



POST-ASH Issue 4, 2014

**Single-Agent Ibrutinib for
Patients with CLL with and
without Deletion 17p**

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 the management of chronic lymphocytic leukemia (CLL) 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

- Apply recent clinical research findings with the newly FDA-approved combination of obinutuzumab and chlorambucil to the management and care of patients with previously untreated CLL.
- Develop an understanding of emerging efficacy and side-effect data with novel agents and combination regimens — including next-generation anti-CD20 antibodies and PI3 kinase, Btk and BCL-2 inhibitors — under evaluation for previously untreated and relapsed/refractory CLL and, where appropriate, facilitate patient access to ongoing trials of these agents.
- Evaluate recent clinical findings with the newly FDA-approved Btk inhibitor ibrutinib, alone and in combination with chemotherapy, for patients with CLL with and without deletion 17p or those with relapsed/refractory disease.
- Compare and contrast the benefits and risks of chemoimmunotherapy with FCR versus bendamustine/rituximab (BR) as first-line therapy for fit patients with CLL.

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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: March 2014

Expiration date: March 2015

To go directly to slides and commentary for this issue, [click here](#).

Throughout a recent interview with investigator Dr Brad Kahl about the breathtaking developments in the treatment of chronic lymphocytic leukemia (CLL), my mind kept flashing back 24 hours to a similar recording session for our *Visiting Professors* audio series focused on the care of patients with a variety of advanced gastrointestinal cancers. One of the themes that regularly emerged during that discussion was the sense of desperation and hopelessness felt by patients and clinicians regarding the modest research advances that have recently taken place in that field. Coming from that concerning landscape, my conversation with Dr Kahl about CLL was a different story and hopefully the model for the future of oncology for patients, families and healthcare professionals.



Brad S Kahl, MD

Indeed, one might argue that in the short (50+ years) history of contemporary oncology the recent clinical research progress in CLL is unprecedented, as the confluence of a variety of research efforts has culminated in an abundance of new treatment options. To provide some insight into how emerging data will inform the integration of these exciting treatments into practice, here are Dr Kahl's perspectives on some of the most important CLL papers presented at the annual ASH meeting in New Orleans.

Chimeric antigen receptor (CAR) T-cell immunotherapy

A coming issue of this series will dive deeper into this extraordinary treatment that will eventually be studied in all B-cell cancers, but at ASH most of the data presented on this CAR-based T-cell therapy targeting CD19 were in CLL and acute lymphoblastic leukemia. The bottom line is that frequent, rapid and profound antitumor responses and a delayed cytokine release syndrome that requires a great deal of attention were observed. Stay tuned for full details.

Obinutuzumab

One of two recently approved agents in CLL (with more likely on the way), this type II anti-CD20 antibody was big news in the Big Easy as the plenary presentation of [the CLL11 trial](#) illustrated superior efficacy of obinutuzumab versus rituximab (R) in older patients and those with comorbidities receiving chlorambucil. Dr Kahl notes that clinicians must be aware of the potential for increased toxicity with this drug — particularly manageable infusion reactions mainly with the first treatment — but he believes the clear-cut benefit of obinutuzumab makes it difficult to use R in patients receiving chlorambucil.

Of course, an important related question is how this agent fits in with other chemotherapeutic regimens, and at ASH we saw data from [an ongoing Phase Ib trial](#) evaluating either fludarabine/cyclophosphamide (FC) or bendamustine (B) combined with obinutuzumab. The efficacy findings in this nonrandomized effort seemed similar to those historically observed with R, but this early report also described frequent infusion reactions and some myelosuppression. Dr Kahl believes that until further data become available, these combinations should not be used outside a trial setting.

