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PCI-32765, the First BTK (Bruton's Tyrosine Kinase) Inhibitor in Clinical Trials

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Abstract

Ibrutinib is a potent covalent kinase inhibitor that targets BTK. BTK, or Bruton's tyrosine kinase, is an obvious target for therapy of B cell diseases because inactivating mutations lead to B cell aplasia in humans and the disease X-linked agammaglobulinemia. Ibrutinib has modest cytotoxicity against CLL cells in vitro but also blocks trophic stimuli from the microenvironment. As with other inhibitors of the BCR pathway, ibrutinib causes rapid nodal reduction and response associated with rapid increase in lymphocytosis, which then returns to baseline over time. The ORR of ibrutinib in relapsed refractory CLL is 67 % with PFS 88 % at 15 months. In a cohort of untreated patients 65 years and over, the estimated 15 month PFS is 96 %. Registration trials have been initiated, and the difficult task that remains is to determine where in the course of CLL therapy this drug will have the greatest impact and benefit for patients.

Keywords

PCI32765; BTK; kinase; lymphocytosis; CLL

Introduction

Chronic lymphocytic leukemia (CLL) remains the most common leukemia of adults, and is incurable. Although generally considered indolent, most patients will ultimately die of the disease[1]. Current therapies are effective in inducing initial remission in most patients who can tolerate them, but these therapies are not curative, and resistance ultimately develops[2–4]. In addition, given that the median age of onset of CLL in the United States is 72 years, many older patients are not candidates for the newer more effective chemoimmunotherapy regimens like fludarabine, cyclophosphamide and rituximab (FCR)[3, 4]. Alternative approaches that remain effective in relapsed disease and are well tolerated by elderly patients with comorbid disease are urgently required[5]. Recent results of early clinical trials of targeted kinase inhibitors have suggested that these drugs have the potential to do both, and have, therefore, generated great excitement in the CLL community[6]. This review will focus on one of the most promising of these drugs, PCI-32765, now known as ibrutinib, the first inhibitor of Bruton's tyrosine kinase to enter clinical trials.

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BTK as a Target in B Cell Diseases

The central role of BTK in B cell function is underscored by the human disease X-linked agammaglobulinemia, or Bruton's agammaglobulinemia, which is caused by loss of function mutations in BTK[7]. These mutations result in the virtual absence of all B cells and immunoglobulins, leading to recurrent bacterial infections. The BTK protein itself is a Tec family nonreceptor tyrosine kinase which is activated by SYK following B cell receptor stimulation and which is then required for downstream events including calcium release, activation of the NFκB and NFAT pathways, and cell survival and proliferation[8].

Ibrutinib (PCI-32765) as an Inhibitor of BTK

Ibrutinib is a potent inhibitor of BTK that binds covalently to Cys-481 in the active site of BTK, resulting in inhibition of kinase activity with IC_{50} 0.5 nM[9]. Ibrutinib does have significant activity (IC_{50} < 100 nM) against 19 other kinases, including seven with a cognate cysteine residue[9]. These include BLK, BMX, ITK, TEC, EGFR, ERBB2, and JAK3[9]. However, in the B cell lymphoma cell line DOHH2, a fluorescently tagged derivative of ibrutinib bound only to BTK[9]. In that same cell line ibrutinib was able to block autophosphorylation of BTK and the subsequent phosphorylation of PLCγ and ERK in response to BCR pathway activation. A concentration of ten nM was sufficient to fully occupy the active site of BTK, and blockade was irreversible[9]. These data were sufficiently encouraging that the efficacy of the drug was tested in spontaneous lymphomas in dogs, and three of eight dogs showed partial response[9].

Multiple groups have now studied the effects of ibrutinib in CLL cells in vitro. Induction of apoptosis in vitro is modest, but ibrutinib also blocks signaling and activation in response to BCR and CD40 pathway stimulation, and disrupts the protective effect of stromal cell co-incubation[10]. Ibrutinib can also block integrin-mediated adhesion to fibronectin, as well as signaling and homing in response to CXCL12 and CXCL13[11, 12]. Secretion of the cytokines CCL3 and CCL4, normally stimulated by BCR activation, is also markedly reduced by ibrutinib[12]. Taken together, these data suggest that ibrutinib may work at least in part by modulating the interaction between CLL cells and the microenvironment, rather than by direct cytotoxicity. As discussed below, the data from clinical trials further support this hypothesis.

