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Ibrutinib: a novel Bruton's tyrosine kinase inhibitor with outstanding responses in patients with chronic lymphocytic leukemia

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Abstract

New treatment options are urgently needed for patients with relapsed chronic lymphocytic leukemia (CLL) who fail to respond to currently available therapies or cannot achieve a sustained response. Moreover, targeted agents with less myelotoxicity are necessary to treat patients with multiple comorbidities who would otherwise be unable to tolerate standard regimens. Ibrutinib, a Bruton's tyrosine kinase inhibitor, has shown highly encouraging results in phase I/II trials in patients with treatment-naive, relapsed and refractory CLL even in the presence of high risk disease or poor prognostic markers. In phase I/II trials, ibrutinib 420 mg or 840 mg – given continuously as single agent or at a dose of 420 mg daily in combination with a monoclonal antibody or chemoimmunotherapy – has been associated with high response rates and durable clinical remissions. Phase II and III trials are currently under way for treatment-naive patients, relapsed/refractory patients, and for those patients harboring a 17p deletion.

Keywords: Chronic lymphocytic leukemia, Bruton's tyrosine kinase inhibitor, ibrutinib

Introduction

Chronic lymphocytic leukemia (CLL) is a malignancy of mature B cells that involves blood, lymphoid tissues and bone marrow [1]. It is the most common leukemia in the Western hemisphere, and it is most often diagnosed incidentally during work-up of lymphocytosis. The clinical course is heterogeneous, with median survival reported at ~10 years, but patients with high risk disease have a historical survival of less than 2–3 years [2,3]. Regimens for CLL can have substantial toxicity, and generally become less effective with recurrent treatment. Since CLL cells interact with the stroma in bone marrow or other peripheral lymphoid tissues to survive [4], these interactions are currently being explored as targets of innovative therapies. B-cell receptor (BCR) signaling promotes survival and proliferation of the B cell clone *in vitro* [5], and several kinases in the BCR pathway can be targeted by small molecule inhibitors. The purpose of this article is to review ibrutinib (previously called PCI-32765), a potent novel treatment option that specifically targets Bruton's tyrosine kinase (BTK).

Targeting Bruton's tyrosine kinase

BTK is a cytoplasmic tyrosine kinase involved in BCR and chemokine receptor signaling [6–8]. Ibrutinib targets BTK by forming a covalent bond with cysteine-481. It inhibits BTK at low nanomolar concentrations and achieves target inhibition with once-daily oral dosing. *In vitro* and *in vivo* models demonstrate that ibrutinib inhibits survival, proliferation and migration of CLL cells [7,9,10]. Ibrutinib inhibits secretion of chemokine ligand 3 (CCL3) and CCL4 by CLL cells, and at least part of this occurs in a BCR-dependent fashion [8]. Biomarker assessment has demonstrated a rapid reduction and normalization of plasma levels of CCL3 and CCL4 in patients receiving ibrutinib [8].

Although continued use of ibrutinib was hypothesized to interfere with normal B-cell function and lead to hypogammaglobulinemia, to date a decrease of immunoglobulin G (IgG) levels during administration of ibrutinib has not been observed [11]. Interestingly, patients with CLL on therapy display an unexpected clinical response with ibrutinib: an acute dramatic rise in lymphocytosis accompanied by a marked reduction in lymphadenopathy, which is reversible upon temporary cessation of drug administration [11]. Other agents that target the B-cell signaling pathway (spleen tyrosine kinase [SYK] and phosphoinositide 3-kinase [PI3K] inhibitors) show a similar redistribution phenomenon in clinical trials of patients with CLL.

Clinical experience with ibrutinib

Ibrutinib monotherapy (phase I studies)

The first in-human study of ibrutinib enrolled patients with B-cell malignancies, as reported by Dr. R. Advani and colleagues in the *Journal of Clinical Oncology* in 2013 [11].

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The study evaluated five cohorts with interrupted dosing (28 days on, 7 days off) and two cohorts with continuous dosing. Fifty-six patients were enrolled, with a median of 3 prior regimens. The highest response rate was observed in patients with mantle cell lymphoma (78%) and CLL/small lymphocytic lymphoma (intention to treat [ITT], 69%; evaluable, 79%). All patients with CLL experienced rapid reductions in lymphadenopathy during the first cycle of treatment accompanied by an increase in absolute lymphocyte count, suggesting an egress of malignant cells from lymph nodes into peripheral blood. This early evidence of clinical activity in 16 patients with CLL strongly supported continued evaluation.

