5 Minute JournalClub

Hematologic Oncology
Issue 2, 2013

Activity of Single-Agent Ibrutinib in Patients with Chronic Lymphocytic Leukemia with Chromosome 17 Deletion

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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 Clinical Oncology (ASCO) annual meeting and the International Conference on Malignant Lymphoma (ICML), 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 are aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because not only are they confronted almost overnight with thousands of new presentations and data sets, 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 novel agents in chronic lymphocytic leukemia from the latest ASCO and ICML meetings, including expert perspectives on how these new evidence-based concepts may 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

- Appraise recent data on therapeutic advances and potentially practice-changing clinical data in chronic lymphocytic leukemia, and consider this information in clinical practice.
- Evaluate the efficacy, safety, pharmacodynamics and pharmacokinetics of idelalisib as a single agent or in combination with rituximab for patients with relapsed/refractory or previously untreated chronic lymphocytic leukemia.
- Determine the preliminary efficacy and safety of ABT-199, a selective BCL-2 inhibitor, for patients with relapsed or refractory chronic lymphocytic leukemia.
- Determine the benefits and risks associated with chlorambucil in combination with obinutuzumab (GA101), an anti-CD20 antibody, or rituximab versus chlorambucil alone for patients with previously untreated chronic lymphocytic leukemia and preexisting comorbidities.
- Assess the preliminary safety and response outcomes observed in studies of the orally bioavailable, small molecule inhibitor of Bruton tyrosine kinase ibrutinib as a single agent for patients with chronic lymphocytic leukemia with chromosome 17 deletion.

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This activity is supported by educational grants from Genentech BioOncology/Biogen Idec, Onyx Pharmaceuticals Inc 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: September 2013
Expiration date: September 2014

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

Imagine...

Ten days ago your life was instantly turned upside down. After a few months of having less energy than usual, to appease a concerned spouse you visit your primary care physician who detects lymphadenopathy in your neck and a spleen tip. A blood count suggests chronic lymphocytic leukemia (CLL), and that night one of your colleagues does a bone marrow biopsy and initiates a workup that soon demonstrates you meet the criteria to initiate treatment. You consult with a noted CLL investigator who reviews with you the following options:

A. FCR
B. FR
C. BR
D. A clinical trial that includes 1 or more unapproved agents in clinical development

Which treatment would you choose to receive?

I asked this impossible question to investigator Dr Brad Kahl last week during a conversation that focused on the blindingly fast evolution of new agents in B-cell neoplasia, particularly CLL. Not surprisingly and without any hesitation Dr Kahl replied "D, clinical trial," and while there are many investigational agents and regimens he might consider, his first choice today would be to enter a study of the Bruton's tyrosine kinase inhibitor ibrutinib combined with rituximab (R), although he did preface his answer by saying, "This is a moving target that could change in 6 months — especially the choice of anti-CD20 antibody, which might be different after ASH" (see below). If and when relapse occurred, at this moment Dr Kahl would elect to be enrolled on a trial of the BCL-2 inhibitor ABT-199 with obinutuzumab (O) for its added effect on cell death. He noted that his choices would be the same with del17p disease.

One of the oldest homilies in medical oncology is "The best treatment option is participation in a clinical trial," and although in the past, study options rarely provided opportunities not available in daily practice, currently in specific corners of the field the data for one or more unapproved treatments are so compelling that oncologists who don't make patients aware of these research options are not delivering the type of care they would likely want to receive themselves.

Nowhere is this more relevant currently than in CLL, and on this issue of our short series summarizing key summer heme-onc meeting presentations we review findings with 4 classes of agents rapidly generating impressive data and speeding toward clinical practice.

1. Type II monoclonal antibodies to CD20

Perhaps the most surprising oral CLL paper at ASCO 2013 provided us with a first glimpse of data from a major Phase III, 3-arm German study in patients with comorbidities — mostly aged 65 and older — evaluating chlorambucil alone or combined with either R or O, a third-generation glycoengineered Type II agent designed to enhance antibody-dependent cellular cytotoxicity and induce actin-dependent programmed cell death independent of BCL-2 overexpression and caspase activation.

