How will B-cell-receptor–targeted therapies change future CLL therapy?

Jeffrey A. Jones1,2 and John C. Byrd2

1Division of Medicinal Chemistry, College of Pharmacy, and 2Division of Hematology, Department of Internal Medicine, The Ohio State University, Columbus, OH

For many years there has been considerable disassociation between the understood biology of chronic lymphocytic leukemia (CLL) and the therapeutics used to treat this disease. With the introduction of the first targeted CD20 antibody rituximab and its addition to chemotherapy came the first observation that minimal residual disease–negative (MRD-negative) complete responses (CRs) could be obtained with dramatically improved progression-free survival and overall survival. This advance was soon to be surpassed by the introduction of therapeutics that target B-cell receptor (BCR) signaling. New data show that BCR-inhibiting agents are very active for the treatment of relapsed CLL, despite the lack of MRD-negative CR, with durability of response being considerably more impressive than previously observed with other agents not producing MRD-negative CRs. This perspective provides a view of where these agents may take us in the future as CLL therapy evolves with this exciting new class of drugs. (Blood. 2014;123(10):1455-1460)

Introduction

Recognition that B-cell receptor (BCR) signaling is essential for the proliferation and survival of chronic lymphocytic leukemia (CLL) cells stands as one of the most important insights into the pathobiology of the disease. Accumulated evidence supports that antigen-dependent and independent BCR signaling plays a central role in the pathogenesis of CLL (reviewed in Stevenson et al1 and Woyach et al2). Well-characterized molecular markers correlated with adverse prognosis, such as unmutated immunoglobulin heavy-chain chains3 and ZAP-704,5 expression, are now understood to be associated with and/or potentiate BCR-signaling activity, likely accounting for the more rapid progression of disease in cases where these features are present. Examination of CLL cells in the blood, bone marrow, and nodal compartment demonstrates that the BCR pathway is activated in the former two with enhanced proliferation of tumor cells.6 This matches the current concept of CLL expanding as a consequence of proliferation centers in the bone marrow, lymph nodes, and spleen. More recently, kinases immediately downstream of the BCR, including spleen tyrosine kinase (SYK) and phosphatidylinositol 3-kinase (PI3K), have been found to be constitutively activated in the majority of CLL patients.7,8 These kinases and downstream amplification kinases such as Bruton agammaglobulinemia tyrosine kinase (BTK) appear essential not only for activation of multiple survival pathways (Akt, Erk, nuclear factor κB) but also for chemokine-mediated migration and adhesion of B cells in the microenvironment.

Several small molecules have been developed to inhibit a variety of kinases in the BCR pathway, including LYN, SYK, BTK, and PI3K, with varied specificity. Pharmacologic inhibition of these kinases promotes apoptosis of CLL cells in vitro.9-12 After treatment with the SYK inhibitor fostamatinib,13 the first BCR-targeted agent to reach the clinic, rapid reduction in nodal volume, disease-related symptoms, and cytopenias was accompanied by a so-called “redistribution lymphocytosis.” This phenomenon is now recognized as a class effect of BCR antagonists, further supporting the role of BCR signaling in homing and retention of CLL cells within their supporting microenvironment and does not constitute progressive disease.14 The emergence of orally bioavailable, relatively nontoxic inhibitors of BCR-signaling kinases, particularly those directed at BTK and the p110δ PI3K isoform, represents not only a triumph of translational science but also a therapeutic advance of as yet undetermined clinical implications for CLL. As data emerge from clinical trials with these and other highly active therapies, clinicians caring for CLL patients are left with questions of how best to incorporate these agents into their treatment approaches.15 This article provides some insight on how these agents might alter future CLL therapy.

