

# Spotlight on ibrutinib and its potential in frontline treatment of chronic lymphocytic leukemia

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**Abstract:** Chronic lymphocytic leukemia (CLL) is the most prevalent leukemia in the adult population. Current efforts are focused on better understanding the intricate pathophysiology of the disease to develop successful targeted therapies. Ibrutinib is emerging as an important agent in this new age of targeted treatment for CLL. As a Bruton's tyrosine kinase inhibitor, it blocks the signaling pathway that malignant B-lymphocytes need for growth and maturation. Ibrutinib's role in therapy was further expanded recently when the US Food and Drug Administration approved its use in both frontline and salvage treatment for patients with CLL. This review assesses the effectiveness of ibrutinib in the frontline setting, its efficacy in various types of patients with CLL, and its safety and tolerability.

**Keywords:** ibrutinib, CLL, frontline therapy

## Background

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western adult population.<sup>1</sup> In 2015, ~14,620 new CLL cases were reported in the USA. CLL is more prevalent among whites, in particular males, and the median age at diagnosis is 72 years.<sup>2</sup> The hallmark of this disease is the accumulation of clonal B lymphocytes in the bone marrow, peripheral blood, and lymphoid tissues. These lymphocytes have a characteristic immunophenotype with co-expression of CD5, CD19, and CD23; expression of CD20<sup>dim</sup>, CD79b, and surface immunoglobulins (sIg); and Ig light chain restriction.<sup>3</sup> Constitutive activation of B-cell receptor (BCR) signaling is also a hallmark of CLL. This signaling pathway is critical for B-cell survival<sup>4,5</sup> and has a central role in proliferation, apoptosis, differentiation, and cell migration during normal B-cell development. Stimulation of the BCR depends on phosphorylation of Bruton's tyrosine kinase (BTK), a kinase located downstream of the BCR. The development of novel inhibitors that target these specific kinases responsible for BCR signal transduction, such as BTK, has revolutionized the treatment of CLL. Consequently, treatment guidelines for this disease have also been updated.

## Indication for therapy in CLL

CLL is a remarkably heterogeneous disease with a variable clinical course. Although a small proportion of patients may never require clinical intervention, most patients eventually need treatment at some point in their disease course. The pattern of disease progression also varies among patients. Thus, there are multiple indications for initial treatment of CLL, including rapidly proliferating lymphocytosis, bulky lymphadenopathy, disease-associated cytopenias, and worsening constitutional symptoms. Specific indications for treatment based on the 2008 International Workshop

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on Chronic Lymphocytic Leukemia (IWCLL)-sponsored Working Group recommendations are summarized in Table 1.<sup>6</sup> Multiple factors, including patient age, performance status, comorbidities, molecular markers, and cytogenetic characteristics, must be considered before selecting the optimal treatment regimen and initiating therapy for patients with CLL.

## Risk stratification in patients requiring frontline therapy

Once a CLL patient presents with an indication for frontline treatment, it is essential to evaluate the patient's disease characteristics and overall performance status before deciding on the appropriate therapy. One of the primary considerations is patient's age. Typically, a patient >65 years would not be considered as a candidate for frontline chemoimmunotherapy, either with fludarabine, cyclophosphamide, and rituximab (FCR) or with combined bendamustine and rituximab (BR). These regimens have higher toxicities in this population, most notably myelosuppression, and associated infective complications.<sup>7</sup> In addition, older patients do not respond as well to chemoimmunotherapy, as demonstrated by the lack of improvement in their progression-free survival (PFS) and overall survival (OS) statistics.<sup>8</sup> The standard-of-care treatment in this patient population is chlorambucil combined with a CD20-targeting monoclonal antibody such as rituximab, obinutuzumab, or ofatumumab. The median PFS in patients receiving chlorambucil and CD20-targeting monoclonal antibodies combination therapy was between 16 and 29 months, whereas in patients receiving chlorambucil monotherapy, the median PFS was between 11 and 13.1 months.<sup>9</sup> The German CLL Study Group reported median PFS of 26.7 months with obinutuzumab–chlorambucil combination, and 16.3 months with rituximab–chlorambucil, compared with PFS of 11.1 months with chlorambucil alone.<sup>10</sup> For physically fit

patients who are <65 years, chemoimmunotherapy is still an option, given the possibility of long-lasting remissions in patients with favorable prognostic factors.