The findings unveiled at ASCO were from the first stage of the study and revealed that both of the monoclonal antibodies added significant efficacy to chlorambucil. However, the data also hinted that O might be more effective than R. Importantly, in July a **press release** announced that the second stage of this historic study had reached statistical maturity and that indeed the primary endpoint of superior progression-free survival in favor of O had been met. O may have more tolerability issues, particularly infusion reactions and neutropenia, but the new data have been submitted to ASH and we shall soon have a much better idea of whether this fascinating agent could potentially replace R in treating CLL and perhaps other B-cell cancers.

2. PI3 kinase delta inhibitors: Idelalisib (idel)

The other 2 ASCO oral CLL presentations this year focused on this much-discussed oral small molecule B-cell receptor signaling inhibitor. The first was a Phase I study in relapsed disease that demonstrated a 72% response rate with a waterfall plot for nodal response that pretty much all points down. The second was a Phase II trial of R and idel in older patients with previously untreated CLL, which revealed a response rate of 97%, including all 9 patients with del17p and/or TP53 mutations. The presenter, Dr Susan O'Brien, noted that as with other novel agents in development, treatment was often initially associated with both rapid lymph node regression and simultaneous lymphocytosis that then gradually receded. She also pointed out that with a median follow-up of 14.1 months, no patient has experienced disease progression. Both studies confirmed prior data demonstrating that the key tolerability issues are diarrhea/colitis and abnormal liver function tests, which resolve with treatment withdrawal or dose reduction.

3. Bruton's tyrosine kinase inhibitors: Ibrutinib

Perhaps the most talked about "emerging agent" in all of oncology, ibrutinib has been the subject of a plethora of recent research reports in an array of B-cell cancers.

In Lugano, the database grew even larger with provocative results illustrating the impact of this agent in a CLL subset that is relatively resistant to chemotherapy-R, patients with del17p. The data reveal that nodal responses were documented in 22 of 25 patients (88%), spleen size decreased in every patient with splenomegaly and the 12-month event-free survival rate was 90%. As in prior studies, side effects and complications were minimal.

4. BCL-2 inhibitors: ABT-199 (GDC-0199)

A final exciting class of agents that has burst onto the CLL scene targets the antiapoptotic protein BCL-2, and in a Phase I study of the orally bioavailable selective BCL-2 inhibitor ABT-199 presented at ASCO and Lugano, an extraordinary 84% response rate was observed in 55 evaluable patients with relapsed/refractory disease, including 13 of 16 patients with del17p. The rapid and profound effect of this agent has led to problems with tumor lysis syndrome, and new studies are evaluating alternate dosing strategies and enhanced measures of prophylaxis, monitoring and management. Moving forward, a key macro issue will be how to combine and sequence these and other new agents with or without chemotherapy.

Much more is happening in CLL research, including chimeric antigen receptor therapy, a promising but technologically complex approach, and as a result we are starting to hear leukemia investigators like Dr Hagop Kantarjian raise the possibility that CLL in the near future could resemble CML with indefinite disease control. In good conscience the trials seeking to achieve this lofty goal must be made available to all patients.

Next on this series, we talk about T-cell lymphoma, a corner of hematologic oncology that is witnessing exciting advances in new drug development after a long period in the doldrums.