Data from a large ($n = 116$ patients) multi-institutional, multi-cohort phase Ib/II trial of ibrutinib in treatment-naive (TN) or relapsed/refractory (RR) patients with CLL was presented by Dr. J. Byrd and colleagues at the 2012 annual meeting of the American Society of Hematology (ASH) [12]. The primary objective of this study was to determine the safety of two dosing regimens (420 mg vs. 840 mg daily). Secondary objectives included establishing efficacy, pharmacokinetics and long-term safety. The 840 mg daily cohort closed prior to full accrual after comparable activity and safety between the two doses was shown in relapsed/refractory patients. The overall response rate (ORR), inclusive of complete and partial responses (CR and PR, respectively), was assessed per international workshop on CLL (IWCLL) guidelines (Table I). In addition, those patients who achieved a PR with the exception of lymphocytosis were categorized as PR with lymphocytosis. The majority of patients had lymphocytosis due to redistribution of tissue CLL cells into the blood during the first months of therapy, but over time the lymphocytosis resolved. Overall, patients experienced a high frequency of disease control extending to 26 months in both cohorts, including those with high risk genomic features (del17p, del11q, unmutated immunoglobulin heavy chain variable gene [*IGHV*]). The estimated progression-free survival (PFS) at 26 months for del 17p, del 11q and no del17p/11q was reported as 57%, 73% and 93%, respectively. The estimated overall survival (OS) at 26 months was 83% for patients with relapsed or refractory disease, including those with high risk disease and 96% for treatment-naive patients (Figure 1). This was achieved with minimal toxicities, including grade ≤ 2 diarrhea (49%), fatigue (28%), upper respiratory tract infection (30%), rash (26%), nausea (25%) and arthralgias (26%). Hematologic toxicity grade ≥ 3 was infrequent, without evidence of cumulative toxicity or long-term safety concerns, with a median follow-up of 20 months of the 116 treated patients.

Table I. Best response by risk factor (courtesy of Dr. Byrd and colleagues [12]).

	Treatment-naive		R/R + HR	
	n	ORR (%)	*n*	ORR (%)
All patients	31	68	85	71
> 70 years	23	61	30	73
$B_2M > 3$ mg/L	8	63	39	72
Rai stage III/IV	15	60	55	71
IGHV unmutated	17	82	69	77
17p−	2	100	28	68
11q23−	1	100	31	77
Bulky disease > 5 cm	6	67	44	77
> 3 prior chemotherapy regimens	NA		58	69

ORR, overall response rate; R/R, relapsed/refractory; HR, high risk; B_2M, β_2-microglobulin; *IGHV*, immunoglobulin heavy chain variable gene; NA, not applicable.

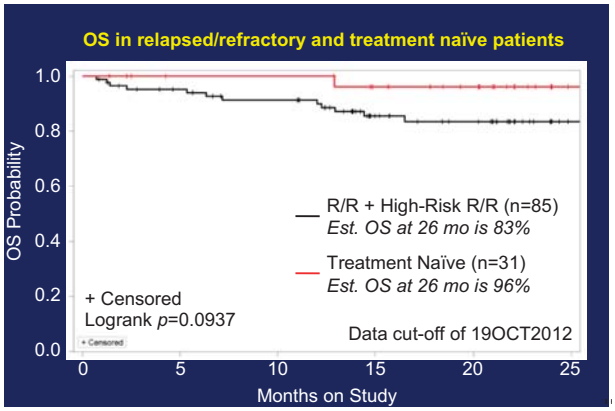

Figure 1. Overall survival in relapsed/refractory and treatment-naive patients (courtesy of Dr. Byrd and colleagues [12]).

