EXPERT REVIEWS

The emerging role of ibrutinib in the treatment of chronic lymphocytic leukemia

Expert Rev. Hematol. Early online, 1–4 (2013)

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Evaluation of: Byrd JC, Furman RR, Coutre SE *et al.* Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N. Engl. J. Med.* 369(1), 32–42 (2013).

Drugs that selectively inhibit Bruton's tyrosine kinase (BTK), such as the new orally administered agent ibrutinib, are currently under investigation for the treatment of several types of B-cell malignancies. In this article, the authors present results of a Phase Ib/II study of ibrutinib in 85 patients with relapsed or refractory chronic lymphocytic leukemia (CLL). The enthusiasm generated by this paper relies on the fact that ibrutinib given orally on a daily basis produces very high response rates that are durable with minimal side effects. Interestingly, the favorable therapeutic index of ibrutinib may facilitate its use in combination with other agents active in the treatment of CLL. In addition, the use of an effective oral agent like ibrutinib whose efficacy does not translate into a high burden of toxicity should be considered in choosing therapy in the elderly. A challenging issue with ibrutinib is the possibility of overcoming chemotherapy in the treatment of CLL.

Keywords: BTK inhibitors • chronic lymphocytic leukemia treatment • ibrutinib

A major progress in chronic lymphocytic leukemia (CLL) treatment has been represented by the introduction of chemoimmunotherapy. Accordingly, fludarabine, cyclophosphamide and rituximab (FCR), a combination tested in the recent CLL8 trial represents the gold standard of therapy for younger and fit CLL patients [1]. However, FCR cannot abrogate the poor response to chemoimmunotherapy related to the presence of 17p deletion, furthermore an extensive use of FCR is compromised by comorbidities and poor performance usually present in elderly, the most prevalent CLL population [1–3]. In this scenario, the paper recently published by Byrd *et al.* dealing with the use of ibrutinib in relapsed or refractory CLL or small lymphocytic lymphoma (SLL) represents an important step forward in the treatment of CLL [4].

Ibrutinib (Pharmacyclics, Inc., Sunnyvale, CA, USA) is an orally bioavailable, potent inhibitor that covalently binds to the cysteine-481 amino acid of the Bruton's tyrosine kinase (BTK) enzyme CLL [5]. BTK, an essential component of B-cell-receptor (BCR) signaling, mediates interactions with the tumor microenvironment and promotes the survival and proliferation of CLL cells [6]. Consequently, targeting this kinase is an attractive strategy and a recently published Phase I study of ibrutinib showed significant clinical antitumor activity in patients with relapsed or refractory B-cell cancers [7–9]. These encouraging results led to start this Phase Ib/II study including CLL patients with relapsed or refractory disease who received two different doses of inbrutinib [4].

Methods & results

In the study in question, Byrd *et al.* evaluated safety, efficacy, pharmacokinetics and pharmacodynamics of ibrutinib (PCI-32765) in patients with relapsed or refractory CLL or SLL [4]. The trial is based on 85 patients (median age 66 years; range, 37–82) who were enrolled in a Phase Ib/II multicenter study. The authors considered eligible three different cohorts of patients: the first and second cohorts had received at least two previous therapies, including a purine analog

 10.1586/17474086.2013.831324 ISSN 1747-4086

while a third cohort consisted of patients with high-risk disease non-responsive to chemoimmunotherapy or progressing within 24 months after completion. Fifty-one received a fixed daily dose of 420 mg, and 34 received a daily dose of 840 mg, with both doses administered orally on a continuous schedule. The primary end point of study was the safety while secondary end points were the overall response rate (ORR), progression-free survival (PFS), pharmacodynamics and pharmacokinetics.

As far as patient characteristics are concerned, 65% had advanced-stage disease, 33% had 17p deletion and 36% had 11q deletion. After a median follow-up time of 20.9 months (range, 0.7–26.7) from the starting of ibrutinib, 54 patients (64%) were still on therapy while in 31 (36%) treatment with ibrutinib was stopped. Interruption of ibrutinib was due to disease progression only in 11 patients (13%).

According to the Internation Workshop on CLL (IWCLL) response criteria [10], ORR was virtually the same in the group that received 420 or 840 mg (71% in both). Interestingly, an additional 20 and 15% of patients in the respective groups had a 'partial response (PR) with lymphocytosis'.

The response to ibrutinib was not affected by the presence of 17p deletion. In fact, it was 68% among patients with a 17p deletion and 71% among those without this deletion. Interestingly, a PR was observed in 4 of the 12 patients with a mutated IGVH gene (33%) and in 53 of the 69 patients with an unmutated IGVH gene (77%).

PFS and OS curves projected at 26 months revealed respectively 75 and 83% rate. Among the 28 patients with 17p deletion, the 26-month PFS was 57% and OS 70%.

