INTERVIEW

Bruce D Cheson, MD

Dr Cheson is Professor of Medicine, Head of Hematology and Director of Hematology Research at the Georgetown Lombardi Comprehensive Cancer Center in Washington, DC.

Tracks 1-18

Tracks 1-2, 5-6

DR LOVE: What are the current evidence-based treatment options for up-front management of chronic lymphocytic leukemia (CLL)?

Select Excerpts from the Interview

DR CHESON: Bendamustine was recently evaluated versus chlorambucil in a Phase III trial in newly diagnosed CLL, and it resulted in a higher overall response rate and a higher complete response rate. More importantly, the primary endpoint of progression-free survival was significantly improved with bendamustine (Knauf 2009), leading to approval by the FDA.

A potential advantage of bendamustine is that data do not suggest that it's associated with an increased incidence of secondary cancer, at least in lymphoma (Rummel 2009). It remains to be seen in randomized trials whether that's true in CLL.

DR LOVE: Are any up-front trials in CLL ongoing that you'd like to comment on or that you're enrolling patients on?

DR CHESON: I believe the most important ongoing study right now is the German CLL-10 trial, which is evaluating fludarabine/cyclophosphamide/rituximab (FCR) versus bendamustine/rituximab (BR). The results of that trial may revolutionize how we approach this disease (1.1). An Intergroup study in the United States is evaluating FCR versus fludarabine/rituximab (FR) versus FR followed by lenalidomide maintenance for at least six months. In fact, we have administered FR → lenalidomide to more than 20 patients at our institution, and a few of the responses after FR have converted from partial responses to complete responses.

Lenalidomide is another potentially interesting drug in CLL. In the relapsed setting, two studies have taken place — one from MD Anderson (Ferrajoli 2008) with a response rate of approximately 35 percent and the other from Roswell Park (Chanan-Kahn 2006) with a response rate of approximately 45 percent. It has some unique adverse effects — notably, tumor lysis syndrome (TLS) and a tumor flare reaction.

1.1

Phase III Trial of Combined Immunochemotherapy versus Bendamustine and Rituximab as Up-Front Treatment for Chronic Lymphocytic Leukemia (CLL)

Protocol IDs: GCLLSG-CLL10, EUDRACT-2007-007587-21, EU-20883
Target Accrual: 550

Eligibility

B-cell CLL with Binet Stage C or Stage B or A requiring treatment (B symptoms; progressive lymphocytosis; progressive marrow failure; massive, progressive or painful splenomegaly or hypersplenism; massive lymph nodes or lymph node clusters)

R

- Fludarabine + cyclophosphamide + rituximab x 6
- Bendamustine + rituximab x 6

Primary Endpoint: Progression-free survival rate after 24 months

www.clinicaltrials.gov. Identifier NCT00769522.

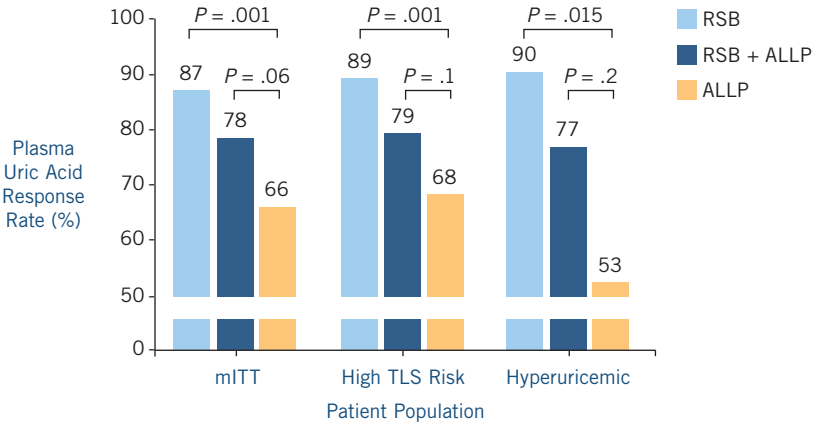
DR LOVE: What's your experience with tumor lysis in CLL and in general?

DR CHESON: In the past, TLS was uncommon with fludarabine, but now with more effective drugs such as lenalidomide we're seeing it more often — fortunately not always clinical TLS, sometimes just chemical. The more potent the drugs, the more likely you are to encounter tumor lysis (Cheson 2009).

For patients at higher risk for TLS it becomes a question of prevention: Is it fluids? Is it allopurinol or rasburicase (Cortes 2010; [1.2])? We tend to use rasburicase in patients at high risk who we believe may experience rapid tumor lysis from therapy. I have had no toxicity issues with that agent at all.

1.2

Control of Plasma Uric Acid in Adults at Risk for Tumor Lysis Syndrome (TLS): Rasburicase (RSB), RSB Followed by Allopurinol (ALLP) or ALLP Alone



Cortes J et al. *J Clin Oncol* 2010;28(27):4207-13. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved.

Track 11

DR LOVE: Would you talk about the ASH 2010 presentation on "watch and wait" versus rituximab monotherapy in follicular lymphoma (FL)?