Early Clinical Experience

The initial phase I study of ibrutinib enrolled patients with B cell lymphomas including CLL, and evaluated five cohorts with punctuated dosing (28 days on, 7 days off) and two cohorts with continuous dosing[13]. Fifty-six patients were enrolled with a median of three prior regimens. No dose limiting toxicities were observed and the drug was well-tolerated. BTK occupancy was assessed by a competitive binding assay in which the probe binds to the target cysteine residue in the absence of drug, but is excluded from binding when drug has previously bound. Using this assay, BTK occupancy was found to be complete at doses ≥ 2.5 mg/kg. Although the half-life of the drug is 6 – 11 hours, occupancy and BTK inhibition remain complete for 24 hours due to the irreversible covalent nature of binding. Doses of 420 and 840 mg were selected for further study.

Of note, in the above phase I study, the overall response rate across all histologies was 60 %, with a 79 % ORR in the 14 CLL patients[13]. The 75 % response rate in four mantle cell lymphoma patients was also notable. The 13 follicular lymphoma patients had a relatively poor response rate of 23 %, while six DLBCL patients had a 17 % response rate. CLL was, therefore, a disease of significant interest for further study. Also of interest on this study was the observation that CLL patients started on drug had rapid shrinkage of lymph nodes along

with an increase in lymphocyte count that would revert back to baseline on the punctuated schedule, when drug was stopped.

Pattern of Ibrutinib Response

This pattern of response was seen to be common to CLL patients as more were studied. CLL specific data were reported at ASH 2010, for 54 patients treated on the phase Ia as well as a phase Ib/II study[14]. What was particularly notable was that 87 % of patients had a dramatic nodal response >50 %, while at the same time many of them showed an essentially immediate increase in lymphocyte count. According to established CLL response criteria, this increase in lymphocyte count was technically consistent with progressive disease (PD) [15]. However, a number of features of this lymphocytosis were not consistent with PD. For example, the increase would generally peak at cycle 1 – 2 and level off. In addition, the elevation in lymphocyte count would persist while patients were taking ibrutinib, but would return to baseline if the drug was stopped on the intermittent schedule. The lymphocyte count would then rise again when drug was resumed. This pattern of disease behavior, namely rapid nodal shrinkage and symptomatic improvement, with simultaneous increase in lymphocyte count, was strongly suggestive of a redistribution phenomenon whereby ibrutinib was causing CLL cells to leave the lymph node and/or bone marrow microenvironment, to circulate in the peripheral blood. This hypothesis was supported by the observation that over time the lymphocyte count would stabilize and then slowly decline in many patients. In addition, in an adoptive transfer TCL1 mouse model of CLL, a similar pattern of response was observed, with increased lymphocyte count while the mice nonetheless showed profound inhibition of CLL growth and clinical benefit[12].

In these initial studies, then, evaluation of response was a bit complicated[15]. In these patients the lymphocyte count might go up five-fold, but would be associated with clinical improvement on all other parameters, and would eventually come down. The investigators involved in these studies, therefore, made a decision that isolated increase in lymphocyte count as described above would not be considered progressive disease, and discordant response between lymphocyte count and lymph node shrinkage would be labeled as discordant response, or nodal response with lymphocytosis. This approach has now been formally endorsed for the evaluation of kinase inhibitors that affect the B cell receptor pathway[16].

Ongoing Clinical Studies of Ibrutinib in CLL

Between May 2010 and July 2011, 117 patients were enrolled in single agent studies of ibrutinib in CLL. Three of these cohorts focused on the relapsed/refractory population, with one cohort each at 420 mg per day and 840 mg per day, and a third higher risk group enrolled at 420 mg per day. Two cohorts focused on previously untreated patients age 65 years and over, with the majority enrolled at 420 mg/day and a small number at 840 mg/day.