Any underlying medical conditions, if present, also influence the choice of treatment. Patients with renal insufficiency have a higher risk of toxicity with many chemotherapy agents including fludarabine and bendamustine, due to delayed excretion and metabolism of the drugs.<sup>11</sup> It is thus prudent to consider agents that have milder adverse effects or that have less impact on renal function. For patients with a history of hepatitis, special consideration must be made before initiation of treatment with CD20 monoclonal antibodies, since their use has been associated with reactivation of viral hepatitis.<sup>12</sup> Patients with chronic comorbidities including chronic obstructive pulmonary disease, diabetes, and congestive heart failure are at higher risk of infective complications while receiving therapy; thus, therapy choices for these patients should include agents with fewer myelosuppressive effects and carefully selected antimicrobial prophylaxis.<sup>13</sup>

The somatic hypermutation status of the immunoglobulin heavy chain variable (*IGHV*) gene is yet another factor to consider when making treatment decisions. As part of the natural maturation of B cells, mutations are introduced into the *IGHV* genes, equipping the B cells with the ability to confront foreign elements as part of the immune response.<sup>14</sup> Patients whose CLL cells have <2% deviation from the germ line and thus have fewer introduced mutations are classified as having unmutated *IGHV*, whereas those with >2% deviation are classified as having mutated *IGHV*. Patients with unmutated *IGHV* have a poorer prognosis and have fewer lasting responses to chemoimmunotherapy combinations.<sup>15</sup>

Genomic abnormalities that are identified by fluorescence in situ hybridization studies before the start of therapy are very important, particularly in patients with del17p. Various studies have reported that patients with TP53 deletions (deletion 17p13.1) have more aggressive disease characteristics due to the role of these genes in maintaining genomic stability.<sup>16</sup> The *TP53* gene is a key part of tumor suppression since it codes for a protein that regulates cell division and prevents cells from undergoing uncontrolled duplication.<sup>17</sup> Because part of the mechanism of action of chemotherapeutic agents is initiating apoptosis by stimulating the DNA damage response pathway, patients with deletions in the *TP53* gene do not respond as effectively to therapy.<sup>18</sup> Overall, a *TP53* deletion, due to its direct involvement in tumor suppression, is commonly viewed as the worst prognostic marker in CLL and is associated with the most rapidly advancing disease.<sup>19,20</sup>

**Table 1** Indications for treatment initiation according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL)<sup>6</sup>

1	Advanced clinical stage of the disease (Rai stage III or IV, Binet stage C)
2	A significant or progressive lymphadenopathy (longest dimension >10 cm) or splenomegaly (>6 cm below the costal margin)
3	Cytopenia due to disease progression or autoimmune disorders (lack of response to corticosteroids or other standard treatments)
4	General symptoms (weight loss, fever, fatigue, infection)
5	Lymphocyte doubling time of <6 months or an increase of >50% in <2 months (in patients with lymphocytosis <30 g/L, this doubling time should not be the only indication for treatment)
6	Richter transformation

## Ibrutinib

Ibrutinib is classified as a BTK inhibitor. BTK is a member of the TEC kinase family and has been implicated in the pathogenesis of several B-cell disorders, including CLL. BTK is a signaling molecule in the B-cell antigen receptor and in cytokine receptor pathways. Without functional BTK molecules, malignant tumor B cells fail to receive appropriate growth and maturation signals.<sup>21</sup> Blocking BTK-initiated pathways thereby renders CLL cells unable to proliferate. Specifically, ibrutinib works by selectively and irreversibly binding the Cys-481 residue in the allosteric inhibitory domain TK/SH1 of BTK. Selective binding of the Cys-481 residue inhibits autophosphorylation of BTK at Tyr-223, preventing the activation of BTK.<sup>22,23</sup>