Toxicity related to therapy with ibrutinib was mild with a prevalence of grade 1–2 adverse events. The most common side effects included diarrhea, fatigue and upper respiratory tract infection. Ibrutinib was discontinued in two patients in the 420-mg cohort (4%) and in four patients in the 840-mg cohort (12%). The grade 3–4 adverse events observed were pneumonia (in 10 patients [12%]) and dehydration (in 5 patients [6%]). Infections were generally encountered in earlier phase of therapy. IgG and IgM levels remained relatively stable throughout treatment, whereas IgA levels increased at 3, 6 and 12 months.

Discussion

In the study under evaluation, Byrd *et al.* demonstrate that orally administered ibrutinib is well tolerated and induces significant objective responses in patients with CLL or SLL with relapsed or refractory disease [4]. Generally, side effects were mild and despite the immunocompromised condition of the patients, who had received a median of four previous therapies, treatment with ibrutinib did not translate into increased incidence of grade 3–4 infections [4]. This observation compares favorably with results of studies of relapsed or refractory CLL patients who received traditional therapy of salvage [11].

Fifteen patients (18%) in the study of Byrd *et al.* had more than 50% reduction in lymphadenopathy with residual lymphocytosis and were not considered as clinical progression but rather as a form of response described as 'PR with lymphocytosis' [4]. Previous published studies have demonstrated that ibrutinib, likewise SYK and PI3K inhibitors, can mobilize CLL cells from tissues into the peripheral blood, interfering with their homing [12] . From a clinical standpoint, Cheson *et al.* suggest to revise response criteria for CLL to correctly interpret results obtained with new agents with novel mechanisms of actions [13].

A relatively unexpected result was represented by better response to ibrutinib observed in patients without mutations of IGHV which does not translate, however, into a longer survival expectancy [4]. Generally, the BCR in leukemic CLL cells with unmutated IGVH is competent and responds more rapidly to stimulation or inhibition, while those cells with mutated IGVH are typically unresponsive [6].

A novelty with ibrutinib as single agent is represented by its efficacy in relapsed/refractory patients with 17p deletion CLL [4]. This observation suggests that ibrutinib should be further investigated alone or in combination in high-risk CLL patients, for instance, those patients with 17p deletion or mutations of the p53 gene who have poor outcomes when treated with FCR [1–2].

Treatment of elderly with CLL is today an unmet clinical need [3]. These patients, representing the majority of CLL population, frequently have major coexisting comorbidities. The use of an effective oral agent like ibrutinib whose efficacy does not translate into a high burden of toxicity should be considered in choosing the therapy in this subset of patients, especially when the end point is that of maintaining a good quality of life.

Finally, the study of Byrd *et al.* points out that the paradigma of CLL treatment is changing since we are moving from a chemotherapy-based approach to treatments targeting biologic mechanisms of disease [4]. A challenging question is represented by cost–effectiveness of these new strategies that should be carefully weighed [14].

Five-year view

The favorable therapeutic index observed with ibrutinib led to test this BTK inhibitor in combination with different drugs active in CLL. Phase Ib/II studies evaluated the association of ibrutinib with rituximab or ofatumumab [15,16]. Results of these trials, although interesting, did not reveal any increase of ORR in comparison with ibrutinib single agent [15,16].

The possibility of using ibrutinib in combination with bendamustine and rituximab (BR) has been explored in a Phase Ib/II clinical trial in relapsed/refractory CLL patients. This study included 30 patients with relapsed/refractory CLL who had received 1–3 prior regimens. ORR was 93%, with 13% being complete responses, and estimated 11-month PFS was 90% [17]. These results seem to be encouraging especially if compared with BR alone, for which the ORR was 59% [18].

The HELIOS trial is a randomized, double-blind, placebo-controlled, Phase III study of ibrutinib in combination with BR in patients with relapsed or refractory CLL or SLL.

Primary end point of study is PFS and recently, Pharmacyclics, Inc. (Nasdaq: PCYC) announced that the enrollment target of 350 patients was achieved [101]. We would expect to have a read out from the interim analysis during the first quarter of 2014.

RESONATE is a Phase III study of ibrutinib versus ofatumumab in patients with relapsed or refractory CLL. Primary end point is PFS and estimated study completion date is December 2015 [102].

RESONATE 2 is an open-label, Phase III study of the ibrutinib versus chlorambucil in patients 65 years or older with treatment-naive CLL or SLL. The primary end point of this study is PFS as assessed by IWCLL 2008 criteria with modification for treatment-related lymphocytosis. The study started in January 2013 and the estimated date of study completion is February 2016 [103].

The RESONATE 17 is an open-label, single arm Phase II study of the ibrutinib in patients with relapsed or refractory CLL or SLL with 17p deletion. The primary end point of study is ORR. The study was activated in January 2001 and the estimated completion date is March 2016 [104].

When available, results of these Phase III studies will contribute to define the role of ibrutinib in the treatment of elderly as well its activity in patients with 17p deletion who represent the CLL category with worst clinical outcome. Furthermore, ibrutinib should be evaluated as possible maintenance therapy for high-risk patients who have had a response to more conventional treatment.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Ibrutinib, a selective and potent inhibitor of Bruton's tyrosine kinase (BTK), results in a high rate of durable remissions in a majority of patients with relapsed or refractory chronic lymphocytic leukemia (CLL).
- The safety profile results reveal a relatively low incidence of serious adverse events.
- There was no significant difference in the overall response rate (ORR) of patients with either advanced disease or those who exhibited the 17p deletion.
- Additional answers on the role of ibrutinib will be provided by ongoing Phase III randomized clinical trials comparing ibrutinib with other therapeutic agents in patients with CLL.

