Phase II Study Comparing Consolidation with $^{90}$Y Ibritumomab Tiuxetan to Rituximab Maintenance in Newly Diagnosed Follicular Lymphoma

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OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they’re aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on therapeutic options in the management of non-Hodgkin lymphomas from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Compare the efficacy of consolidation therapy with a single dose of \(^{90}\)Y-ibritumomab tiuxetan to that of rituximab maintenance for patients with newly diagnosed follicular lymphoma (FL).
- Examine the utility of early disease progression within 2 years of R-CHOP therapy as a way to identify a subset of patients with FL who are at high risk of death.
- Assess the efficacy and safety of short-term versus long-term rituximab maintenance in FL.
- Evaluate the benefits and risks of brentuximab vedotin for newly diagnosed cutaneous T-cell lymphoma or relapsed or refractory B-cell lymphomas and the effect of CD30 expression on response to this agent.

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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:

- Andrew M Evens, DO, MSc
  Professor of Medicine
  Chief, Division of Hematology/Oncology
  Tufts Medical Center
  Director, Lymphoma Program
  Interim Director, Tufts Cancer Center
  Boston, Massachusetts
  Advisory Committee and Contracted Research: Celgene Corporation, Millennium: The Takeda Oncology Company, Seattle Genetics.

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BioOncology/Biogen Idec, Millennium: The Takeda Oncology
Company, Onyx Pharmaceuticals Inc, Seattle Genetics and
Spectrum Pharmaceuticals Inc.
Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari
3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio
Last review date: February 2014
Expiration date: February 2015
To go directly to slides and commentary for this issue, click here.

The rapid integration of novel systemic agents into the management of B- and T-cell lymphomas has the rapt attention of all medical oncologists who see these patients in their practices every day. In the next issue of this series we focus on chronic lymphocytic leukemia (CLL), as Dr Brad Kahl reviews the newly approved type II anti-CD20 monoclonal antibody obinutuzumab and 3 new and exciting small molecules, the Bruton tyrosine kinase inhibitor ibrutinib (now FDA endorsed for mantle-cell lymphoma [MCL] and CLL), the PI3 kinase delta inhibitor idelalisib and ABT-199, an anti-BCL2 pro-apoptotic agent.

Similarly, a future edition of the series will delve into ASH papers on Hodgkin lymphoma, where brentuximab vedotin (BV) continues to shake up traditional paradigms. But for this program we turned our full attention to non-Hodgkin lymphoma (NHL) and asked Dr Andrew Evens, principal investigator of one of the few ongoing major randomized US Cooperative Group NHL trials — ECOG-E2408, a 3-arm Phase II study evaluating bendamustine and rituximab (R) with or without bortezomib followed by R with or without lenalidomide — to provide his perspectives on a number of ASH data sets and what these mean to current practice and future research.

**R² (rituximab/lenalidomide) up front in MCL**

As has been observed in follicular lymphoma (FL), useful objective responses to this well-tolerated nonchemotherapy regimen are common, and perhaps not surprisingly, in this Phase II study 87% of patients with treatment-naive MCL derived benefit from therapy. A major Phase III trial (RELEVANCE) compares R² to R-chemotherapy followed by R in previously untreated FL, and a number of studies, including Dr Evens’, are evaluating the equally interesting concept of R² maintenance. However, the sudden and very welcome appearance of ibrutinib in MCL and the obvious logic of evaluating it up front has complicated current discussions regarding new trial designs. While R² involves 2 approved agents and is tempting to consider for older patients and those for whom chemotherapy may be problematic, most investigators, including Dr Evens, are currently conservative about attempting to use the regimen up front in patients with lymphoma, although it is a consideration with refractory disease.
Crizotinib in ALK-positive lymphomas, mainly anaplastic large cell lymphoma (ALCL)

ALK expression is present in more than 50% of patients with ALCL, and an intriguing 2011 New England Journal report revealed the impressive short-term therapeutic activity of crizotinib in 2 individuals with ALK-positive lymphoma. At ASH 2013 we saw a small but stunning new series in which all 9 patients with ALK-positive, refractory ALCL experienced complete responses (CRs) on crizotinib. In addition, 1 partial response was observed among 2 patients with ALK-positive diffuse large B-cell lymphoma (DLBCL) treated with the drug. This important development has Dr Evens and others scratching their heads about how to integrate crizotinib into current lymphoma practice and where it will fit in with the other fairly new kid on the block, BV, as part of new research initiatives.