FCR versus BR

Seems like eons ago when all we had to talk about was this important clinical question that was the subject of the [German CLL10 trial](#) in fit patients presented at ASH. Results from this much-awaited study demonstrated pretty much what most people expected and were already acting on in their practices — slightly greater efficacy in terms of complete response (CR) rates and progression-free survival (PFS) with FCR but considerably more toxicity, particularly in older patients. These data reinforce Dr Kahl's current nonprotocol approach to up-front treatment of CLL as follows:

- For younger patients, consider but do not insist on FCR, or, alternatively, administer BR.
- For older but not particularly frail patients (about age 60 to 75), usually opt for BR.
- For the difficult-to-define "very elderly," use chlorambucil/obinutuzumab.

Others will argue that few patients are too frail to receive bendamustine, but now that a new generation of novel agents has arrived, these issues are all being completely reconsidered anyhow.

Ibrutinib in relapsed/refractory (RR) CLL

Just approved in CLL, this Bruton tyrosine kinase inhibitor was the centerpiece of several Phase I-II ASH papers, all of which also continue to demonstrate high levels of activity, including in patients with del(17p) disease.

– Ibrutinib alone

A report from the NCI of the first 53 patients enrolled on [a Phase II trial](#) demonstrated that two thirds of these individuals responded. Most of the remaining patients responded in nodes and other sites but with increasing rather than decreasing white blood cell counts. This lymphocytosis is observed with a variety of the new small B-cell receptor inhibitors and may be part of a demargination syndrome with cells being discharged into circulation from the protected microenvironment of the marrow, spleen and the lymph nodes. With time the white counts eventually decrease — often normalizing — and this has led to a special response classification of “partial response with lymphocytosis” that occurred in 28% of 47 evaluable patients for an overall response rate of 94%. Dr Kahl views these cases as essentially CRs because the circulating cells eventually die, and it’s not clear if abrogating this phenomenon with another antineoplastic agent like R or chemotherapy adds to long-term treatment benefit.

– Ibrutinib with R

Thirty-eight of 40 (95%) patients on [this Phase II trial](#) experienced objective responses, and Dr Kahl views this higher rate compared to ibrutinib monotherapy as mainly the result of counteracting the initial lymphocytosis and notes it remains to be seen if this will affect long-term outcome and survival. An ongoing randomized Phase II trial in RR CLL evaluating ibrutinib alone or with R will hopefully provide part of the answer to this important question.

– Ibrutinib with BR

Although 93% of 30 patients responded in [this Phase Ib trial](#), as per Dr Kahl it’s not clear that bendamustine is adding anything to ibrutinib or as previously stated that R provides long-term benefit. Dr Kahl, like most or all investigators, is currently using ibrutinib in relapsed CLL as per the indication, but it will be interesting to see how this evolves as more data accumulate on earlier use, particularly in cases with adverse cytogenetic factors and for the elderly.

Idelalisib

Another major story at ASH was a “late breaker” and *New England Journal* publication (along with the CLL11 obinutuzumab trial) detailing the results from [a Phase III trial](#) evaluating R with or without this PI3 kinase-delta inhibitor in 220 patients with relapsed disease who were not candidates for chemotherapy (median age 71). An overwhelming advantage was seen in the combination arm — 81% versus 13% overall response rate and marked improvement in PFS (HR = 0.15) and overall survival (HR = 0.28), both statistically significant. However, Dr Kahl wonders if the comparison to R, a notoriously ineffective monotherapy in CLL, will be enough to elicit FDA approval.

ABT-199

This fascinating small molecule inhibits BCL-2, which is frequently overexpressed in lymphoid cancers and a cause of dysregulation of apoptosis. While ABT-199 may still be in need of a name, it is quickly gaining a great deal of attention, and according to Dr Kahl the most significant problem may be that it “works too well,” with an overall response rate of 84% among 56 evaluable patients and similar response rates irrespective of del(17p) status. Specifically, the rapid and profound antitumor activity associated with the agent frequently results in tumor lysis syndrome. As such, [an ongoing Phase I study](#) presented at ASH attempted to define the optimal dosing strategy to prevent this worrisome side effect. Regardless, Dr Kahl believes that ABT-199 will eventually prove to be as efficacious in CLL as ibrutinib — the agent he currently feels is the most effective available for the disease.

