5 Minute JournalClub

Key ASH Presentations
Issue 2, 2011

Rituximab versus Watch and Wait in the Management of Previously Untreated Asymptomatic Nonbulky Follicular Lymphoma

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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 from a plethora of ongoing clinical trials 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 and other cancer clinicians in the formulation of optimal clinical management strategies for hematologic cancer.

LEARNING OBJECTIVE

- Counsel patients with asymptomatic nonbulky follicular lymphoma about the benefits and risks of observation versus immediate initiation of rituximab.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Bruce D Cheson, MD
Professor of Medicine
Head of Hematology
Director of Hematology Research
Georgetown University Hospital
Lombardi Comprehensive Cancer Center
Washington, DC

Advisory Committee: Allos Therapeutics, Celgene Corporation, Cephalon Inc, GlaxoSmithKline, Millennium Pharmaceuticals Inc; Consulting Agreement: Millennium Pharmaceuticals Inc.

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To go directly to slides and commentary, **click here**.

It's no secret that the anti-CD20 antibody rituximab has profoundly affected clinical research and management approaches in B-cell neoplasms, and in 2010 we heard about two more landmark trials that help to expand our knowledge of this very interesting agent. First, at ASCO the PRIMA study demonstrated that two years of R maintenance after prior induction with R/chemo delayed disease progression, and the ASH update of this historic study further solidified these outcomes with more follow-up. The second recent important data set came from an **Intergroup trial** that was just presented at ASH. The study randomly assigned patients with asymptomatic nonbulky advanced FL to either rituximab — for what turned out to be two years — or watch and wait (or as our prostate cancer colleagues call it, watch and worry). The trial showed that R led to a substantial delay in progression and in the need for further treatment (usually chemo).

Both of these data sets have sparked considerable debate, and as promised, last Friday in our Miami recording studio I asked the eight distinguished faculty members who participated in our clinical investigator Think Tank the bottom line on these and other seminal ASH data sets:

1. PRIMA: R maintenance after R/chemo
All of the investigators except the always free-thinking Dr Cheson offer but do not insist that patients receive two years of R maintenance.

2. Intergroup study: R versus watch and wait
None of the faculty believe that using R earlier substantially changes the natural history of the disease or overall survival, although it is important to note that there were only 21 total deaths reported in the Intergroup study and less than three years of follow-up. The Think Tank group did acknowledge that many patients find a delay in disease progression appealing in return for the modest and unchemo-like risks of this treatment.

For all the good that R has done, FL and CLL are still not curable and a litany of approaches are being evaluated in these diseases to offer patients even more. At ASH many presentations focused on other promising agents, and at our Think Tank I asked the faculty which ones they found most exciting. Here are some of their thoughts and key related data sets.

Lenalidomide
At ASH **Alessandra Ferrajoli** presented some interesting data on lenalidomide in combination with rituximab for patients with relapsed and refractory CLL. The study demonstrated a 64 percent overall response rate, and the Think Tank faculty showed considerable interest in new trials evaluating this combination up front as a means to potentially avoid the **increased incidence of therapy-related myeloid neoplasia** associated with FC and particularly FCR reported at ASH.

Bortezomib
A much-awaited ASH presentation by **Bertrand Coiffier** reported better PFS, response rate and time to next lymphoma treatment when bortezomib was added to rituximab in FL, but this study did not meet the primary endpoint of a 33 percent improvement in PFS. Ongoing cooperative trials are looking at the agent in the up-front setting, and there was uncertainty among the faculty as to whether these studies will demonstrate an acceptable benefit-risk ratio.

Small molecules
At the Think Tank Brad Kahl presented a patient responding to a new agent, CAL 101, and perhaps not surprisingly there were encouraging data **(click here to view abstract)** at ASH on this oral, relatively nontoxic PI3 kinase inhibitor and several other small molecules targeting the CD20 pathway.

Next up on this series, ASH data sets on a new generation of BCR-ABL TKIs in CML.

Neil Love, MD
Research To Practice
Miami, Florida

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Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

Rituximab versus Watch and Wait in the Management of Previously Untreated Asymptomatic Nonbulky Follicular Lymphoma

Presentation discussed in this issue

Ardeshna KM 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**.

