment? The Phase III ECHELON-1 study is

4.2

AETHERA: Results of a Phase III Trial of Brentuximab Vedotin (BV) as Consolidation Therapy After Autologous Stem Cell Transplant in Patients with Hodgkin Lymphoma at Risk of Relapse or Progression

	Per independent review		Per investigator	
Progression-free survival (PFS)	BV (n = 165)	Placebo (n = 164)	BV (n = 165)	Placebo (n = 164)
Median PFS	42.9 mo	24.1 mo	—	16.0 mo
Two-year PFS rate	63%	51%	65%	45%
Hazard ratio (*p*-value)	0.57 (0.0013)		0.50	
	BV (n = 167)		Placebo (n = 160)	
Select adverse events	Any grade	Grade ≥3	Any grade	Grade ≥3
Peripheral sensory neuropathy	56%	10%	16%	1%
Neutropenia	35%	29%	12%	10%
Fatigue	24%	2%	18%	3%

Moskowitz CH et al; AETHERA Study Group. *Lancet* 2015;385(9980):1853-62.

now evaluating ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine) versus A^{2}VD (brentuximab vedotin/doxorubicin/vinblastine/dacarbazine) as front-line therapy for classical HL (NCT01712490). That's an important study because the preliminary Phase I/II data appear exceptionally promising (Connors 2014).

However, just when we thought you couldn't get better than brentuximab vedotin, along come nivolumab and pembrolizumab. For patients with relapsed/refractory disease, response rates are higher than 80% with nivolumab, and adverse events were mostly low grade (Ansell 2015). The response rate was not quite as high with pembrolizumab, but the patient populations were a bit different and it was a small number of patients (Moskowitz 2014), so those variables could have influenced that.

The question is what to do with these agents. Do you want to save them for the end? I would think not. We are now developing an up-front trial for older patients with HL who don't fare well with ABVD evaluating brentuximab vedotin with nivolumab. When you take 2 drugs with 80% response rates and you put them together up front, instead of after transplant, hopefully they will be more effective and well tolerated. ■

SELECT PUBLICATIONS

Ansell SM et al. **PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma.** *N Engl J Med* 2015;372(4):311-9.

Cheson BD et al. **Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification.** *J Clin Oncol* 2014;32(27):3059-68.

Connors JM et al. **Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed advanced stage Hodgkin lymphoma: Long term outcomes.** *Proc ASH* 2014;**Abstract 292**.

Moskowitz CH et al; AETHERA Study Group. **Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): A randomised, double-blind, placebo-controlled, phase 3 trial.** *Lancet* 2015;[Epub ahead of print].

Moskowitz CH et al. **PD-1 blockade with the monoclonal antibody pembrolizumab (MK-3475) in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: Preliminary results from a Phase 1b study (KEYNOTE-013).** *Proc ASH* 2014;**Abstract 290**.