5 Minute JournalClub

POST-ASH Issue 3, 2014

High Response Rates to Crizotinib in Advanced, Chemoresistant ALK-Positive Lymphoma

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CME INFORMATION

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.
- Appraise recent clinical findings on the use of front-line lenalidomide with rituximab in mantle-cell lymphoma and of single-agent crizotinib in advanced, chemoresistant ALK-positive non-Hodgkin lymphoma.

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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
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POST-ASH Issue 3, 2014

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

Andrew M Evens, DO, MSc

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.

R^2 (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-naïve MCL derived benefit from therapy. A major Phase III trial (**RELEVANCE**) compares R^2 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 R^2 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 R^2 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.

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High Response Rates to Crizotinib in Advanced, Chemoresistant ALK-Positive Lymphoma

Presentation discussed in this issue

Redaelli S et al. **High response rates to crizotinib in advanced, chemoresistant ALK+ lymphoma patients.** *Proc ASH* 2013;**Abstract 368**.

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

Background

- Anaplastic large cell lymphomas (ALCL) represent an aggressive group of lymphomas with a tendency to invade known nodal sites, such as mucosa and skin.
- Anaplastic lymphoma kinase (ALK) expression is present in more than 50% of patients with ALCL.
- Patients with ALK-positive ALCL respond well to cytotoxic treatment, but relapses are possible and typically bear a poor prognosis (*Crit Rev Oncol Hematol* 2012;83:293).
- Crizotinib is an orally bioavailable small-molecule ALK and c-MET inhibitor active in ALK-positive lung cancer (*N Engl J Med* 2010;363:1693).
- Impressive short-term therapeutic activity has been reported in 2 patients with ALK-positive lymphoma (*N Engl J Med* 2011;364:775), but no long-term data are available.
- **Study objective:** To report the long-term follow-up results for patients with advanced, resistant, ALK-positive lymphomas treated with crizotinib.

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Gambacorti Passerini C et al. *J Natl Cancer Inst* 2014;106(2):djt378.

Study Methods

- Patients were diagnosed with ALK-positive non-Hodgkin lymphoma by IHC and FISH using an ALK break-apart probe (n = 11).
  - ALCL histology (n = 9)
  - Diffuse large B-cell lymphoma histology (n = 2)
- Patients had relapsed/refractory disease after at least 1 prior chemotherapy regimen (typically CHOP) and measurable disease.
  - Resistant to 1 to 4 lines of treatment (median = 3), including:
    - Autologous bone marrow transplant (BMT) (n = 3)
    - Allogeneic BMT (n = 2)
- Patients received 250 mg of crizotinib twice daily as monotherapy until disease progression.
- Response to therapy was assessed according to the RECIST criteria.

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Response Rate

n (%)	n = 11
Overall response rate	10 (90.9%)
Complete response (CR)	9 (81.8%)*
Partial remission	1 (9.1%)†

* All 9 patients were diagnosed with ALCL; † This patient was diagnosed with diffuse large B-cell lymphoma.

- Median follow-up for all patients = 8 months (range 1–40)
- Median follow-up for patients still on crizotinib = 32.5 months (range 21–40)

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Disease Status as of Last Follow-Up (October 2013)

- Patients in CR under continuous crizotinib administration (n = 4):
  - At months >21, >30, >35, >40
- Patients experiencing disease progression (n = 4):
  - At months 1, 2, 2, 2
- Patients who obtained CR on crizotinib received an allogeneic BMT and remain in CR (n = 1).
- Two patients (treated before and/or after allogeneic BMT) obtained and are still in CR but have stopped crizotinib.

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Survival

	n = 11
2-year overall survival	72.7%
2-year progression-free survival	63.7%

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Grade 1/2 Adverse Events

	n = 11
Ocular flashes	91%
Peripheral edema	27%
Skin rash	9%
Erectile dysfunction	9%
Neutropenia	18%
Thrombocytosis	9%
Liver function test elevation	9%

- All toxicities were of Grade 1 or 2.
- Crizotinib-related toxicities observed were mild.
- No patient died from a cause related to treatment.
- No treatment-related event led to treatment discontinuation.

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Author Conclusions

- These positive results extend our initial observation on 2 patients and provide long-term follow-up data (*New Engl J Med* 2011;364:775).
- Crizotinib was well tolerated, with objective responses observed within 30 days after starting treatment in 10 of 11 patients.
  - Nine patients obtained CR.
- These data indicate that patients with heavily pretreated ALK-positive lymphoma have a high chance of responding to crizotinib.
  - Approximately half of the patients on the study did not experience relapse within the first months and attained long-lasting responses.
  - However, no available pretreatment parameter is able to predict durable CRs.
- These data will be useful for the management of this aggressive disease.

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Gambacorti Passerini C et al. *J Natl Cancer Inst* 2014;106(2):djt378.

Investigator Commentary: Crizotinib in Advanced, Chemoresistant ALK-Positive Lymphomas

The authors of this study reported impressive activity with crizotinib in ALK-positive lymphomas. Most of the patients had ALCL, but 2 had diffuse large B-cell lymphoma. The overall response rate was approximately 90% (10 of 11 responders), and the complete response rate was approximately 82%.

If these data held true, that would mean crizotinib would be even more active than brentuximab vedotin (B-vedotin) for CD30-positive lymphomas. I emailed the author, Dr Gambacorti-Passerini, to ask him whether any of the patients on this study had received prior B-vedotin, and he replied that none of the patients in this study had.

But he and his colleagues are now running a trial in which at least 2 patients with ALCL for whom B-vedotin has failed are responding to crizotinib. B-vedotin had its "foot in the door" first, so it will be difficult to replace, but these data are exciting and make you wonder whether crizotinib could replace B-vedotin. It also raises the question of whether the combination of these agents could bear fruit in this setting.

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

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