Slides from a presentation at ASH 2010 and transcribed comments from a recent interview with Bruce D Cheson, MD (12/23/10)

Eligibility

- Follicular lymphoma Grade 1, 2, 3a
- Stage II, III, IV
- Asymptomatic (no B symptoms or pruritus)
- Entry within 3 months of biopsy with no prior therapy
- Low tumor burden
  - Normal LDH
  - Largest nodal or extranodal mass <7 cm
  - No more than 3 nodal sites with diameter >3 cm
  - Spleen enlargement ≤16 cm by CT
  - Hb >10 g/dL, neutrophils >5 x 10^9/L, platelets >100 x 10^9/L
  - No significant serous effusions by CT
  - Less than 5 x 10^9/L circulating tumor cells

Ardeshna KM et al. *Proc ASH* 2010;Abstract 6.

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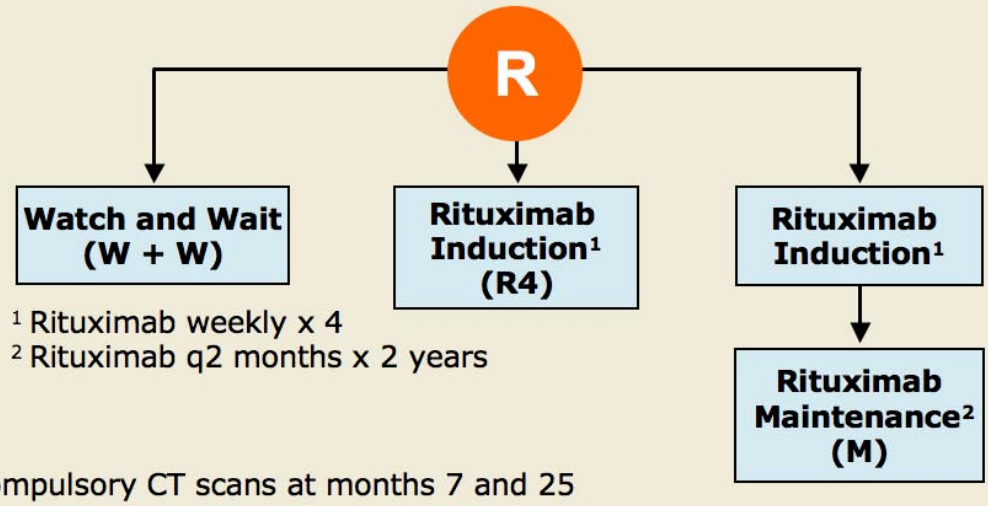
Study Schema



[1] Rituximab weekly x 4
[2] Rituximab q2 months x 2 years

Compulsory CT scans at months 7 and 25

CT scans at month 13 only if clinical CR

Bone marrow evaluation for histology and MRD only if CT shows CR at months 7, 13 and 25

Ardeshna KM et al. *Proc ASH* 2010;Abstract 6.

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Endpoints

- Primary
  - Time to initiation of new therapy (TTINT)
    - New therapy = chemotherapy or radiotherapy
- Secondary
  - Progression-free survival (PFS)
  - Overall survival
  - Response at 25 months
  - Frequency of spontaneous clinical remissions

Ardeshna KM et al. *Proc ASH* 2010;Abstract 6.

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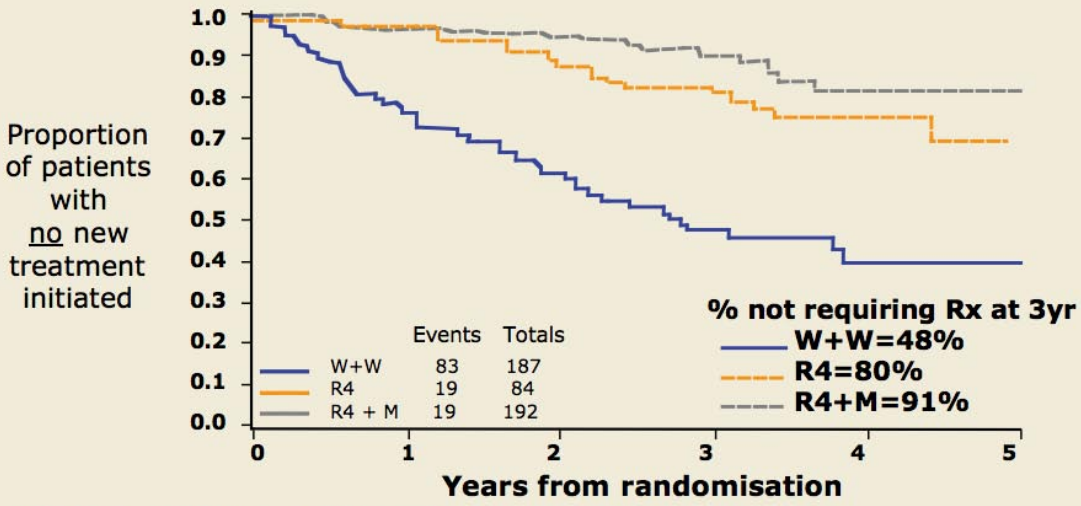
Time to Initiation of New Therapy



HR (R4 vs W+W) = 0.37, 95% CI = 0.25, 0.56, p <0.001
HR (R4 + M vs W+W) = 0.20, 95% CI = 0.13, 0.29, p <0.001
HR (R4 + M vs Rituximab) = 0.57, 95% CI = 0.29, 1.12, p =0.10

With permission from Ardeshna KM et al. *Proc ASH* 2010;Abstract 6.