### Pharmacology

Ibrutinib is orally administered and rapidly absorbed, with a peak plasma concentration at 2 h after dosing. A phase 1, open-label, dose-escalation trial demonstrated that administration of ibrutinib in fasting patients, compared with its co-administration with food, reduced absorption by ~60%.<sup>24</sup>

Ibrutinib is metabolized primarily in the liver through CYP3A. Co-administration of ibrutinib with CYP3A inhibitors is not recommended because strong CYP3A inhibitors can increase the concentration of ibrutinib 24- to 29-fold.<sup>25</sup> The metabolites of ibrutinib are primarily eliminated in feces, with <10% being eliminated by the kidneys.<sup>23</sup> For this reason, ibrutinib remains a feasible option for CLL patients with renal insufficiency.

### Administration

The current recommended dose of ibrutinib in CLL patients is 420 mg (three 140-mg capsules) orally once a day.<sup>22</sup>

### Toxicities

The most common adverse effects of ibrutinib are neutropenia, anemia, thrombocytopenia, diarrhea, musculoskeletal pain, nausea, rash, bruising, fatigue, pyrexia, upper respiratory infection, dizziness, and hemorrhage, occurring in >20% of patients.<sup>26–30</sup> Other less frequent adverse reactions include atrial fibrillation (in 6%–9% of patients) and hypertension (in 6%–17% of patients).<sup>25</sup> The adverse effect most commonly encountered in clinical trials with ibrutinib is diarrhea; however, diarrhea associated with the use of ibrutinib usually does not require treatment and resolves without discontinuation of this agent. Although myelosuppression (grade 1 or 2) has also been reported with ibrutinib, it is usually not as severe as that associated with chemotherapy regimens and only

occasionally warrants treatment discontinuation.<sup>31</sup> Despite irreversible inhibition of BTK, the risk of immunosuppression appears to decline with continued use of ibrutinib. A clinical study that examined this trend found that the average rate of infection declined from 7.1 per 100 patient-months during the first 6 months to 2.6 per 100 patient-months with an accompanying increase in IgA levels.<sup>32</sup>

Ibrutinib has been associated with an increased incidence (3.5%–6.5%) of atrial fibrillation. The cause of this effect has been hypothesized to be the inhibition of cardiac PI3K–Akt associated with BTK-related kinases present in the atrial wall.<sup>33</sup> In a number of trials, an increased risk of bleeding events, even with normal platelet counts, was shown to be another hematological adverse effect associated with ibrutinib use.<sup>26,32,34</sup> Because the prothrombin time was unaffected in these patients, researchers attributed the bleeding events to platelet dysfunction, such as a collagen- and ADP-dependent platelet response secondary to CLL and/or ibrutinib. It was later discovered that BTK is a non-redundant mediator of platelet glycoprotein VI signaling, which was inhibited by ibrutinib; cessation of the drug reversed this inhibition.<sup>35</sup> Given these effects, it is recommended that the use of ibrutinib be discontinued 3–7 days before any planned surgical procedures. Concomitant therapy with warfarin is also contraindicated; low-molecular-weight heparin is preferred.<sup>24,26</sup>