References

1 Hallek M, Fischer K, Fingerle-Rowson G *et al*. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukemia: a randomized, open-label, phase 3 trial. *Lancet* 376(9747), 1164–1174 (2010).

2 Zenz T, Eichhorst B, Busch R *et al*. TP53 mutation and survival in chronic lymphocytic leukemia. *J. Clin. Oncol.* 28(29), 4473–4479 (2010).

3 Molica S, Brugiatelli M, Morabito F *et al*. Treatment of elderly patients with chronic lymphocytic leukemia: an unmet clinical need. *Exp. Rev. Hematol.* (2013) (In Press).

4 Byrd JC, Furman RR, Coutre SE *et al*. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N. Engl. J. Med.* 369(1), 32–42 (2013).

5 Wiestner A. Emerging role of kinase-targeted strategies in chronic lymphocytic leukemia. *Blood* 120(24), 4684–4691 (2012).

6 Woyach JA, Johnson AJ, Byrd JC. The B-cell receptor signaling pathway as a therapeutic target in CLL. *Blood* 120(6), 1175–1184 (2012).

7 Advani R, Buggy JJ, Sharman JP *et al*. The Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J. Clin. Oncol.* 31, 88–94 (2013).

8 Byrd J, Blum K, Burger J *et al*. Activity and tolerability of the Bruton's tyrosine kinase (BTK) inhibitor PCI-32765 in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): interim results of a phase Ib/II study. *J. Clin. Oncol.* 29(15), abstract 6508 (2011).

9 Tai YT, Anderson KC. Bruton's tyrosine kinase: oncotarget in myeloma. *Oncotarget* 3(9), 913–914 (2012).

10 Hallek M, Cheson BD, Catovsky D *et al*. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the international workshop on chronic lymphocytic leukemia updating the national cancer institute-working group 1996 guidelines. *Blood* 111(12), 5446–5556 (2008).

11 Perkins JG, Flynn JM, Howard RS, Byrd JC. Frequency and type of serious infections in fludarabine-refractory B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma: implications for clinical trials in this patient population. *Cancer* 94(7), 2033–2039 (2002).

12 Burger JA, Montserrat E. Coming full circle: 70 years of chronic lymphocytic leukemia cell redistribution, from glucocorticoids to inhibitors of B-cell receptor signaling. *Blood* 121(9), 1501–1509 (2013).

13 Cheson BD, Byrd JC, Rai KR *et al*. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. *J. Clin. Oncol.* 30(23), 2820–2822 (2012).

14 Foà R, Guarini A. A mechanism-driven treatment for chronic lymphocytic leukemia? *N. Engl. J. Med.* 369(1), 85–87 (2013).

15 Burger JA, Keating MJ, Wierda WG *et al*. The BTK inhibitor ibrutinib (PCI-32765) in combination with rituximab is well tolerated and displays profound activity in high-risk chronic lymphocytic leukemia

doi: 10.1586/17474086.2013.831324

(CLL) patients. Presented at: ASH Annual Meeting, Atlanta, GA, USA, 8–11 December 2012 (Abstracts 187).

16 Jaglowski SM, Jones JA, Flynn JM *et al.* A phase Ib/II study evaluating activity and tolerability of BTK inhibitor PCI-32765 and ofatumumab in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and related diseases. Presented at: ASCO Annual Meeting 2012, Chicago, IL, USA, 1–5 June, 2012 (Abstracts 6508).

17 O'Brien SM, Barrientos JC, Flinn IW *et al.* Combination of the Bruton's tyrosine kinase (BTK) inhibitor PCI-32765 with bendamustine (B)/rituximab (R) (BR) in patients (pts) with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): Interim results of a Phase Ib/II study. *J. Clin. Oncol.* 30(Suppl.), Abstract 6515 (2012).

18 Fischer K, Cramer P, Busch R *et al.* Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J. Clin. Oncol.* 29(26), 3559–3566 (2011).

Patents

101 A Study of Ibrutinib in Combination With Bendamustine and Rituximab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma. CLINICALTRIALS.GOV IDENTIFIER: NCT01611090.

102 A Phase 3 Study of Ibrutinib (PCI-32765) Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia (RESONATE). CLINICALTRIALS.GOV IDENTIFIER: NCT01578707.

103 A Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor PCI-32765 Versus Chlorambucil in Patients 65 Years or Older With Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (RESONATE-2). CLINICALTRIALS.GOV IDENTIFIER: NCT01722487.

104 A Multicenter Phase 2 Study of PCI-32765 (Ibrutinib) in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) With 17p Deletion. CLINICALTRIALS.GOV IDENTIFIER: NCT01744691.