From the perspective of the general oncologist, the deluge of new agents and therapies in CLL is likely to result in frequently changing clinical algorithms during the next few years as trials evaluate various sequences, combinations and predictive factors. It seems inevitable that the outcomes of patients will improve significantly, and the best-case scenario is cure or a functional cure with normal life expectancy as with chronic myelogenous leukemia. It remains to be seen whether this type of exciting clinical paradigm will enter mainstream oncology in the future and include the many patients with GI cancers and other solid tumors who currently face much more limited options.

Next on this ASH review series, Dr Rafael Fonseca talks about new therapies in multiple myeloma, with more on the recently approved agents carfilzomib and pomalidomide, and a wave of promising other molecules, including several monoclonal antibodies attempting to become the “rituximab of myeloma.”

Neil Love, MD

[Research To Practice](#)

Miami, Florida

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Single-Agent Ibrutinib for Patients with CLL with and without Deletion 17p

Presentation discussed in this issue

Farooqui M et al. **Single agent ibrutinib (PCI-32765) achieves equally good and durable responses in chronic lymphocytic leukemia (CLL) patients with and without deletion 17p.** *Proc ASH 2013*; **Abstract 673.**

Slides from a presentation at ASH 2013 and transcribed comments from a recent interview with Brad S Kahl, MD (2/13/14)

Single Agent Ibrutinib (PCI-32765) Achieves Equally Good and Durable Responses in Chronic Lymphocytic Leukemia (CLL) Patients with and without Deletion 17p

Farooqui M et al.

Proc ASH 2013; Abstract 673.

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Background

- Chemoimmunotherapy has markedly improved the outcomes of patients with CLL.
- However, patients harboring the del(17p) chromosome abnormality have inferior outcomes with current standard treatments, with the possible exception of allogeneic stem cell transplantation.
- In addition, elderly patients are in need of less toxic regimens.
- Ibrutinib (PCI-32765) is a covalent inhibitor of the Bruton tyrosine kinase with significant antitumor activity in CLL (*NEJM* 2013;369:32).
- **Study objective:** To determine the efficacy and safety of ibrutinib in patients with CLL who are elderly or those harboring the del(17p) chromosomal abnormality.

Farooqui M et al. *Proc ASH* 2013;Abstract 673.

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Ongoing Phase II Trial Design

NCT01500733

Target accrual (n = 86)

Cohort 1:

Treated or untreated CLL or SLL
Age ≥65 years
No del(17p) abnormality

Cohort 2:

Treated or untreated CLL or SLL
Age ≥18 years
Presence of del(17p) abnormality

Ibrutinib
420 mg daily (oral)

- **Primary endpoint:** Overall response rate after 6 months
- **Secondary endpoints include:** Overall survival, progression-free survival and safety

Farooqui M et al. *Proc ASH* 2013;Abstract 673.

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Baseline Characteristics

Characteristic	All patients (n = 53)*
Median age (range)	66 years (33-85)
Rai Stage III/IV	70%

* First 53 patients enrolled on the study

- Cohort 1 (n = 24)
- Cohort 2 (n = 29)

Farooqui M et al. *Proc ASH 2013*;Abstract 673 (abstract only).

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Response at 6 Months

Outcome	All patients (n = 47)	Cohort 1 (n = 21)	Cohort 2 (n = 26)	p-value
Partial response (PR)	66%	81%	53%	0.04
PR with lymphocytosis	28%	9%	43%	0.02
Stable disease	4%	9%	0%	0.11
Progressive disease	2%	0%	4%	0.35
Nodal response (>50% reduction)	100%	100%	100%	NA

NA = not applicable

- Median follow-up: 14 months
- The apparent difference in response rates (PR vs PR with lymphocytosis) is due to a slower clearance of the treatment-induced lymphocytosis in Cohort 2
- The estimated event-free survival at 14 months was 93%

Farooqui M et al. *Proc ASH 2013*;Abstract 673 (abstract only).

