



POST-ASH Issue 4, 2014

Activity and Tolerability of Ibrutinib with Bendamustine/Rituximab for Relapsed/Refractory CLL/SLL

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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 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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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:

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Advisory Committee: Celgene Corporation, Genentech BioOncology, Millennium: The Takeda Oncology Company, Roche Laboratories Inc; Contracted Research: Genentech BioOncology, Roche Laboratories Inc.

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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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Activity and Tolerability of Ibrutinib with Bendamustine/ Rituximab for Relapsed/Refractory CLL/SLL

Presentation discussed in this issue

Brown JR et al. **Ibrutinib in combination with bendamustine and rituximab is active and tolerable in patients with relapsed/refractory CLL/SLL: Final results of a Phase 1b study.** *Proc ASH 2013*; **Abstract 525**.

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

Ibrutinib in Combination with Bendamustine and Rituximab Is Active and Tolerable in Patients with Relapsed/Refractory CLL/ SLL: Final Results of a Phase 1b Study

Brown JR et al.

Proc ASH 2013; Abstract 525.

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Background

- Ibrutinib is a potent small molecule that binds covalently to a cysteine residue (Cys-481) in the Bruton tyrosine kinase active site, resulting in inhibition of proliferation, migration and adhesion in chronic lymphocytic leukemia (CLL) cells.
- Previously, oral ibrutinib monotherapy demonstrated activity in relapsed/refractory (R/R) CLL (*NEJM* 2013;369:32).
 - Overall response rate (ORR): 71%
 - 26-month progression-free survival (PFS): 75%
- The chemoimmunotherapy regimen of bendamustine and rituximab (BR) is active and well-established in the treatment of R/R CLL.
- **Study objective:** To evaluate the efficacy and safety of ibrutinib in combination with fludarabine/cyclophosphamide/rituximab (FCR) or BR in patients with R/R CLL.

Brown JR et al. *Proc ASH* 2013;Abstract 525.

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Phase Ib PCYC 1108 Trial Design

Eligibility (n = 33)

Confirmed diagnosis of CLL
or small lymphocytic
leukemia (SLL)
R/R disease

28-d cycles x 6

Ibrutinib + FCR
(n = 3)

Ibrutinib + BR*
(n = 30)

Ibrutinib: 420 mg orally, once daily

F: 25 mg/m² d1-3

C: 250 mg/m² d1-3

R: 375 mg/m² d1 cycle 1; 500 mg/m² d1 cycles 2-6

B: 70 mg/m² d1-2

- **Primary endpoint:** Safety
- **Secondary endpoints:** ORR, PFS

* At study completion 21 patients (70%) who were still receiving ibrutinib monotherapy after completion of BR continued ibrutinib on a long-term extension study.

Brown JR et al. *Proc ASH* 2013;Abstract 525.

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Efficacy Results

| Clinical variable | Ibrutinib + BR (n = 30) |
|------------------------|----------------------------|
| ORR | 93.4% |
| Complete response (CR) | 16.7% |
| Partial response (PR) | 66.7% |
| Near PR | 10.0% |
| 15-month PFS | 78% |

- Median duration of treatment: 16 months
- Median PFS was not reached
- One patient who achieved a PR with lymphocytosis was not included in ORR

Brown JR et al. *Proc ASH* 2013;Abstract 525.

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Sustained Hematologic Improvement for Patients with Baseline Cytopenias

| Ibrutinib + BR arm | |
|---|----------------------------|
| Baseline cytopenia category | Sustained improvement rate |
| ANC $\leq 1.5 \times 10^9/L$ (n = 8) | 63% |
| Hemoglobin ≤ 11 g/dL (n = 7) | 71% |
| Platelets $\leq 100 \times 10^9/L$ (n = 14) | 57% |

ANC = absolute neutrophil count

Brown JR et al. *Proc ASH* 2013;Abstract 525.