Maintenance treatment for FL

A fascinating report from the Swiss group comparing R monotherapy followed by short-course (4 doses) or extended (5 years) R maintenance revealed that although the primary endpoint of event-free survival was not statistically different, an impressive prolongation of progression-free survival (PFS) was observed with longer treatment (3.5 years for patients on short maintenance versus 7.4 years with the long-term approach). These intriguing findings seem out of place given that the previously reported results of the ECOG RESORT trial were somewhat unimpressive, and because of this Dr Evens’ personal standard for low-risk disease remains watchful waiting or at most 4 weeks of R with no maintenance. At ASH we also saw more follow-up from the classic PRIMA trial evaluating 2 years of R maintenance after R-chemotherapy in indolent lymphoma, and the 73-month follow-up continues to demonstrate a significant delay in disease progression.

A somewhat surprising Phase II report compared radioimmunotherapy (RIT) consolidation with $^{90}$Y-ibritumomab tiuxetan to 2 years of R maintenance in patients with newly diagnosed FL responding to R-CHOP. At 3 years, a clear PFS advantage (77% versus 63%; $p = 0.044$) in favor of R maintenance was observed. Based in part on these data, Dr Evens believes that 2 years of R maintenance remains the standard, but he will still consider RIT consolidation in highly select situations in which a patient’s life plans don’t meld well with regular infusions.

Finally, another report from the now well-publicized National LymphoCare Study in FL provides some solid evidence to back up the collective impression that the approximately 20% of patients who experience relapse in the first 2 years after R-chemotherapy have a poor prognosis. In this analysis of 122 such patients who received R-CHOP up front with a median follow-up of 7 years, the 5-year overall survival rate was approximately 50%. When this is compared to the almost 100%
survival rate for those who did not relapse within 2 years, it seems clear that these individuals should be considered for clinical trials designed to find ways to reverse the rapid downhill trajectory in this situation.

**BV in cutaneous lymphomas and NHL**

Two fascinating papers at ASH reported on Phase II studies evaluating this always-exciting antibody-drug conjugate in several unique lymphoma subsets. *In cutaneous disease* (primarily mycosis fungoides) 34 of 48 patients obtained objective responses (71%), of which half (35%) were CRs, and in *the NHL study* 21 of 50 patients with DLBCL (42%) responded, including 16% CRs. What was intriguing and a bit confusing was that activity was observed across a broad range of CD30 expression, including in patients with low or undetectable CD30 expression by standard immunohistochemical staining. Dr Evens believes that while it is possible that BV has off-target antitumor effects, the more likely explanation is that current assays for CD30 are not detecting lower but clinically significant levels of antigen. While this is sorted out, oncologists in practice must consider that useful clinical responses have been seen with BV in patients with a variety of heavily pretreated lymphomas and that perhaps referral for trial participation should be explored for interested individuals regardless of CD30 positivity.

As stated previously, next we check in with Dr Brad Kahl about perhaps the most exciting area of new drug development in oncology — chronic lymphocytic leukemia.

Neil Love, MD

*Research To Practice*

Miami, Florida
Phase II Study Comparing Consolidation with 90Y Ibritumomab Tiuxetan to Rituximab Maintenance in Newly Diagnosed Follicular Lymphoma

Presentation discussed in this issue

Lopez-Guillermo A et al. A randomized Phase II study comparing consolidation with a single dose of 90Y ibritumomab tiuxetan (Zevalin®) (Z) vs maintenance with rituximab (R) for two years in patients with newly diagnosed follicular lymphoma (FL) responding to R-CHOP. Preliminary results at 36 months from randomization. Proc ASH 2013; Abstract 369.