DR CHESON: The study reported a significantly higher rate of disease progression in the watch-and-wait population. Time to next treatment, which was the primary endpoint, was significantly longer in the patient population who received treatment with rituximab, but no survival difference was evident (Ardeshna 2010).

I hope we will learn from the ongoing RESORT trial — which is evaluating four weekly doses of rituximab and then re-treatment upon relapse versus four weekly doses and indefinite maintenance — what the role of continuous treatment is in this setting.

Some older studies suggest that you can use rituximab again and the benefit may be equivalent to what you obtained from maintenance. Issues arise with rituximab maintenance — the expense, the nuisance, the risk of late infections and cytopenias and the risk of impairing responsiveness to subsequent treatments.

This has been seen in the transplant arena when patients who received rituximab previously had worse outcomes than patients who didn't. I believe we need longer follow-up on these data to ascertain if more toxicity occurs or if any survival benefit manifests itself. I'm not changing my practice currently.

Tracks 14-15

DR LOVE: What new treatment approaches for mantle-cell lymphoma (MCL) are being evaluated in clinical trials?

DR CHESON: We are planning an Intergroup study evaluating R-hyper-CVAD followed by transplant versus BR followed by transplant for younger patients who require treatment. The BR data in up-front MCL show a response rate of more than 90 percent and a progression-free survival significantly better than R-CHOP with considerably less toxicity (Rummel 2009).

For older patients, *the* standard regimen is R-CHOP, and it's a terrible standard. It has a median time to progression of approximately 18 months. So we are also planning a study for elderly patients evaluating a BR-based regimen followed by a few nontransplant maintenance options.

Track 18

DR LOVE: Over the past six months or year, throughout the field of hematologic oncology, have any other data sets caught your eye?

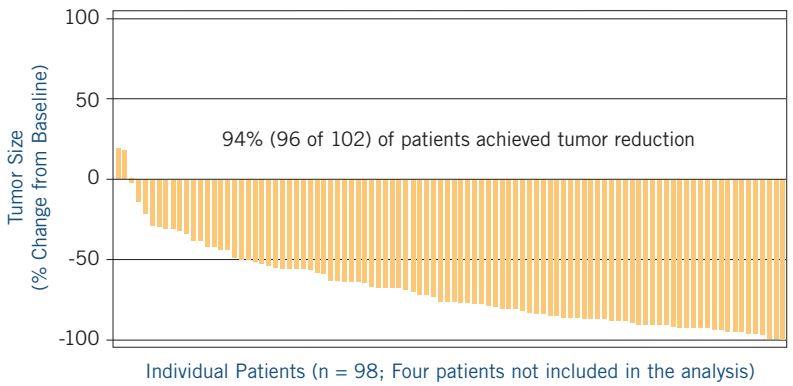
DR CHESON: One of the most exciting drugs out there is brentuximab vedotin (SGN-35). Previously, we had an anti-CD30 antibody, SGN-30, which was basically inactive in the treatment of Hodgkin lymphoma and had a little bit of activity in anaplastic large cell lymphoma (ALCL). However, when the antibody is conjugated with monomethyl auristatin E, which is a tubulin poison, what do you get?

In Hodgkin lymphoma, you obtain a response rate of 75 percent in patients with relapsed/refractory disease with a fair number of complete remissions (Chen 2010; [1.3]).

In relapsed/refractory ALCL, you obtain a response rate of 86 percent, most of which are complete remissions (3.3, page 14). We've never seen results of this magnitude before. ■

1.3

Maximum Tumor Reduction from Brentuximab Vedotin (SGN-35) in Patients with Relapsed or Refractory Hodgkin Lymphoma (HL)



"Brentuximab vedotin was associated with manageable adverse events and, based on investigator assessment, demonstrated encouraging activity in heavily pretreated patients with relapsed or refractory HL. Tumor shrinkage was observed in 95%* of patients and the B symptom resolution rate was 83%."

* Original data from abstract, updated to 94% in final presentation

With permission from Chen R et al. *Proc ASH* 2010;**Abstract 283**.

SELECT PUBLICATIONS

Ardeshna M et al. **An Intergroup randomised trial of rituximab versus a watch and wait strategy in patients with Stage II, III, IV, asymptomatic, non-bulky follicular lymphoma (Grades 1, 2 and 3a). A preliminary analysis.** *Proc ASH* 2010;**Abstract 6**.

Chanan-Khan A et al. **Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: Results of a phase II study.** *J Clin Oncol* 2006;24(34):5343-9.

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**.

Cheson BD. **Etiology and management of tumor lysis syndrome in patients with chronic lymphocytic leukemia.** *Clin Adv Hematol Oncol* 2009;7(4):263-71.

Cortes J et al. **Control of plasma uric acid in adults at risk for tumor lysis syndrome: Efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone — Results of a multicenter phase III study.** *J Clin Oncol* 2010;28(27):4207-13.

Ferrajoli A et al. **Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia.** *Blood* 2008;111(11):5291-7.

Knauf WU et al. **Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia.** *J Clin Oncol* 2009;27(26):4378-84.

Rummel MJ et al. **Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized Phase III study of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2009;**Abstract 405**.