5 Minute JournalClub

Key ASH Presentations
Issue 1, 2012

GELCC Phase II Trial of Rituximab Maintenance in Patients with CLL After Up-Front R-FCM

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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 and new information 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, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Evaluate the efficacy and toxicity outcomes of maintenance rituximab versus rituximab re-treatment upon disease progression, and incorporate this information into your personal treatment algorithm for patients with low tumor burden follicular lymphoma.
- Assess the efficacy of maintenance rituximab in disease settings in non-Hodgkin lymphoma for which standard treatment is not well established, including for elderly patients with advanced follicular lymphoma.

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Key ASH Presentations
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To go directly to slides and commentary for this issue, **click here**.

Last month's annual American Society of Hematology (ASH) meeting seems like a blur, particularly because it partially overlapped the San Antonio Breast Cancer Symposium. So in addition to poring over hundreds of abstracts I recently turned to a couple of my favorite hem-onc investigators to help piece together what happened in San Diego, beginning with the always colorful Brooklyn-born Yankees and Jets fan, Memorial's Dr Craig Moskowitz.

The first topic we dove into was perhaps the most anticipated lymphoma paper of the meeting, Dr Brad Kahl's presentation of the results of ECOG's Phase III RESORT trial evaluating indefinite rituximab (R) maintenance versus short-term R induction with R re-treatment on progression in patients with low tumor burden follicular lymphoma (FL). For years listeners to our audio programs have heard Dr Kahl describe the rationale for and early safety data from this historic study, but the mood in the huge convention hall was downright somber when the disappointing and overlapping curves for time to treatment failure popped up, although at 3 years fewer patients required chemo on the indefinite R arm (5% versus 14%). Always a creative thinker, Dr Moskowitz had another take on the findings.

"Patients in the RESORT control arm got just 4 weeks of rituximab — that's a month of treatment — and their median time to progression was almost 4 years. I'm thinking that's not terrible." Like many lymphoma investigators, Dr Moskowitz has in the past been very pro "watch and wait" in indolent lymphoma, and I was curious about his current perspective. "Already since ASH, based on RESORT I've given a patient rituximab who could have been monitored. People are taking a negative view of RESORT because of the maintenance issue, but I think of it another way. Here's my 76-year-old guy who may never need chemotherapy. That could be pretty cool for him. My sense is that it's not a totally negative study." Craig further explained that his R monotherapy strategy is based on the **SAKK regimen** of a total of 8 R courses over 9 months.

I also turned to another trusted and candid investigator, Rush University lymphoma scholar Dr Stephanie Gregory, for her perspectives, and she too had a lot to say about RESORT, quickly pointing out that in spite of the data we still have not defined the optimal duration of R maintenance, including after R/chemo up front. She also referred to a number of trials evaluating this crucial question, including a German study of 2 versus 4 years of R maintenance.

Click here for the RESORT slides and **here** for another, smaller study of R maintenance in FL, and see below for other related ASH lymphoma data sets.

R maintenance in mantle-cell lymphoma (MCL)

This was an update of a practice-changing European study that was first reported last year at EHA in London. The favorable outcome with R maintenance has now led most investigators, including Dr Gregory, to routinely use R maintenance after R/chemo induction in patients with MCL who are not candidates for transplant. A major ECOG trial is evaluating R maintenance alone or with lenalidomide in this cohort.

R maintenance in chronic lymphocytic leukemia (CLL)

The results from this Phase II Spanish study have not changed Dr Gregory's approach to R maintenance in CLL (she doesn't use it), and she noted that R is believed to have less antitumor effect in CLL than, for example, in FL. She voiced more optimism about an experimental strategy we have heard a lot about in multiple myeloma, namely lenalidomide maintenance.

R/chemo followed by radioimmunotherapy (RIT) followed by R maintenance in untreated FL

Although the results of this MD Anderson report were considered promising, there were 3 cases of MDS out of 47 total patients. Dr Gregory thinks the choice of chemo preceding RIT (R-FND and specifically the fludarabine) was problematic and notes that Dr Mark Kaminski's classic up-front FL study of 76 patients treated with RIT alone reported only 1 case of MDS (in a patient who had received chemo after relapse).

Next we proceed to a prominent part of the Moskowitz ASH lymphoma highlight reel, the continued fascinating story of the antibody-drug conjugate brentuximab vedotin.

Neil Love, MD
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GELCC Phase II Trial of Rituximab Maintenance in Patients with CLL After Up-Front R-FCM

Presentation discussed in this issue

Bosch F et al. **Rituximab maintenance in patients with chronic lymphocytic leukemia (CLL) after upfront treatment with rituximab plus fludarabine, cyclophosphamide, and mitoxantrone (R-FCM): Final results of a multicenter Phase II trial on behalf of the Spanish CLL Study Group (GELLC).** *Proc ASH* 2011;**Abstract 293**.

Slides from a presentation at ASH 2011 and transcribed comments from recent interviews with Stephanie A Gregory, MD and Jonathan W Friedberg, MD, MMSc (1/11/12)

Background

- Rituximab, a chimeric antibody against CD20, has been shown to improve clinical outcome in patients with B-cell CLL when used as consolidation and maintenance therapy (*Cancer* 2008;112:119).
- The effectiveness of rituximab, fludarabine, cyclophosphamide and mitoxantrone (R-FCM) in the treatment of CLL has been studied in a Phase II trial with 2 treatment phases, induction and maintenance (*JCO* 2009;27:4578).
- This study, the second part of the Phase II trial, investigates the effects of rituximab maintenance in patients who achieved a CR or PR after R-FCM treatment.