## Ibrutinib in the frontline setting

### Ibrutinib as a single agent

The proven efficacy of ibrutinib in patients with relapsed and refractory CLL prompted investigators to conduct clinical trials with ibrutinib as a first-line agent. In an open-label, phase 1b/2 trial, 31 patients aged 65 years or older with CLL or small lymphocytic lymphoma received first-line treatment with ibrutinib.<sup>36</sup> Of these patients, 71% demonstrated an objective response, defined as either a complete or partial response. In addition to responses based on standard criteria, the study reported that 13% of patients showed a partial response with lymphocytosis. Importantly, at follow-up (at a median of 22.1 months), disease progression had occurred in only one patient receiving ibrutinib who developed Richter's transformation. This study also showed a favorable toxicity profile for ibrutinib. The majority of noted adverse events were grade 2 or lower, and there were no deaths due to treatment-related adverse events. In addition, only two patients discontinued ibrutinib due to toxicities, one for grade 3 fatigue and another for grade 2 viral infection.<sup>36</sup>

The RESONATE study, a multicenter, randomized, phase 3 clinical trial, found that PFS in patients with *TP53* deletions

who were treated with ibrutinib was significantly superior to that in patients treated with ofatumumab.<sup>37</sup> At 6 months, the rate of PFS was 88% for patients receiving ibrutinib and 65% for those receiving ofatumumab. At 12 months, the OS rates were 90% in the ibrutinib group and 81% in the ofatumumab group, with overall response rates of 42.6% and 4.1%, respectively.

A more recent study performed at the National Institutes of Health Clinical Center further supported the efficacy of ibrutinib in patients with a *TP53* aberration. In this study, 33 patients with untreated CLL and 16 patients with relapsed or refractory disease were treated with ibrutinib. In the untreated CLL group, 97% of patients achieved an objective response at 24 weeks, with only one patient experiencing disease progression before this end point. Of the previously treated patients, 80% achieved an objective response and 20% had stable disease at 24 weeks. At 2 years, the cumulative incidence of progression was only 9% in the untreated patients and 20% in the previously treated patients, both of which were impressive figures compared with the cumulative incidence of progression observed in previous studies, which was much higher in these patient populations.<sup>38</sup>

In a single-arm trial that enrolled 132 patients with CLL, 31 had newly diagnosed disease for which they had received no previous treatment. To investigate the efficacy of ibrutinib as a frontline therapeutic agent, the data from these 31 patients were analyzed separately. The overall response rate in these patients was 84%, with a complete response in 23%. PFS and OS at 20 months were achieved by 96% and 97% of the patients, respectively. A subsequent report with a longer follow-up showed that responses to treatment with ibrutinib are sustained, with 96% of patients being free of progression at a median follow-up of 30 months.<sup>39</sup>

One of the most relevant studies illustrating the efficacy of ibrutinib in treatment-naïve patients is the RESONATE-2 trial, an international, open-label, randomized phase 3 trial comparing ibrutinib and chlorambucil in untreated older patients with CLL or small lymphocytic lymphoma.<sup>31</sup> At a median follow-up of 18 months, PFS was 90% in the ibrutinib group compared with 52% in the chlorambucil group. Furthermore, the risk of progression or death was 84% lower with ibrutinib than with chlorambucil. What is remarkable in the initial results of this trial was that the favorable outcomes of ibrutinib therapy extended to high-risk populations, including patients with Rai stage III or IV disease, those with chromosome 11q22.3 deletion, and those with unmutated *IGHV*, all subgroups that have tended to have inferior responses to previous standard-of-care therapies. For example, PFS at 18 months

was equal in the unmutated *IGHV* and mutated *IGHV* subgroups at 89%. In addition to efficacy, the RESONATE-2 trial supported the overall safety and tolerability of ibrutinib. The frequency of adverse events, specifically fatigue, nausea, vomiting, and myelosuppression, was higher in the chlorambucil group. Moreover, only 9% of patients in the ibrutinib group required discontinuation of therapy due to adverse events, compared with 23% of patients receiving chlorambucil.<sup>31</sup>