Ibrutinib in Relapsed/Refractory CLL

Twenty-seven relapsed/refractory patients were enrolled on a 420 mg/day dosing cohort and 34 on an 840 mg/day dosing cohort[17]. Median follow-up of these cohorts is now up to 17.5 and 13.8 months, respectively, with about 75 % of patients still on study. These patients had a median age of 64 years and a median of four prior regimens. Fifty-four percent had bulky lymphadenopathy > 5cm, and 46 % were fludarabine refractory, where this was defined as a less than 12 month treatment free interval after the most recent fludarabine-containing regimen. Thirty-six percent had 17p deletion, and 79 % had unmutated *IGHV*.

The drug was generally well-tolerated, with the major adverse events including diarrhea, cough, fatigue and URI symptoms. Hematologic toxicity was minor, <10 % grade 3 – 4 neutropenia, anemia or thrombocytopenia in the 420 mg cohort. In the 840 mg cohort, there was a suggestion of more hematologic toxicity, with 21 % grade 3 – 4 neutropenia. Infectious toxicity grade 3 – 4 was seen in 26 % of the 420 mg cohort, but is quite common in relapsed/refractory CLL patients.

The expected pattern of initial rapid nodal response with sometimes marked lymphocytosis was observed. Responses were categorized as CR, PR or SD according to standard IWCLL 2008 criteria[15], and as nodal response with lymphocytosis if nodes decreased by at least 50 % but lymphocyte count was stable or increased. An isolated increase in lymphocyte count was not considered progressive disease in the absence of other signs or symptoms like increase in lymphadenopathy, B symptoms or new cytopenias due to disease. Using these criteria and looking at response development over time in the 420 mg cohort, the cycle 2 response rate was 19 % (all PRs), plus 59 % nodal responses with lymphocytosis. Over time, as the lymphocyte count came down, the nodal responses with lymphocytosis progressively converted to partial or even complete responses, so that at best response at 12.6 months follow-up in the 420 mg cohort, the ORR was 67 % with 4 % CRs and 22 % additional nodal responses with lymphocytosis. Best response was virtually identical in the 420 mg and 840 mg cohorts, so 420 mg was selected as the preferred dose to take forward, particularly given the possible increase in neutropenia in the 840 mg cohort. In addition to the nodal responses, sustained improvements in cytopenias were seen in 58 – 67 % of patients. Interestingly, response rates appeared to be largely preserved, ranging between 61 and 74 %, across different prognostic groups, including 17p deletion, bulky disease, unmutated *IGHV* and refractory disease[17].

Ibrutinib in Previously Untreated CLL/SLL

At ASCO 2012, the results of the phase Ib/II study in treatment naïve CLL patients 65 years of age or older were presented[18]. This study enrolled 26 patients at a dose of 420 mg per day, with median follow-up 14.4 months, and five patients at a dose of 840 mg per day, with 7.4 month median follow-up. The 840 mg cohort stopped enrollment early due to the comparable efficacy and perhaps improved safety of the 420 mg dose level in the relapsed or refractory patients; only four patients were actually treated with the 840 mg dose. The median age of all 31 patients was 71, and 60 % had Rai 3 – 4 disease, and 43 % unmutated *IGHV*. Only two patients had 17p deletion, however, in this untreated cohort. The therapy was well-tolerated, with the most frequent side effects including easily manageable diarrhea, nausea, fatigue, rash and contusion. Grade 3 – 4 toxicities included 13 % diarrhea, 10 % infection and only 12 % hematologic, split between anemia and thrombocytopenia.

Interestingly these treatment naïve patients showed much less increase in absolute lymphocyte count, in contrast to the previously treated cohorts. The ORR was 74 %, with 10 % CRs, and an additional 13 % of patients had nodal response with lymphocytosis. Fifty percent of patients with pretreatment cytopenias, either anemia or thrombocytopenia, showed significant improvement, defined as improvement by at least 50 %, or Hb > 11 g/dL or platelets > 100,000/μl, sustained for two months. All but five subjects remain on study, with treatment discontinuation due to adverse events in four cases and progressive disease in one case. Compared to the previously treated patients, the treatment naïve patients showed faster response, and higher overall and complete response rates. The estimated 15 month PFS in this treatment naïve cohort is an impressive 96 %.