BCR-signaling antagonists in late-stage clinical development

PI3K

Idelalisib (CAL-101, GS-1101) is a first-in-class, selective oral inhibitor of the p110δ isoform of PI3Kδ. Preclinical work with this molecule demonstrated that this small molecule inhibited both intrinsic and extrinsic survival signals, including those generated by BCR signaling in CLL.9,16,17 and prior studies of a PI3Kδ mutant mouse suggested predominantly a B-cell phenotype, further supporting targeting this kinase.18 A phase 1 study that enrolled 54 patients with heavily pretreated relapsed/refractory CLL treated them with continuous once- or twice-daily doses ranging from 50 to 350 mg per dose.19 Responses, characterized by regression of lymphadenopathy and organomegaly and normalization of cytopenias, were observed within weeks of starting treatment (median, 1.9 months). After a median 9 months of drug exposure, an overall response rate (ORR) of 39% using the International Workshop on...
Chronic Lymphocytic Leukaemia (IWCLL) 2008 criteria was observed. Nodal response (>50% reduction from baseline) was observed in a larger proportion of patients (81%) who did not meet criteria for objective response, largely as a consequence of persisting peripheral blood lymphocytosis. Median progression-free survival (PFS) was 17 months; it increased to 29 months for those receiving 150 mg twice per day or greater. Dose-limiting toxicities were not observed, and potentially treatment-related adverse events (chiefly fatigue, rash, diarrhea, respiratory tract infections, and reversible increases in hepatic transaminases) resulted in discontinuation of treatment in only 7% of patients. Because PI3Kδ influences clonal expansion and differentiation of suppressor T cells, some of these events, particularly diarrhea and/or colitis, may represent on-target toxicities of idelalisib.20–22

IPI-145 is the second PI3K-targeted agent to enter clinical development. IPI-145 potently inhibits both the p110δ and p110γ isoforms of the enzyme at pico- and nanomolar concentrations, respectively. Clinically, a lower dose of 25 mg twice daily predominately inhibits p110δ, while the maximally tolerated dose of 75 mg twice daily appears to inhibit both isoforms. Preliminary results of the phase 1 trial were recently presented.19 Relapsed/refractory CLL patients (N = 34; 22 evaluable for response) were treated with escalating doses from 8 to 100 mg twice per day; at the higher dose, 2 dose-limiting toxicities were reported (grade 3 rash, grade 3 elevation of hepatic transaminases). The median time to response (1.9 months) and pattern of response (ORR, 55%) was similar to the δ-specific agent. Similar to idelalisib, the nodal response rate was impressive (87%), and responses were observed without regard to genetic features or extent of prior therapy. However, the addition of p110γ inhibition at higher doses of IPI-145 appeared to result in more significant immune suppression; Pneumocystis pneumonia has been observed, and prophylaxis for opportunistic infections will be mandated going forward. Accrual continues to expansion cohorts enrolling both relapsed/refractory and treatment-naïve disease.

BTK

The first BTK inhibitor to enter the clinic was the orally bioavailable, irreversibly binding small molecule ibritinib (PCI-32765).23 Mutation of BTK also occurs naturally in humans, resulting in a phenotype characterized by humoral insufficiency. Preclinical work with ibritinib in CLL demonstrated inhibition of both intrinsic and extrinsic survival signals mediated by BTK.24,25 A phase 1 study of ibritinib in B-cell malignancies was initiated in which durable clinical activity was noted in non-Hodgkin lymphoma and 9 of 16 CLL/small lymphocytotic lymphoma patients.26 No dose-limiting toxicity was identified, and toxicity, including myelosuppression, was modest. In a recently published phase 1b study of ibritinib, 85 patients with relapsed/refractory CLL/small lymphocytotic lymphoma were enrolled at two different doses (420 or 840 mg daily).27 Extended therapy with ibritinib was well tolerated, with common adverse events including grade 1 to 2 diarrhea, cough, fatigue, upper respiratory infections, nausea, fever, peripheral edema, myalgias, and petechiae/ecchymoses. Most adverse events with ibritinib resolved despite continued treatment. Grade 3 or greater infections occurred more frequently early in therapy; the average rate per 100 patient-months within the first 6 months was 7.1 but 2.6 thereafter. After subarachnoid hemorrhages were reported in several patients receiving concomitant warfarin treatment, but not other anticoagulants or antiplatelet agents, concurrent therapy with oral vitamin K antagonists has been prohibited. Further, the manufacturer has provided guidance for holding the drug around the time of invasive procedures. BTK does not appear essential for platelet activation, but a role for BTK inhibition in stable thrombus formulation has been postulated.28 Yet despite the fact that platelets from patients with X-linked agammaglobulinemia demonstrate abnormalities of collagen and collagen-related peptide-induced aggregation,29 bleeding diatheses are not observed clinically.30

Ongoing randomized trials will help better characterize the potential risk for significant bleeding complications attributable to pharmacologic BTK inhibition.