### Ibrutinib in combination

Additional trials are trying to identify agents that can be used in combination with ibrutinib in a frontline setting. The combination of ibrutinib and rituximab in a phase 2 study showed a reduction in the duration of redistribution lymphocytosis in high-risk CLL patients along with a higher rate of clinical responses, with an objective response rate of 93%.<sup>29</sup> Another example is an ongoing phase 1b/2 study of ibrutinib combined with obinutuzumab in untreated patients.<sup>40</sup> The primary objectives of this study are to gauge the safety, tolerability, dose-limiting toxicity, and overall response rate of this combination. In addition to the combination of ibrutinib with monoclonal antibodies, other clinical studies are assessing the role of ibrutinib combined with chemotherapy. In a randomized, placebo-controlled, phase 3 HELIOS trial, the addition of ibrutinib to bendamustine and rituximab improved clinical outcomes without compromising safety. Furthermore, it reduced the risk of progression and death by 80%.<sup>41</sup> Ongoing trials are seeking to establish additional combination drug regimens with ibrutinib that may prove beneficial. For example, an ongoing phase 2 study at The University of Texas MD Anderson Cancer Center is investigating the efficacy of first-line therapy with ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab in patients with mutated *IGHV*.<sup>42</sup> The growing number of such trials suggests ibrutinib's potential in the future of CLL treatment. Table 2 lists the studies using ibrutinib as frontline treatment for CLL.

### Future prospects

Ibrutinib is emerging as an effective and safe targeted oral agent for the treatment of CLL. In the era of increasing concern for developing resistance to chemotherapeutic agents, ibrutinib provides an alternative to cytotoxic drugs and has become a viable choice of treatment in both frontline and relapsed settings. However, additional research is critical to improving our understanding of ibrutinib's long-term efficacy, toxicity, and methods of resistance. Further work is

**Table 2** Studies with ibrutinib as frontline treatment for chronic lymphocytic leukemia

Study	No of patients	R/R	Treatment	Median age, range (years)	ORR%	PFS (months)	OS (months)
Burger et al <sup>29</sup>	40	Yes: 36 No: 4 <sup>a</sup>	Ibrutinib + rituximab	63 (35–82)	95	18 (78%)	18 (83.8%)
O'Brien et al <sup>36</sup>	31	No	Ibrutinib (low dose vs high dose)	71 (65–84)	71	24 (96%)	24 (96%)
Byrd et al <sup>39</sup>	31 <sup>b</sup>	No	Ibrutinib	71 (65–84)	84	20 (96%)	20 (97%)
Farooqui <sup>38</sup>	33 <sup>b</sup>	No	Ibrutinib (untreated vs treated)	62 (33–82) vs 62 (56–79)	97	24 (91% vs 80%)	24 (84% vs 74%)
Burger et al <sup>31</sup>	269	No	Ibrutinib vs chlorambucil	73 (65–89) vs 72 (65–90)	86 vs 35	18 (90% vs 52%), P<0.001	24 (98% vs 85%), P=0.001

**Notes:** <sup>a</sup>Four patients with untreated disease. <sup>b</sup>Data only of those patients receiving initial therapy with ibrutinib are shown.

**Abbreviations:** ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

needed to understand the characteristics and aggressiveness of the CLL clones that emerge in patients who are resistant to ibrutinib and to determine optimal second-line therapy for these patients. One mechanism of resistance to ibrutinib is the development of a BTK (C-481S) mutation that is associated with reduced affinity for ibrutinib and reduced inhibition of this agent.<sup>43</sup> Understanding the mechanisms associated with the development of resistance to ibrutinib will be an important step in moving forward.

An additional area of focus in this age of targeted oral therapy for CLL is determining the best timing for administering these drugs in the frontline setting. The German Cooperative Study Group is currently addressing this question in its CLL12 trial, a placebo-controlled, double-blind, phase 3 study investigating whether early intervention with ibrutinib in intermediate- or high-risk patients improves event-free survival.<sup>21</sup> Results from this ongoing trial and from similar studies, together with long-term follow-up in large randomized studies, will further define the future role of ibrutinib in the initial treatment of patients with CLL.

## Disclosure

The authors report no conflict of interest in this work.

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