Combination Studies of Ibrutinib in CLL

The extraordinary single agent activity of ibrutinib in CLL raises several possibilities about how to use it in combination. One possibility to consider is to try to obviate the need for chemoimmunotherapy entirely, in an effort to create safer and better tolerated therapy. The second is to consider whether combining ibrutinib with chemoimmunotherapy might be so effective as to raise the possibility of cure. Studies to date are starting to explore both possibilities.

Ibrutinib – Antibody Combinations

The first option of avoiding chemotherapy entirely would probably lead to combination therapy with antibody, most likely CD20 antibody, given the efficacy of the latter in B cell malignancies. Ofatumumab is an anti-CD20 antibody that confers more effective CDC than rituximab against CLL cells that express low levels of CD20. Ofatumumab has been approved for CLL refractory to fludarabine and alemtuzumab based on a 45 % response rate in this setting[19,20]. At ASCO 2012, the Ohio State group presented early results of a single center phase Ib/II study evaluating three different combination dosing regimens of ibrutinib and ofatumumab[21]. Data were presented for one of those dosing schedules, in which ibrutinib is started as a single agent 4 weeks prior to the addition of ofatumumab on cycle 2 day 1. Twenty-seven patients were enrolled with median age 66 years and a median of three prior regimens. Forty-eight percent had advanced Rai stage 3 – 4 disease and 41 % were refractory to purine analogues. Ninety-one percent had unmutated *IGHV*, 37 % had 17p deletion and 33 % 11q deletion.

As might be expected, the addition of ofatumumab brought the early lymphocytosis down rapidly. The ORR was 100 % in the CLL/SLL/PLL patients with 4 % CR (1 CR). Improvement in cytopenias was also seen. Among three patients with Richter's syndrome enrolled in the study, two responded and one remained on study in ongoing response at 10.1 months. At a median follow-up of 9.8 months, 89 % of patients remain on study, with one off for progressive disease, one to undergo stem cell transplant and one deceased. Adverse events were similar to the single agent with the exception of neuropathy, which was seen in 25 % of patients, but was likely more related to ofatumumab than to ibrutinib. Ecchymoses were also seen in almost half of patients, and likely reflect the fact that ibrutinib inhibits platelet function through a direct effect on BTK. The clinical significance of this platelet inhibition is not entirely clear but several intracranial hemorrhages have been observed in patients on all the ibrutinib studies, so caution in combining ibrutinib with anticoagulation or antiplatelet agents is warranted.

Ibrutinib with Chemoimmunotherapy

The second possibility, namely combinations with chemoimmunotherapy, has also begun to be explored in CLL. A phase Ib/II study of ibrutinib with BR and with FCR in relapsed/refractory CLL has been completed and presented at ASCO 2012[22] and EHA 2012[23]. Eligibility was limited to patients with 1 – 3 prior regimens, and for the FCR arm, patients were required to be fludarabine naïve. The latter requirement proved difficult for accrual and as a result the FCR arm was closed to enrollment after only three patients accrued. The treatment program combined continuous dosing with ibrutinib at 420 mg/day with BR at standard relapsed doses, namely 70 mg/m^2 days 1 – 2 with rituximab 375 mg/m^2 in cycle 1, escalating to 500 mg/m^2 for cycles 2 – 6. FCR was also given at the standard MD Anderson doses, to the three patients who enrolled, together with ibrutinib 420 mg/day. Thirty patients were enrolled on the BR arm, with a median age of 62 years, a median of two prior therapies, 53 % with bulky disease and 47 % with Rai 3 – 4 disease at screening. Thirty-seven percent were purine analog refractory and 13 % bendamustine refractory, where

refractory was defined as a ≤ 12 month treatment free interval. Twenty-three percent of patients had deletion 17p and 43 % deletion 11q.