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Select Adverse Events (AEs) in $\geq 20\%$ of Patients

| All grades | Ibrutinib + BR (n = 30) |
|------------------------------------|-------------------------|
| Diarrhea* | 70% |
| Nausea | 67% |
| Fatigue* | 47% |
| Neutropenia [†] | 40% |
| Upper respiratory tract infection* | 37% |
| Peripheral edema | 33% |
| Constipation | 30% |
| Headache | 30% |
| Vomiting* | 30% |
| Arthralgia | 27% |
| Sinusitis* | 27% |

* Included Grade 3 AEs; [†] Only Grade 3 and 4 AEs observed

• AEs include: insomnia (23%), squamous cell cancer (20%), contusion (20%)

Brown JR et al. *Proc ASH* 2013;Abstract 525.

Treatment-Emergent AEs Occurring in ≥ 2 Patients

| Grade ≥ 3 | Ibrutinib + BR (n = 30) |
|---------------------|----------------------------|
| Neutropenia | 40% |
| Rash | 10% |
| Fatigue | 10% |
| Thrombocytopenia | 7% |
| Cellulitis | 7% |
| Febrile neutropenia | 7% |

Brown JR et al. *Proc ASH* 2013;Abstract 525.

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Second-Line Ibrutinib + FCR Results

- There is limited experience with second-line ibrutinib/FCR.
- This arm was closed due to a limited number of patients with fludarabine-naïve disease in the relapsed setting.
- Safety profile of patients who received treatment (n = 3):
 - Serious gastritis (n = 1)
- All 3 patients received all 6 cycles of FCR:
 - Dose reduction (n = 1)
- Efficacy results:
 - ORR: 100%
 - Confirmed minimal residual disease (MRD)-negative CR: 67%
 - Confirmed MRD-positive CR: 33%
- All 3 patients remain progression free on ibrutinib after 22 months of follow-up.

Brown JR et al. *Proc ASH* 2013;Abstract 525.

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Author Conclusions

- The combination of ibrutinib with BR had an acceptable safety profile.
 - No prolonged myelosuppression during cycle 1 was observed (data not shown).
 - Response to ibrutinib + BR was associated with improved hemoglobin and platelet counts.
 - Continuous treatment with ibrutinib after BR therapy was well tolerated.
- In this study, treatment with ibrutinib + BR resulted in:
 - ORR: 93.4%
 - Median PFS: Not yet reached
- A previous Phase II study of BR alone demonstrated an ORR of 59% and median PFS of 15.2 mo (*JCO* 2011;29:3559).
- An ongoing Phase III trial is evaluating the combination of ibrutinib with BR in R/R CLL or SLL (NCT01611090).

Brown JR et al. *Proc ASH* 2013;Abstract 525.

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Investigator Commentary: PCYC 1108 — Phase Ib Trial of Ibrutinib in Combination with FCR or BR in R/R CLL or SLL

This study evaluates the combination of ibrutinib with BR or FCR for patients with R/R CLL or SLL. The big questions are, does combining ibrutinib with chemotherapy exert synergistic effects, and is the combination worthwhile in terms of safety? In this study, patients received a lower dose of bendamustine (70 mg/m²), because it was in the relapsed setting, in combination with the standard dose of rituximab.

From the results, it's difficult to tell if the combination is measurably better than ibrutinib alone. Ibrutinib is setting a high bar. In this cohort of 30 patients, the ORR was 93%, which is an outstanding result. Compared to studies of ibrutinib alone, the results are similar. The difference is that patients don't experience lymphocytosis.

A certain proportion of patients who receive ibrutinib cannot be called "responders" by traditional criteria because their white blood cell count has increased.

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However, by all other measures they've clinically improved, with smaller lymph nodes, smaller spleen size and improved cytopenias. These patients are often classified as having achieved PR with lymphocytosis. When these factors are considered, the response rate with single-agent ibrutinib becomes 80% to 90%, which is similar to what was observed with ibrutinib/BR on this study. This raises the question whether the addition of BR to ibrutinib is beneficial.

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

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