Ibrutinib in combination with rituximab

Historically, patients with "high risk disease" have had inferior responses to standard chemo-immunotherapy, with shorter PFS and OS than low risk patients, as there is no "standard" treatment. At the 2012 ASH meeting, Dr. J. Burger reported a single-institution study targeting patients with high risk CLL, defined as having a del17p or TP53 mutation (treated or untreated), PFS < 36 months after frontline chemo-immunotherapy, or relapsed CLL with del11q [8]. Patients received ibrutinib at the standard dose of 420 mg PO daily. Rituximab was given weekly for the first 4 weeks, and then monthly for another 5 months, and then discontinued. After 6 months, patients continued on single-agent ibrutinib, and could continue after 12 months if there was treatment benefit (Figure 2). A similar phenomenon of transient lymphocytosis (from phase I monotherapy studies) occurred. The lymphocytosis peaked after 1 week of therapy, and then continuously declined, with a 50% reduction from baseline after ~12 weeks. With the short follow-up of this study, response assessment was done at 3 or 6 months. One patient had a CR and 32 a PR, accounting for an overall response rate of 83%. Three patients had a PR with persistent lymphocytosis, two had stable disease and two were too early for assessment. Treatment was well tolerated: diarrhea, bone pain and fatigue were the most frequent side effects ($\leq 25\%$). Two patients discontinued treatment because of aspergillosis and oral ulcers. These data support further study of ibrutinib in patients with high risk CLL.

Ibrutinib in combination with ofatumumab

Dr. S. Jaglowski reported a single-institution study evaluating the safety and efficacy of the combination of ibrutinib and ofatumumab with three dosing strategies, at the annual American Society of Clinical Oncology (ASCO) meeting in 2012 [13]. In cohort A, patients received 420 mg ibrutinib daily for a 28-day cycle. Ofatumumab was added to ibrutinib at 300 mg on cycle 2 day 1, followed by 2000 mg for

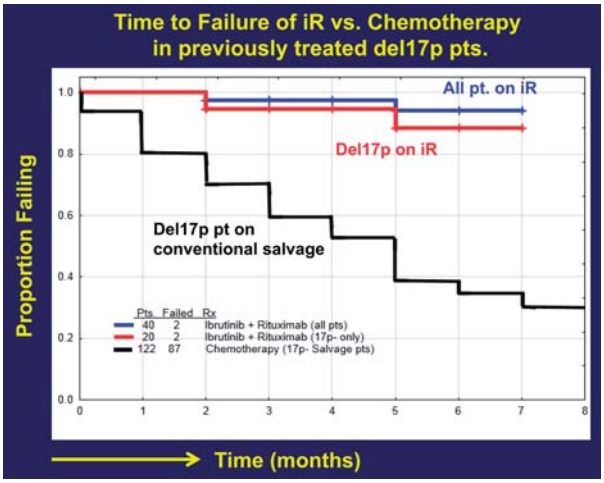

Figure 2. These plots show time to treatment failure in patients treated with ibrutinib and rituximab (iR), in blue, all patients, and in red, patients with del17p. For comparison, the black curve shows time to treatment failure in patients with del17p treated with chemo-immunotherapy salvage (122 patients M. D. Anderson Cancer Center historic control) (courtesy of Dr. Burger and colleagues [8]).

7 consecutive weeks, followed by four monthly maintenance doses as per its package insert. The primary objectives of this study were to evaluate the toxicity of the combination and to determine the ORR at 1 year. Twenty-seven patients were enrolled on this cohort. Patients had to have received at least two prior therapies, including a purine-nucleoside analog, and have at least 10% expression of CD20 on their CLL cells by flow cytometry. The median age of participants was 66 years, with the oldest patient being aged 85 years. Patients had to have a histologic confirmation of CLL, small lymphocytic lymphoma (SLL), prolymphocytic leukemia (PLL) or Richter transformation. Forty-eight percent of patients had Rai stage III/IV disease and 41% of the patients were refractory to purine analogs. The majority of patients had CLL, but three had Richter transformation, with a median of 3 prior therapies. A large number of patients had high risk genomic aberrations: 91% of patients for whom *IGHV* mutation status was available had unmutated *IGHV*s and over a third had del17p. The median follow-up time for these patients on cohort was 9.8 months, and 24/27 patients remained on study at the time of the presentation (Figure 3). Of the three who came off study, one underwent a transplant, one with Richter transformation progressed and the third, also with Richter, suffered a myocardial infarction and subsequently disease progression. There were eight grade 3 infectious events, which included urinary tract infection, pneumonia, enterocolitis, cellulitis and bacteremia. No grade 4 infectious events were observed. Among the 24 patients with CLL, SLL or PLL, 23 had a partial response by IWCLL criteria and one had a complete response as the best response to therapy. Ibrutinib in combination with ofatumumab is well tolerated and highly active in patients with relapsed/refractory CLL/SLL/PLL. Among patients with these conditions, the combination resulted in a 100% ORR irrespective of prognostic markers.