Slides from a presentation at ASH 2013 and transcribed comments from a recent interview with Andrew M Evens, DO, MSc (2/12/14)
Background

- Patients with follicular lymphoma (FL) can survive for a long time, but disease progression typically occurs 3 to 5 years after treatment.
- Consolidation with $^{90}$Y-ibritumomab tiuxetan after initial therapy, mainly in the prerituximab era, significantly improved progression-free survival (PFS) and time to next treatment (TTNT) (J Clin Oncol 2013;31:1977).
- Rituximab maintenance has also demonstrated a substantial benefit in terms of PFS and TTNT in patients who initially received immunochemotherapy (Lancet 2011;377:42).
  - This approach can be considered a standard for patients with FL.
- **Study objective:** To compare $^{90}$Y-ibritumomab tiuxetan consolidation to rituximab maintenance for patients with FL responding to the R-CHOP regimen.


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Phase II ZAR2007 Trial Design

<table>
<thead>
<tr>
<th>Registration</th>
<th>Induction</th>
<th>Consolidation/maintenance</th>
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<tbody>
<tr>
<td>Untreated FL Stages II–IV</td>
<td>R-CHOP $\times$ 6</td>
<td>$^{90}$Y-ibritumomab tiuxetan 1 dose ($n = 64$)</td>
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</tbody>
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| CR = complete response  
PR = partial response  
PD = progressive disease  
SD = stable disease | R* | CR/PR |
| | | Follow-up 5 years |
| | | Rituximab maintenance 1 dose every 8 weeks for 24 months ($n = 62$) |

* Stratification by response (CR/PR)

**Primary endpoint:** PFS

**Secondary endpoints:** Complete response rate at end of maintenance period, event-free survival, time to re-treatment, overall survival (OS), safety and toxicity profile, quality of life

ZAR2007 Trial Design (continued)

- **CONSOLIDATION:** $^{90}\text{Y}-\text{ibritumomab tiuxetan}$
  - 0.4 mCi/kg IV (total dose capped at 32 mCi)
  - Rituximab 250 mg/m$^2$ days -8 and 0
  - Between 60 and 90 days after last dose of rituximab (induction period)

- **MAINTENANCE:** Rituximab
  - 375 mg/m$^2$ administered by IV infusion every 8 weeks x 12 doses (24 months)
  - Starting 60 to 90 days after last dose of rituximab (induction period)
  - No dose adjustment


Patient Disposition

- Patients registered: n = 146
- R-CHOP x 6
- Patients randomly assigned: n = 126 (PR 57; CR 69)
- $^{90}\text{Y}-\text{ibritumomab tiuxetan}$ (n = 64)
- Rituximab (n = 62)

- Not randomly assigned (n = 20):
  - Incomplete induction treatment or response <PR (n = 8)
  - Low platelet or neutrophil counts (n = 5)
  - Bone marrow infiltration >25% (n = 1)
  - Patient decision (n = 2)
  - Other (n = 4)

**PFS**


**OS**

*Causes of death:* Progression (n = 6), graft-versus-host disease (n = 1)

Author Conclusions

- In patients with FL requiring therapy and responding to R-CHOP, rituximab maintenance was superior to consolidation with $^{90}$Y-ibritumomab tiuxetan in terms of PFS.
  - 3-year PFS: 77% vs 63% (HR = 0.517, p = 0.044)
- However, no significant differences were observed regarding the TTNT (data not shown) or OS.
- The safety profile was reasonable, with no unexpected toxicities observed in either arm (data not shown).


Investigator Commentary: ZAR2007 — Preliminary Results of a Phase II Trial Comparing Consolidation with a Single Dose of $^{90}$Y-Ibritumomab Tiuxetan to Rituximab Maintenance for 2 Years in Patients with Newly Diagnosed FL Responding to R-CHOP

This randomized Phase II trial evaluated either 2 years of rituximab maintenance or 1 dose of consolidation $^{90}$Y-ibritumomab tiuxetan for patients with FL responding to R-CHOP. I was a little surprised by the results. I thought any differences would be insignificant at the end of the day. But the PFS analysis, at least, favored the rituximab arm. These data are not yet mature, and we need to follow the results as they emerge.

I’m not sure these data will change practice per se. I believe the standard is still 2 years of rituximab maintenance, but I might consider administering $^{90}$Y-ibritumomab tiuxetan consolidation in certain situations, eg, for a patient who is planning to be out of town for a significant period — on an 18-month cruise or a year-long trip to Alaska, et cetera. In these circumstances, consolidation with a single dose of $^{90}$Y-ibritumomab tiuxetan may be of benefit for as long as 2 years.

*Interview with Andrew M Evens, DO, MSc, February 12, 2014*