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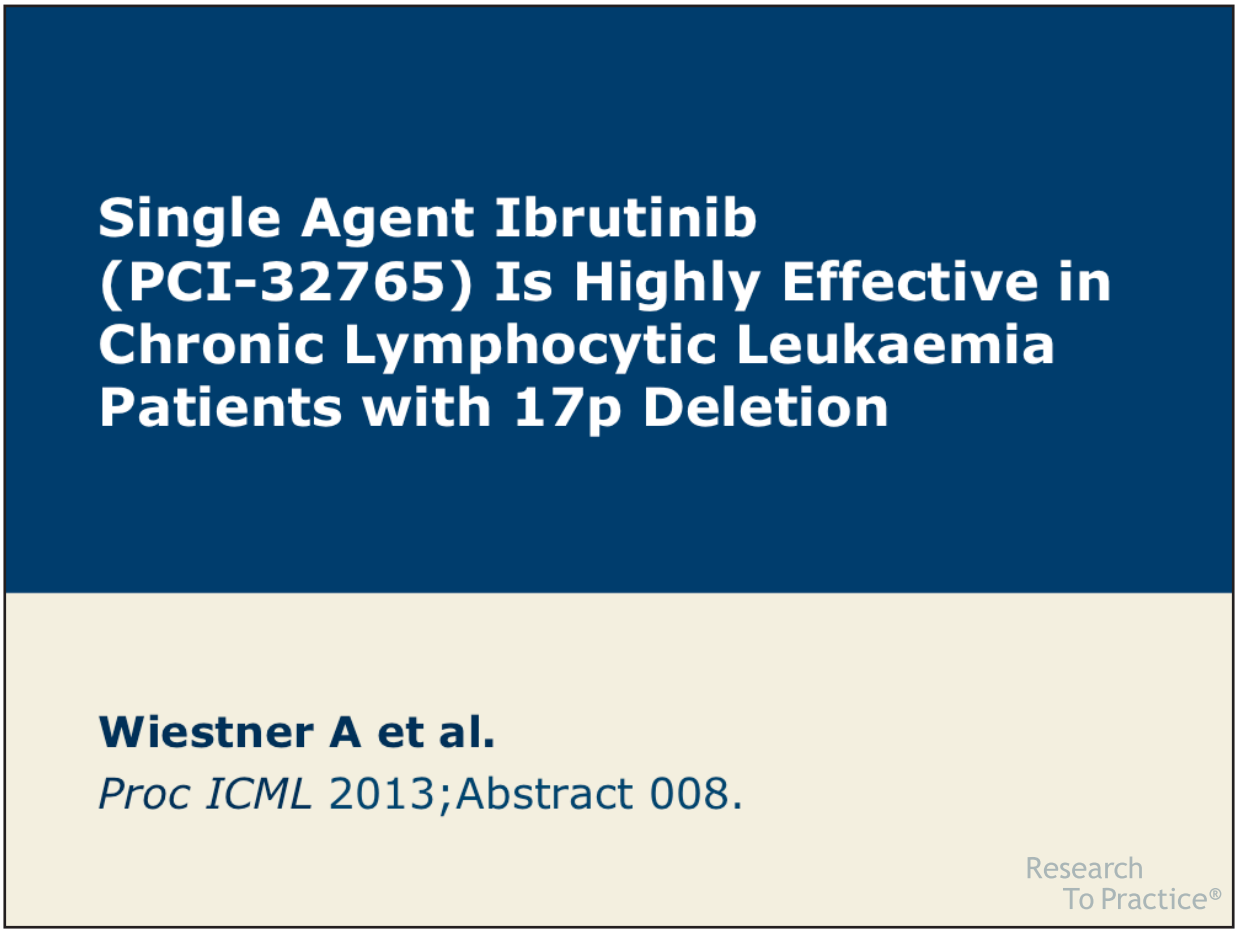
Activity of Single-Agent Ibrutinib in Patients with Chronic Lymphocytic Leukemia with Chromosome 17 Deletion

Presentation discussed in this issue

Wiestner A et al. **Single agent ibrutinib (PCI-32765) is highly effective in chronic lymphocytic leukaemia patients with 17P deletion.** *Proc ICML* 2013;**Abstract 008**.

Slides from a presentation at ICML 2013 and transcribed comments from recent interviews with Jonathan W Friedberg, MD, MMSc (7/18/13) and Brad S Kahl, MD (9/10/13)



Background

- Patients with chronic lymphocytic leukemia (CLL) with deletion 17p experience inferior outcomes with standard chemoimmunotherapy with respect to progression-free survival and overall survival.
- Ibrutinib (PCI-32765), an inhibitor of Bruton's tyrosine kinase, has demonstrated durable antitumor activity in high-risk CLL (*NEJM* 2013;369:32).
- **Study objective:** To determine the safety and efficacy of single-agent ibrutinib in patients with CLL and del(17p).

Wiestner A et al. *Proc ICML* 2013;Abstract 008.