Ibrutinib in combination with bendamustine and rituximab or fludarabine/cytoxan/rituxan

Ibrutinib has also been used in combination with a chemo-immunotherapeutic regimen to evaluate its safety and efficacy. Dr. S. O'Brien (ASCO 2012) and Dr. J. Brown (European Hematology Association [EHA] 2012) presented the result of a pilot study testing ibrutinib in combination with bendamustine and rituximab (BR) or fludarabine/Cytoxan/Rituxan (FCR) in patients with relapsed/refractory CLL [14,15]. Ibrutinib was taken continuously at 420 mg/day in 28-day cycles until disease progression, and it was combined with BR or FCR for up to six cycles. Thirty patients were enrolled to the BR arm, with a median age of 62 years, 50% of patients had Rai stage III/IV, and 37% and 13% were considered refractory (treatment-free interval <12 months) to a purine analog-containing regimen or BR, respectively. Bulky disease was present in 53%. Adverse events (AEs) were consistent with those expected with BR. Grade 3/4 neutropenia and thrombocytopenia were noted in 23% and 7% of patients, respectively. Grade >3 non-hematologic AEs that were potentially related to the study drugs included rash (three patients),

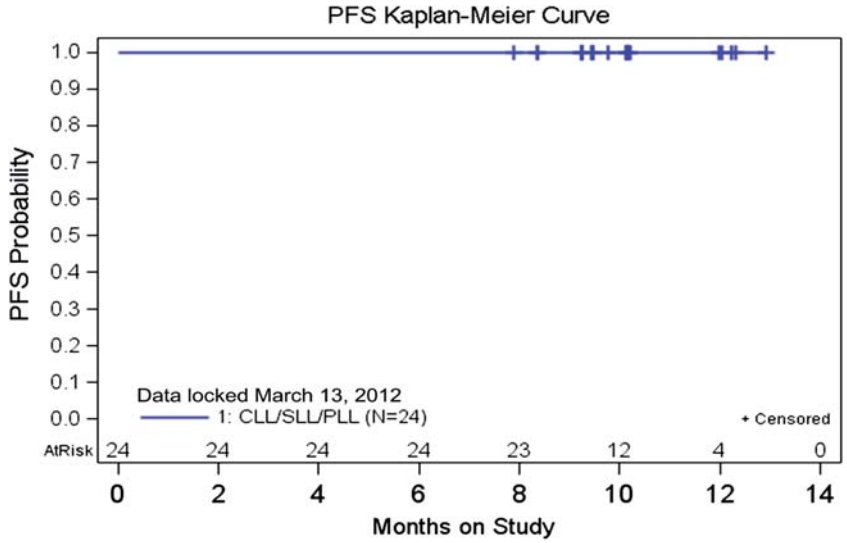

Figure 3. Early Kaplan–Meier curve showing that responses among patients with relapsed and refractory CLL, SLL and PLL have persisted to the date of the data lock. Further follow-up will be required before definitive conclusions can be made (courtesy of Dr. Jaglowski and colleagues [13]).

fatigue and tumor lysis (two patients each). There were no discontinuations due to AEs and no deaths on study. At a median follow-up of 4.9 months, 16 patients completed BR and 14 patients were still receiving BR; the ORR was 93% (28/30 patients) (CR was 13%, PR was 80%). Responses appeared to be independent of high risk clinical or genomic features. The majority of patients (77%) remained on study at the time the data were presented; reasons for discontinuation included two with progressive disease (PD) and five stem cell transplants.

With regard to the FCR + ibrutinib cohort, there were only three patients treated. Enrollment to the FCR cohort was suspended at only three patients due to poor enrollment, as patients were required to be fludarabine-naive. The therapy was well tolerated with only one serious AE (neutropenic fever). All patients were able to complete six cycles of FCR. The ORR was 100% (3/3), with two confirmed minimal residual disease (MRD)-negative CRs (MRD-negative at 10^{-4} by four-color flow cytometry).

Clinical development and future perspectives

The present data demonstrate that ibrutinib through multiple mechanisms, through BCR signaling and inhibition of adhesion and migration of CLL cells, leads to rapid onset of response, a favorable safety profile and durable remissions across all the early phase clinical studies. Ibrutinib as monotherapy should be explored further, as it may represent a new non-cytotoxic treatment strategy for CLL. Nevertheless, the high ORR, long remission duration and good tolerability compare very favorably with historical controls, particularly in patients with high risk disease, warranting additional investigation of this drug in future randomized phase III trials.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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