Like other BCR antagonists, an early increase in lymphocytosis is typically noted by day 7 and persists for 2 to 3 months before slowly declining over time, concomitant with notable reduction in lymph node and spleen size and improvement in cytopenias. The ORR by IWCLL 2008 criteria31 was 71% (2 complete responses [CRs], 34 partial responses) in the 420-mg cohort and 71% (24 partial responses) in the 840-mg cohort. In addition, 10 (20%) and 5 patients (15%) in the 420-mg and 840-mg cohorts, respectively, demonstrated a nodal response with persistent lymphocytosis. Response to ibritinib did not vary on the basis of any adverse feature previously identified in CLL. Most notably, of the 28 patients with del(17p) enrolled on this study, 18 (68%) responded. The 26-month estimated PFS for all patients enrolled on this study was 75%. Unlike response, PFS did differ by genomic group; 26-month estimated PFS was 56% for patients with either del(11q22.3) or del(17p13.1) vs 93% in patients without either of these abnormalities. Collectively, these suggest that ibritinib remissions are quite durable compared with other therapies used in this setting.

Kinase inhibitors and the future of CLL therapy: unanswered questions

There can be no question that the widespread availability of BCR-signaling antagonists will rapidly alter the nature of CLL therapy (Table 1). How they will be used is in part dependent upon the labeled indications, unknown until regulatory agency approval, as well as the outcomes of several ongoing registration studies (Table 2). Nonetheless, the efficacy, durability of remission, and safety profile of ibritinib for most patients will likely lead to rapid adoption in the salvage setting. And while available data suggest that the efficacy, durability of remission, and safety profile of single-agent idelalisib may be less impressive compared with ibritinib, that drug also appears to represent a significant advance over many options CLL patients today receive in the setting of relapse. Idelalisib application might therefore be narrowed initially to patients not appropriate for ibritinib, such as those on warfarin or those who are intolerant of the drug. However, beyond merely replacing older agents in the routine management of CLL, these new agents raise more fundamental questions about the changing natural history of the disease, goals of treatment, and even the prospect of curative therapy. We raise several of these as yet unanswered questions below and provide perspective on each.

Are “remission” and “disease control” still synonymous?

Long-term disease control of CLL in the chemoimmunotherapy era has strongly correlated with quality and depth of remission.32 Achievement of minimal residual disease-negative (MRD-negative) CR after fludarabine-based chemoimmunotherapy has predicted not only longer time to treatment failure but also prolonged PFS and overall survival (OS).32 Failure to achieve at least a PR after
fludarabine, cyclophosphamide, and rituximab therapy generally bodes a dismal prognosis, particularly among patients with genetically high-risk disease.33 On the other hand, most patients treated with BCR-signaling antagonists ultimately achieve durable but no better than partial remissions, and CRs have rarely been observed after single-agent therapy. Although data are limited, bone marrow biopsies typically demonstrate persistence of disease that slowly diminishes over time, even when peripheral blood lymphocytosis and lymphadenopathy are resolved.

Strikingly, long-term remissions are observed, even among patients who never achieved resolution of peripheral blood lymphocytosis. Duration of response, then, may not necessarily correlate with depth of response after kinase inhibitor therapy, and remission may not be necessary to effect durable clinical benefit, provided therapy is continued. The ability to continue BCR-directed therapy for an extended period of time differentiates it from chemotherapy approaches in which this is generally prohibitively toxic. These observations have already prompted reassessment of consensus criteria for clinical trial outcomes,14,31 but they might necessarily prompt a more general re-examination of the end points for CLL therapy. Intermediate end points such as response, appropriate for a relapsing/remitting natural history, may ultimately prove inappropriate when the disease is chronically controlled and the treatment is continuous rather than episodic. Freedom from disease-related complications (infection, transfusion, autoimmune phenomenon) and survival end points will likely emerge as more meaningful outcome measures. CLL investigators will undoubtedly need to develop new intermediate end points predictive of disease outcome that can be efficiently incorporated into clinical trial designs.

On the other hand, enthusiasm for long-term maintenance therapy with drugs, which as single agents promote durable disease control without achievement of MRD-negative remission, must be tempered by related concerns for patient adherence and cost. Here the imatinib experience is informative. Adherence to kinase inhibitor therapy has been associated with the achievement of important treatment end points in chronic myelogenous leukemia such as major molecular response.32 However, factors influencing adherence to oral cancer therapies are poorly understood, and validated strategies to promote compliance are likewise limited.33 There is increasing concern that economic hardship could limit patients’ abilities not only to elect but also to adhere to newer, more effective therapies.36 Although patients’ collective compliance with prescribed medications may be cost-saving from a health system perspective, out-of-pocket costs to individual patients for ever more costly therapies remains an unresolved issue.37,38 While the costs of these newer BCR kinase inhibitors are as yet a matter of speculation, clinicians are rightly concerned for the price tag of innovation.39

<table>
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<th>Agent</th>
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<td>Ofatumumab vs ibrutinib</td>
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</table>

Do accepted genetic risk models still hold in the kinase inhibitor era?