Bosch F et al. *Proc ASH* 2011;Abstract 293.

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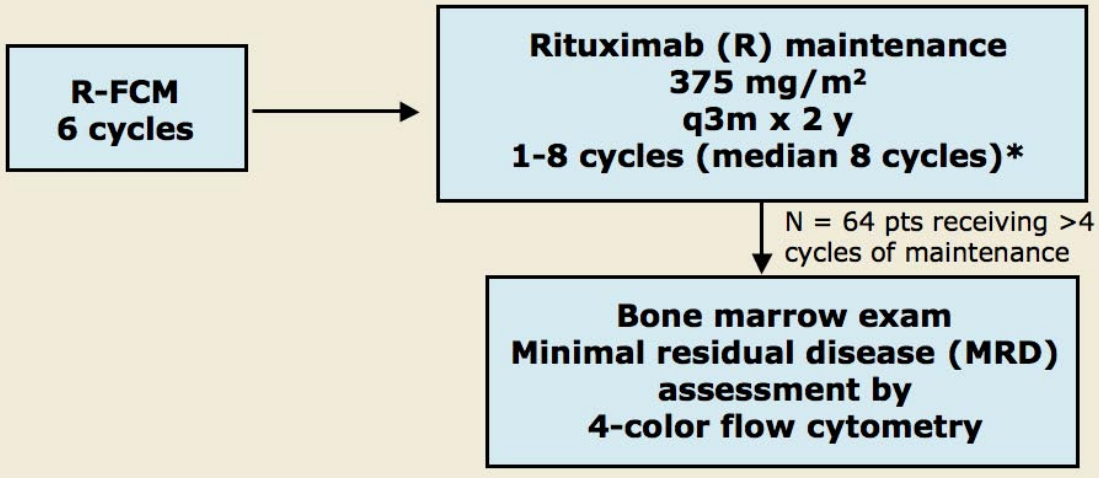
Study Schema



* 76% of patients completed entire planned treatment.
Treatment was considered to have failed in patients who received ≤4 cycles of R due to toxicity.

Bosch F et al. *Proc ASH* 2011;Abstract 293.

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Adverse Events (Abstract Only)

Adverse event (AE)	%
Neutropenia (% of cycles)	31.3%
Thrombocytopenia (% of cycles)	4.6%
Anemia (% of cycles)	1.2%
AE after R maintenance	
Low Ig levels (% of patients) • Low IgA • Low IgG • Low IgM	 45% 37% 66%
Infectious episodes (% of cycles) • With Grade 3/4 neutropenia • With Grade 1/2 neutropenia	 19.5% 3%
Deaths (% of patients)	3%*

* Two deaths, 1 due to multifocal leukoencephalopathy, 1 due to hemophagocytic syndrome

Bosch F et al. *Proc ASH* 2011;Abstract 293.

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Response to R Maintenance (Abstract Only)

Response to R maintenance					
		CR MRD(-)	**CR MRD(+)***	**PR**	**Failure**
Response to R-FCM (N = 64)	**CR MRD(-) (n = 35)**	22 (34.4%)	9 (14.1%)	—	4 (6.3%)
	CR MRD(+) (n = 21)	2 (3.1%)	15 (23.4%)	2 (3.1%)	2 (3.1%)
	PR (n = 8)	2 (3.1%)	2 (3.1%)	3 (4.7%)	1 (1.6%)

* Median time to conversion from MRD(-) to MRD(+) after R maintenance vs after R-FCM: 45.4 mo vs 16.4 mo (p = 0.011)

Bosch F et al. *Proc ASH* 2011;Abstract 293.

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Time to Next Treatment (Abstract Only)

Response	Time to next treatment	*p*-value
CR MRD(+) after R-FCM	44.1 mo	0.049
CR MRD(+) after R maintenance	54.5 mo	
PR after R-FCM	6.5 mo	0.001
PR after R maintenance	54.4 mo	

Three-year progression-free survival = 94%

Bosch F et al. *Proc ASH* 2011;Abstract 293.

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Author Conclusions

- Rituximab maintenance after R-FCM in patients with CLL is feasible and might improve outcome, particularly for patients who do not attain a MRD(-) CR after initial up-front therapy.
- Toxicity in patients receiving R maintenance is not negligible.
- Ongoing studies should clarify the role of R maintenance in the management of CLL.

Bosch F et al. *Proc ASH* 2011;Abstract 293.

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Investigator Commentary: Rituximab Maintenance in Patients with CLL After Up-Front Treatment with R-FCM

This study suggests that the addition of R maintanence to R-FCM induction therapy results in an improvement in progression-free survival. Use of this regimen has not caught on in the United States. Studies are evaluating alternate maintenance therapies such as lenalidomide. Rituximab does not work as well in CLL as it does in follicular lymphoma because of the lower expression of CD20.

Interview with Stephanie A Gregory, MD, January 11, 2012

These data are preliminary and not compelling. The study endpoint, minimal residual disease (MRD), was a purely surrogate endpoint. The data are hypothesis generating, and a group of patients may exist for whom getting to MRD negativity is important. No profound clinical benefit was demonstrated, and more toxicity occurred than would be expected. I do not believe that R maintenance should be considered in CLL.

Interview with Jonathan W Friedberg, MD, MMSc, January 11, 2012

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