5 Minute JournalClub

Key ASH Presentations
Issue 1, 2012

Rituximab Maintenance versus Observation After Response to R-FND and R Consolidation in Elderly Patients with Advanced FL

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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.

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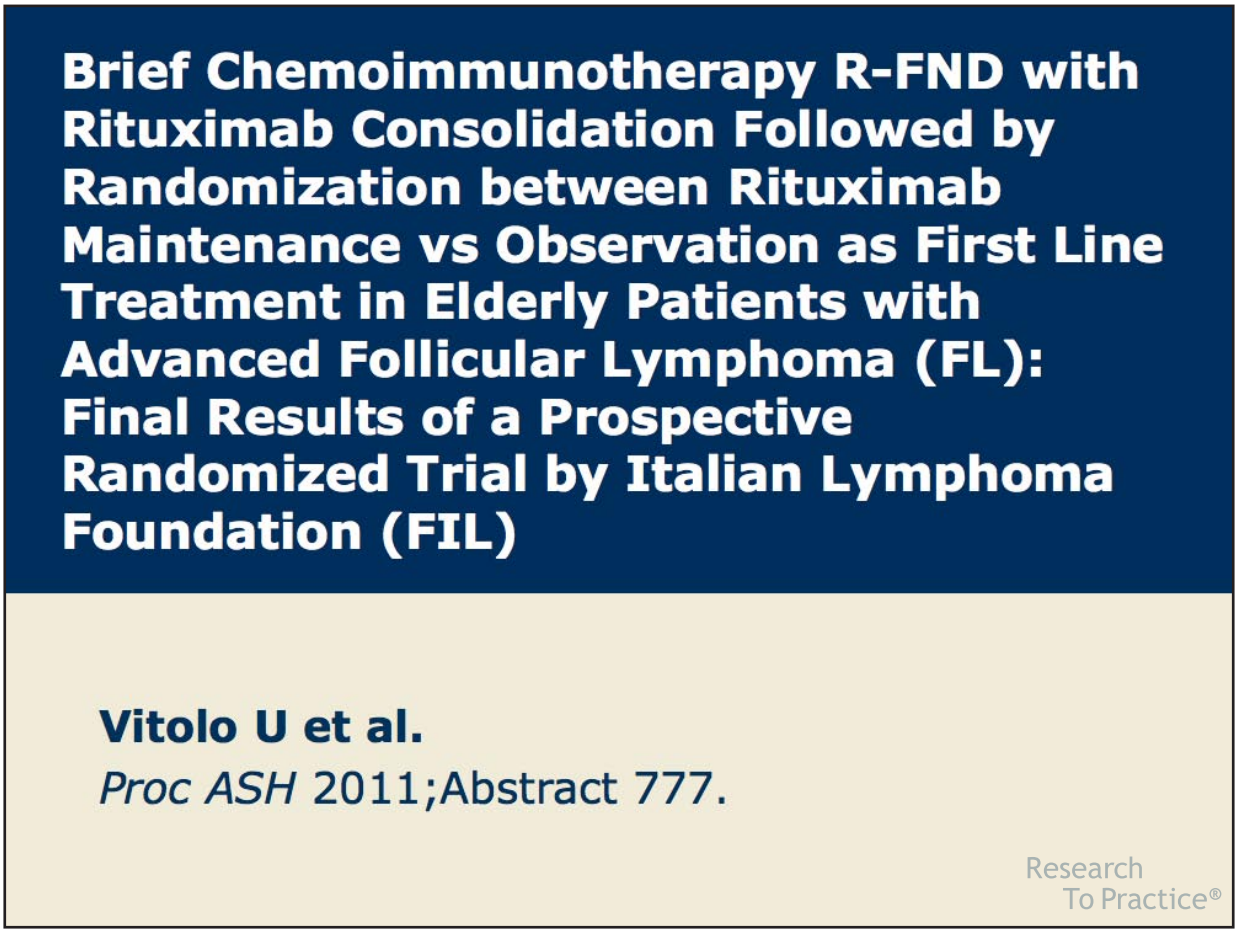
Rituximab Maintenance versus Observation After Response to R-FND and R Consolidation in Elderly Patients with Advanced FL

Presentation discussed in this issue

Vitolo U et al. **Brief chemoimmunotherapy R-FND with rituximab consolidation followed by randomization between rituximab maintenance vs observation as first line treatment in elderly patients with advanced follicular lymphoma (FL): Final results of a prospective randomized trial by Italian Lymphoma Foundation (FIL).** *Proc ASH* 2011;**Abstract 777**.