Treatment guidelines currently recommend that patients with short remissions after chemoimmunotherapy or those with del(17p13.1) consider aggressive therapeutic interventions, including reduced-intensity allogeneic stem cell transplantation, as part of initial therapy.40,41 Although the experience with BCR inhibitors is relatively immature to date, patients with del(17p13.1) demonstrated 57% PFS at 26 months in the initial report of ibrutinib, irrespective of the number of prior treatments.27 In general, patients on these agents feel well and often elect to defer this stem cell transplantation if possible. As ibrutinib data have matured, our own practice has been to counsel patients about all available data but to strongly recommend allogeneic transplantation only to CLL patients who either responded poorly to ibrutinib or who lacked subsequent cytoreductive options that could render transplantation impossible in the event of ibrutinib breakthrough. As genetic mechanisms of resistance to ibrutinib become better characterized, sensitive monitoring techniques for their emergence might also prompt this recommendation.

Perhaps the more pressing concern as BCR inhibitors approach widespread application in the clinic is a more complete understanding of the molecular and genetic factors underlying and predicting for drug resistance. Little data has yet been presented regarding potential mechanisms of idelalisib resistance, and the first report describing mechanisms of resistance among ibrutinib-treated CLL patients has only recently been presented. In the latter case, treatment-emergent single nucleotide variations encoding a cysteine-to-serine substitution at position 481 of BTK (C481S), impairing covalent binding of ibrutinib to BTK, and a potential gain-of-function mutation (R665W) substitution in PLCδ1, have been identified.42 Pretreatment factors predicting emergence of resistance are poorly characterized, although the majority of treatment failures appear to occur among patients with adverse genetic risk features such as complex karyotype, del(11q22.3), and del(17p13.1). The mechanism by which this occurs is uncertain at this time. Whether BCR-inhibitor therapy will influence the natural history of relapsed disease (ie, emergence of Richter’s transformation, clonal evolution) is an important question to which emerging data from randomized studies will hopefully provide a rapid answer.

What is the rationale for combination therapy and which combinations are rational?

Initial trials of both ibrutinib- and idelalisib-based combination therapies have also been conducted. Early results from a phase 1b/2 study of ibrutinib in combination with the standard dose and schedule of ofatumumab have been presented,43 and a more recent phase 2 study exploring conventional doses of rituximab in combination with ibrutinib is ongoing.44 In both studies, redistribution lymphocytosis appears to be attenuated, peaking earlier and resolving more rapidly. Responses have been observed across all commonly accepted genetic risk groups, including del(17p13.1).43,44 Encouraging responses were likewise observed when patients were treated with standard-dose bendamustine and rituximab in combination with ibrutinib.45 The ORR of the combination was 93%, including 71% (14% CR) in the del(17p) subset. Notably, prior studies have failed to report CRs after bendamustine and rituximab treatment of...
of combination chemotherapy are reimagined for a new era and mechanistically distinct targeted agents with nonoverlapping toxicities are combined. For instance, combinations of BCR-signaling antagonists targeting different kinases in the same pathway could optimistically inhibit BCR signaling and potentially prevent emergence of resistance. Alternatively, an equally attractive approach recapitulates in reverse the genetic experiment showing BCL2 rescues BTK-deficient B lymphocytes in normal murine B cells. CLL is a disease in which BCL2 is overexpressed that also appears to be influenced by BTK inhibition. ABT-199, a small molecule inhibitor of BCL2, might be rationally combined with ibritinib in this setting, given the promising results emerging from phase 1 studies. Combinations using immunomodulatory agents also have strong preclinical rationale. For instance, lenalidomide has been shown to inhibit T-regulatory T cells, polarize Th2 T cells to a Th1 phenotype, and enhance natural killer cell function. In CLL patients, these immune-modulating properties of lenalidomide effects T-cell immune synapse repair, observed even when lenalidomide is given at relatively low doses. Ibrutinib, via ITK-mediated inhibition of Th2 T cells, has complementary immune-modulating potential. Combination therapy to target immune reconstitution in CLL remains appealing. Such pairings might also limit the toxicity of combination therapy, mindful that drug-drug interactions mediated by cytochrome P450 enzymes may be a consideration in combining many of these agents. For instance, sequential administration of kinase inhibitors might also attenuate the risk for tumor flare induced by lenalidomide. Clinical trials with these combinations are of great interest.