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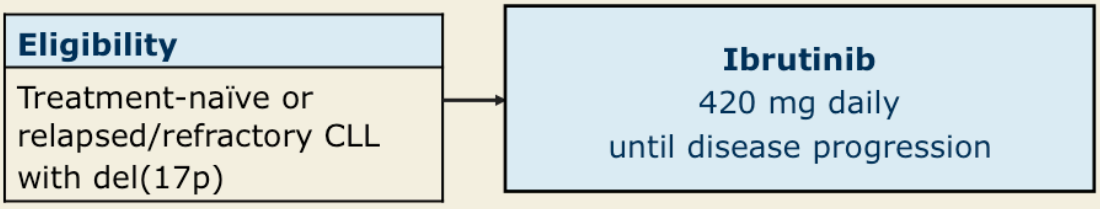
Phase II Trial Design



- Responses evaluated at 6 months and every 6 months thereafter.
- Del(17p) was assessed by FISH cytogenetics.
- Spleen volumetry was determined using CT scans.
- Results reported on first 29 patients enrolled with a median follow-up of 9 months.

Wiestner A et al. *Proc ICML* 2013;Abstract 008.

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Response Rates (Abstract Only)

Response	n = 25*
Nodal response†	88%
Partial response by IWCLL criteria	48%
Partial response with lymphocytosis	40%
Progressive disease‡	4%

IWCLL = International Workshop on Chronic Lymphocytic Leukemia

* Evaluable patients

† Median reduction in lymph node size: 70%

‡ Presumed transformation

Wiestner A et al. *Proc ICML* 2013;Abstract 008.

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Nodal Response by Disease Type (Abstract Only)

Subgroup	Patients achieving response
Patients with relapsed/refractory CLL (n = 14)	93%
Patients with treatment-naïve CLL (n = 15)	82%

- All patients also experienced reduction in splenomegaly.

Wiestner A et al. *Proc ICML* 2013;Abstract 008.

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Survival and Treatment Outcomes (Abstract Only)

Outcome	
Estimated 12-month event-free survival (n = 29)	90%
Median decrease in tumor burden in bone marrow biopsies* (n = 23)	76%

* Assessed by immunohistochemistry for CD79a

- Patients with a reduction in the percentage of tumor cells with del(17p): n = 15 (median reduction = 55%)
- Patients with unchanged percentage of tumor cells with del(17p): n = 1
- Patients with increased percentage of tumor cells with del(17p): n = 3

Wiestner A et al. *Proc ICML* 2013;Abstract 008.

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Author Conclusions (Abstract Only)

- Ibrutinib as a single agent:
  - Is effective in both treatment-naïve and relapsed or refractory CLL with chromosome 17 deletion.
  - Achieves rapid control over disease in blood, nodes, spleen and bone marrow.
  - Elicits durable responses.
  - Has an acceptable safety profile:
    - Grade ≥3 nonhematologic toxicities (regardless of causality) were observed in 14% of patients.
- Ibrutinib will be further investigated as a strategy for patients with high-risk CLL.

Wiestner A et al. *Proc ICML* 2013;Abstract 008.

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Investigator Commentary: Single-Agent Ibrutinib (PCI-32765) Is Highly Effective in Del(17p) CLL

This study demonstrated a high, durable response rate with ibrutinib in patients with 17p deletion, which normally predicts a poor outcome and a poor response to treatment. The study confirms that ibrutinib has similar activity in this patient population to the activity it has in patients without the deletion, and this is exciting. Almost all the patients experienced a decrease in lymph node size with ibrutinib. I believe the response rates probably underestimate the activity because at the end stage of the disease it's typically the bulky adenopathy that contributes to the illness. Even if residual circulating CLL cells are present, if patients achieve a nodal response and are feeling well, that's a victory for me.

Interview with Jonathan W Friedberg, MD, MMSc, July 18, 2013

Ibrutinib is a promising agent in the treatment of CLL, with activity in patients with del(17p) that looks just as good as it does in the rest of the population. Ibrutinib has such high activity, particularly in front-line CLL, that I believe there's a reasonable chance that it could replace cytotoxic chemotherapy in this setting.

Interview with Brad S Kahl, MD, September 10, 2013