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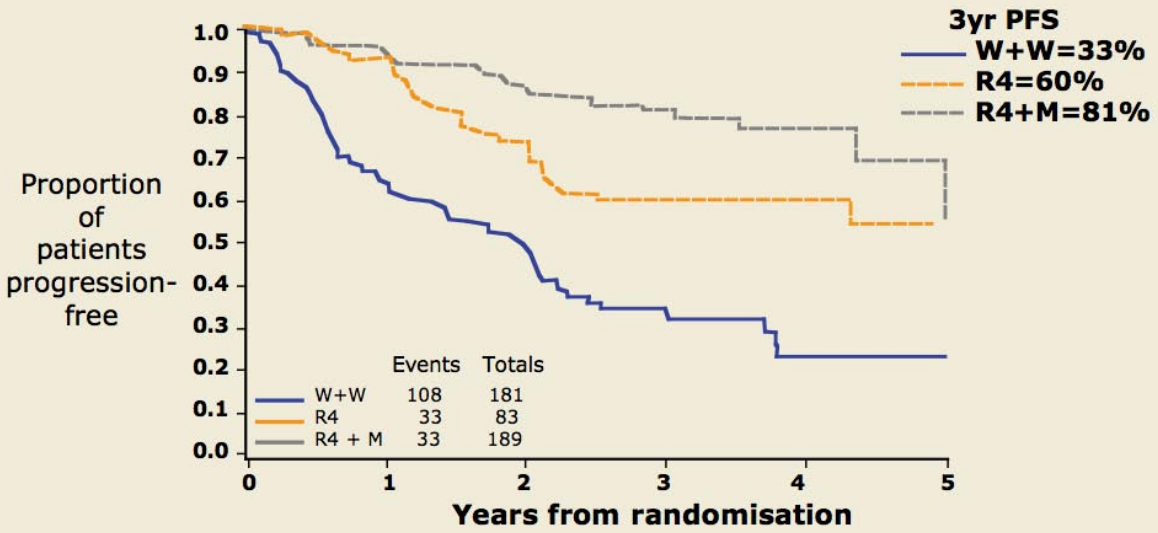
Progression-Free Survival



HR (R4 vs W+W) = 0.46, 95% CI = 0.33, 0.65, p<0.001
HR (R4 + M vs W+W) = 0.21, 95% CI = 0.15, 0.29, p<0.001
HR (R4 + M vs Rituximab) = 0.43, 95% CI = 0.24, 0.72, p=0.001

With permission from Ardeshna KM et al. *Proc ASH* 2010;Abstract 6.

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Conclusions

- Rituximab significantly improves TTINT and PFS in patients with asymptomatic FL when compared with watchful waiting.
- It is currently unclear if overall survival may be impacted by initial rituximab treatment of asymptomatic FL (data not shown).
- Need to determine the effect of prior rituximab on
  - Response to first new treatment
  - Response duration of first new treatment
  - Time to second new treatment

Ardeshna KM et al. *Proc ASH* 2010;Abstract 6.

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Investigator Commentary: Rituximab versus Watch and Wait for Stage II to IV, Asymptomatic, Nonbulky FL

The time to initiation of a new therapy and progression-free survival were significantly longer in the two rituximab-containing arms compared to observation alone. On the surface, it would suggest that this study provides support for early intervention with rituximab in this patient population. However, rituximab is associated with expense, inconvenience and possible side effects. Moreover, no data indicated that survival was prolonged by early intervention.

This is important because several trials suggest that if rituximab is used later, it might be just as effective as if it had been used earlier. So whether or not this early intervention will be beneficial in the long run remains to be seen, because we also don't know how patients will respond to their next line of treatment. In the patients observed with a watch-and-wait approach, the next line of treatment will be systemic treatment. In the other arm, the second line of treatment will be a second systemic therapy. We don't know how they will fare in the long run with this form of early intervention, and it should not be assumed that this is now the standard approach.

Interview with Bruce D Cheson, MD, December 23, 2010