Can initial treatment with biologically based therapy change the natural history of disease?

There are as yet limited data with BCR-signaling antagonists for previously untreated, symptomatic CLL. A study of 31 patients age 65 years or older who were treated with ibritinib has been preliminarily reported. The median age was 71 years, and more than half had advanced Rai stage disease. Only 9% of patients had high-risk genomic features, either del(11q22.3) or del(17p13.1). The ORR by IWCLL criteria was 71%, and an additional 13% achieved PR with lymphocytosis. At median 24 months of follow-up, PFS and OS were 96%. Toxicity was similar to that observed in patients treated for relapsed disease. These results are quite remarkable but only consider predominately low-risk genomic patients. Wiestner et al at the National Heart, Lung, and Blood Institute have reported a small cohort of 15 previously untreated del(17p13.1) patients in whom PFS was 87% at 15 months. Data with idelalisib are available in the same patient population but only when idelalisib is combined with rituximab. A phase 1b study included 64 elderly treatment-naive patients treated with 8 weekly doses of rituximab in combination with idelalisib administered continuously at 150 mg twice per day for 48 weeks, after which time responding patients could continue idelalisib maintenance. Outcomes presented for the first 50 patients included an ORR of 97% (19% CR). PFS at 24 months was 93%, including all 9 patients with poor-prognosis TP53 mutation or del(17p).

The availability of these highly active BCR-signaling agents certainly merits their incorporation into investigational frontline regimens, such as the ongoing Resonate-2 study comparing ibritinib to chlorambucil and the forthcoming Alliance A041202 study of untreated CLL patients age 65 and older, which will include 3 arms (bendamustine + rituximab, ibritinib + rituximab, or ibritinib alone). These trials essentially seek to eliminate chemotherapy from the initial treatment approach for elderly patients with CLL. Another approach particularly adaptable to young patients (age <65-70 years) will address the question of adding BCR-signaling agents to highly effective chemoimmunotherapy in hopes of affecting MRD-negative disease and potentially cure of CLL patients.

Can early intervention with biologically based therapy change the natural history of disease?

Newly diagnosed CLL patients learn that the disease is highly treatable but ultimately incurable. Early intervention with cytotoxic chemotherapy failed to alter the natural history of disease, and results of trials using chemoimmunotherapy in that context have not yet been reported. Consensus treatment guidelines for CLL therefore recommend that therapy be withheld until symptoms intervene or the disease progresses to an essentially arbitrary measure of burden.

Table 2. Selected BCR-signaling antagonists in clinical development for CLL indications

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Manufacturer</th>
<th>Study phase</th>
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<td>BTK</td>
<td>Ibrutinib (PCI-32765)</td>
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<td>ONO-WG-307</td>
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Consequently, much CLL therapy is directed at the alleviation of rather than the prevention of morbidity. But progressive declines in immune function are measurable long before treatment is indicated, and most existing therapies not only fail to reverse that damage but in many cases exacerbate the problem.

An overall reconsideration of the relative risks and merits of early intervention for asymptomatic disease is also now warranted. Particularly when high-risk cytogenetic features are present, a rationale for early intervention persists, since these remain the patients most likely to relapse during BCR kinase-directed therapy. Yet the favorable toxicity profile suggests that we might also upend the conventional wisdom of deferring therapy in elderly populations. Earlier intervention in elderly patients with low-grade lymphoma has been advocated as a strategy to prevent progression to more advanced disease when therapy is less well tolerated. We might then consider clinical trials investigating early intervention in elderly CLL to prevent the morbidity complications of progressive disease and immune dysfunction among a patient population ill-equipped to tolerate the most effective conventional therapies. Trials designed to rigorously assess the clinical benefits of treatment, broadly understood, might substantially improve the lot of the average CLL patient often excluded from clinical trials. Not only the BCR-signaling agents but also immune restorative agents such as lenalidomide might be considered in this context.

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Correspondence: Jeffrey Jones, The Ohio State University, A350B Starling Loving Hall, 320 West 10th Ave, Columbus, OH 43210; e-mail: jjeffrey.jones@osumc.edu; and John C. Byrd, The Ohio State University, CCC Bldg Room 455B, 410 West 12th Ave, Columbus, OH 43210; e-mail: john.byrd@osumc.edu.

References


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