Slides from a presentation at ASH 2011 and transcribed comments from a recent interview with Stephanie A Gregory, MD (1/11/12)

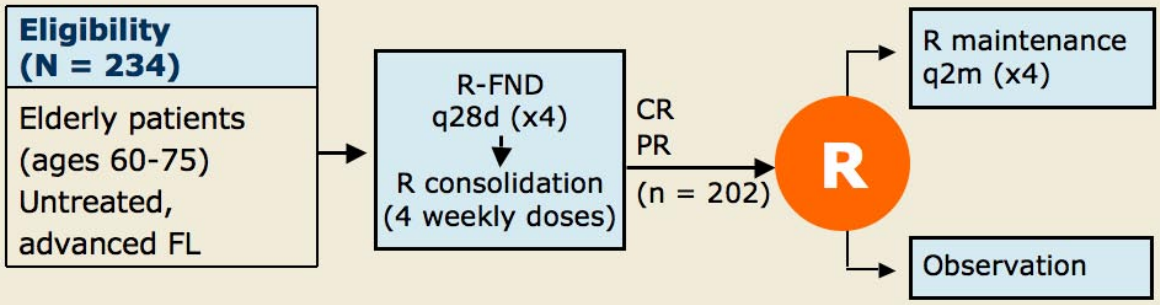


Background

- Management of FL in elderly patients is challenging, and the efficacy and safety of standard regimens in this group of patients is unclear.
- Rituximab maintenance was shown to improve the survival of patients with FL (*J Natl Cancer Inst* 2009;101:248).
- **Current Study Aim:** To determine the efficacy and safety of rituximab maintenance versus observation in elderly patients who respond to brief chemoimmunotherapy with 4 courses of R-FND and 4 doses of rituximab as consolidation.

Vitolo U et al. *Proc ASH* 2011;Abstract 777.

Study Schema



R-FND = rituximab, fludarabine, mitoxantrone, dexamethasone

Vitolo U et al. *Proc ASH* 2011;Abstract 777.

Baseline Characteristics (Abstract Only)

Characteristic	
Median age	66 yrs
Stage of disease • Stage II • Stage III • Stage IV	 14% 21% 65%
Bone marrow involvement	55%
FLIPI score • Low • Intermediate • High	 11% 34% 55%

Vitolo U et al. *Proc ASH* 2011;Abstract 777.

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Response to Therapy (Abstract Only)

After R-FND + R consolidation	(n = 202)	*p*-value
Overall response rate	86%	
Two-year overall survival	93%	NR
Two-year progression-free survival (PFS)	77%	
Two-year PFS after R maintenance/observation		
R maintenance	80%	0.225
Observation	68%	
Two-year PFS by FLIPI score		
Low/intermediate risk	87%	<0.0001
High risk	70%	

Median follow-up = 33 mo
NR = not reported; NS = not statistically significant

Vitolo U et al. *Proc ASH* 2011;Abstract 777.

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Adverse Events (AEs) (Abstract Only)

During rituximab maintenance/observation phase	
AEs (Grade 3/4)	**n**
Neutropenia	15
Cardiac events	8
Infections	4
Secondary malignancies	11

Vitolo U et al. *Proc ASH* 2011;Abstract 777.

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Author Conclusions

- Elderly patients with follicular lymphoma, including those with high-risk FLIPI scores, treated with short-term R-FND and rituximab consolidation can achieve a high CR rate and favorable 2-year PFS.
- Patients receiving R maintenance achieved a promising 2-year PFS of 80%, although there was no statistically significant difference compared to observation.
  - This finding may be due to short follow-up or to the short course of rituximab maintenance or both.

Vitolo U et al. *Proc ASH* 2011;Abstract 777.

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Investigator Commentary: Brief R-FND with Rituximab Consolidation Followed by Rituximab Maintenance versus Observation as First-Line Therapy for Elderly Patients with FL

This study reported no difference between rituximab maintenance and observation. The authors suggest this could be due to the short follow-up or to the short course of rituximab maintenance.

Only 4 doses of R maintenance were administered — 1 dose every 2 months — instead of continuing for 2 years. The results from this study amount to an outlier and do not fit with data from other studies.

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

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