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Degree of Tumor Reduction at 6 Months

Site of tumor reduction	Median reduction			p-value
	All patients (n = 47)	Cohort 1 (n = 21)	Cohort 2 (n = 26)	
Nodes	73%	75%	70%	0.75
Spleen	44%	40%	46%	0.50
Bone marrow	80%	76%	84%	0.51
ALC	62%	71%	60%	0.42

ALC = absolute lymphocyte count

- Clinical benefit and disease control in all tissue sites were equal between cohorts.

Farooqui M et al. *Proc ASH 2013*;Abstract 673 (abstract only).

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Effect of Ibrutinib on del(17p) Clones

- To obtain a direct measure of the relative impact of ibrutinib on tumor cells harboring the del(17p) abnormality, FISH testing was performed at 6 months (n = 20).
 - In the individual patients, del(17p) was present in 12% to 97% of the tumor cells before treatment.
 - At 6 months, del(17p) was present in 0% to 92% of tumor cells.
 - In 80% of patients, there was a decrease in the relative size of del(17p) subclones.
 - Median reduction 34%; $p < 0.02$
 - Four patients (20%) had no evidence of del(17p) after 6 months.

Farooqui M et al. *Proc ASH 2013*;Abstract 673 (abstract only).

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Adverse Events (AEs)

- Most AEs were of Grade ≤ 2 intensity (mostly diarrhea, fatigue, arthralgia/myalgia and rash).
- Grade ≥ 3 infections or cytopenias were uncommon and reported in 15% of patients regardless of causality.
- Treatment-related nonhematologic AEs of Grade ≥ 3 intensity occurred in $< 5\%$ of patients.
- Four deaths occurred on study but were not related to treatment.
- Forty-seven patients were restaged at 6 months.
- Six patients did not reach the restaging endpoint.
 - Unrelated deaths (n = 2)
 - Unrelated secondary malignancies (n = 3)
 - Progressive disease due to presumed transformation at 2 weeks in patients with del(17p) (n = 1)

Farooqui M et al. *Proc ASH 2013*;Abstract 673 (abstract only).

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Author Conclusions

- Ibrutinib as a single agent appears to be equally effective against CLL in the presence or absence of the del(17p) chromosomal abnormality.
- This conclusion is based on a comparison of responses in 2 concomitantly treated cohorts of patients with CLL and supported by the absence of a treatment-related increase in the del(17p) clone in individual patients.

Farooqui M et al. *Proc ASH 2013*;Abstract 673 (abstract only).

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Investigator Commentary: Single-Agent Ibrutinib Achieves Good Responses in CLL with or without del(17p)

Chemotherapy has been notoriously ineffective against CLL harboring 17p deletion. Even with bendamustine/rituximab or fludarabine/cyclophosphamide/rituximab the results have been disappointing. However, the data to date suggest that ibrutinib and some of the other kinase inhibitors have unique activity in CLL with 17p deletion. This is exciting.

In this study of 53 patients, 24 had a normal 17p status while 29 had disease with del(17p). At 6 months the clinical results were similar in the 2 cohorts. For patients without del(17p), the overall response rate was 81% and an additional 9% of patients experienced response but also lymphocytosis. This amounts to a 90% response rate. For patients with disease harboring del(17p), the response rate was 53% using the traditional criteria. Considering this alone, one might believe that patients with del(17p) have worse outcomes. In fact, if you factor in the 43% who experienced response but with lymphocytosis, the response rate becomes 96%.

It appears that patients with CLL or SLL with del(17p) are more likely to experience prolonged lymphocytosis than those without the deletion. The question is whether this will make a difference clinically. It will be interesting to see the follow-up results with these patients over time.

Interview with Brad S Kahl, MD, February 13, 2014