The therapy was well-tolerated with a median of six cycles of BR delivered, and 97 % of the planned ibrutinib dose. Twenty-three percent of patients required a dose reduction of bendamustine. The toxicity was very comparable to the single agent, consisting primarily of easily managed diarrhea, nausea, fatigue and rash. Seventeen percent of patients had grade 3 hematologic toxicity and 10 % grade 4, mostly neutropenia. Serious adverse events included one case of tumor lysis syndrome, two cases of grade 3 cellulitis and one case of febrile neutropenia. The addition of BR obviated the lymphocytosis and led to a 93 % ORR with 13% CRs with a median follow-up of 8.1 months. The CR rate may increase as not all patients have yet had a bone marrow biopsy to establish CR, and are, therefore, currently counted as PRs. The estimated 11 month PFS is 90 %. These data compare favorably to those previously published by Fischer et al. for the BR regimen alone, in which the response rate was 59 %[24].

Only three patients were treated on the FCR arm. They had a median age of 56 years, two of three had bulky disease, and none had 17p or 11q deletion. All three had been treated initially with rituximab and lenalidomide on a clinical trial and, therefore, met the eligibility requirement to be purine analog naïve. FCR-ibrutinib therapy was well-tolerated with all three patients receiving a full six cycles, with one patient having a dose reduction. The ORR was 100 % with two confirmed MRD negative complete remissions. Certainly these data, while preliminary, are encouraging about the potential use of ibrutinib in combination with FCR.

Future Development Plans

Given the extraordinary clinical activity of ibrutinib in these early trials, several phase 3 studies have been or will soon be initiated with the goal of gaining FDA approval for marketing in CLL. The first study is a head-to-head comparison of ibrutinib vs. ofatumumab in relapsed refractory patients who are not candidates for purine analogues. This study known as RESONATE has already started enrollment. The second study which will follow RESONATE is a comparison of BR with ibrutinib vs. BR alone, in early relapsed CLL patients. Additional studies are also planned in upcoming years.

Given the results to date, ibrutinib seems likely to produce results that will lead to its approval for CLL. The more complicated and more important problem that needs to be addressed is how we will most effectively use ibrutinib in the future. Will it be as a single agent or in combination, and if in combination, with antibody or with chemoimmunotherapy? Single agent use or antibody combinations will likely produce mostly partial responses albeit with low toxicity, and this result may be fine if relapses remain rare over extended times. Combinations with chemoimmunotherapy would be designed to achieve negativity for minimal residual disease and ideally very prolonged progression free survival, perhaps even raising the possibility of cure in some cases. In the latter case ibrutinib with chemoimmunotherapy would likely be used more for initial therapy, but the optimal timing of its use is another separate but related question. In addition to use as initial therapy, other options include in relapse or even prior to the requirement for therapy, in order to reduce progression. Ibrutinib could also be used before or after stem cell transplantation, to achieve deeper remission in either setting. At present, the data required to answer these questions is not yet available, but the results of future studies over the next several years will be quite exciting.

Conclusion

Ibrutinib is an oral irreversible inhibitor of BTK which is showing dramatic activity in CLL, likely through modulation of the interaction between the CLL cells and the microenvironment, as well as a possible component of direct cytotoxicity. Although most responses are partial, relapses to date have been few, resulting in excellent PFS on all studies thus far. Registration trials have initiated with the single agent, and additional trials will soon follow. What remains is the difficult work of determining how to optimally integrate ibrutinib into the care of CLL patients, which if the current results hold, may in fact be revolutionized by this exciting drug.

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Table 1

Clinical Trials with Ibrutinib

Study	N	ORR	CR	PFS
Single Agent:				
Relapsed/Refractory[17]	61	67%	4%	88% at 18 months
Treatment Naive[18]	31	74%	10%	96% at 15 months
Combinations:				
Ibrutinib + BR[22,23]	30	93%	13%	90% at 11 months
Ibrutinib + FCR[23]	3	100%	67%	100% at 11 months
Ibrutinib + Ofatumumab[21]	27	100%	4%	89% on study at 10 months