

Review Article

The Emerging Role of Ibrutinib and Idelalisib in the Treatment of Chronic Lymphocytic Leukemia

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Chronic lymphocytic leukemia (CLL) is the most common leukemia in the western world. Recently, significant progress in the better characterization and understanding of the biology and prognosis of CLL has provided new opportunities for the development of innovative, more effective therapies. In particular, the use of B-cell antigen receptor (BCR) signal transduction inhibitors ibrutinib (PCI-32765) and idelalisib (GS-1101, CAL-101) is a promising new strategy for targeted CLL treatment. Ibrutinib is an inhibitor of Bruton's tyrosine kinase (Btk) with potential activity in patients with CLL, including high-risk CLL. Idelalisib is an oral phosphatidylinositol 3-kinase (PI3K) p110 δ -selective inhibitor which also has shown preclinical and clinical activity against CLL. These drugs are available in oral preparations and are given as continuous treatment. They seem to be active in traditionally poor risk disease groups, including fludarabine-refractory patients and patients with bulky lymphadenopathy. Ibrutinib and idelalisib are currently under investigation in the treatment of CLL and show encouraging results. However, definitive data from ongoing and future clinical trials will aid in better defining the status of these drugs in the treatment of this disorder.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a clonal lymphoid disease characterized by the proliferation and accumulation of small CD5/CD19/CD23-positive lymphocytes in the blood, lymph nodes, spleen, liver and bone marrow. CLL is the most common leukemia in the western world accounting for approximately 30% of all leukemias in Europe and North America with an annual incidence rate of three to five cases per 100,000 [1]. The median age at diagnosis is 72 years and the majority of patients with this disease are elderly. A diagnosis of CLL requires the presence of at least 5,000 leukemic B lymphocytes per microliter in the peripheral blood [2]. The natural clinical course of CLL is highly variable and chemotherapy is usually not indicated in early and stable disease. However, patients with progressive and more advanced disease require treatment. CLL is typically sensitive to a variety of cytotoxic drugs, but the disease is considered incurable. There has been an important increase in the range of available therapeutic options in the recent years, and many drugs are now in the process of making the transition to the clinic [3]. Cytotoxic agents still form the basis of the most frequently used therapeutic regimens. However, these agents are not specific for leukemic cells and target normal cells, particular

hematopoietic and immune cells. In consequence, this lack of specificity demonstrated by chemotherapy leads to toxicity and exacerbation of immunosuppression [4]. Chemoimmunotherapy combining anti-CD20 monoclonal antibodies (mAbs) with purine nucleoside analogs (PNA) represents a substantial advance for patients with CLL and results in increased response rates, progression-free survival (PFS), and overall survival (OS). In newly-diagnosed patients, primary therapy with a fludarabine-based regimen demonstrates high response rates. Specifically, a combination of fludarabine, cyclophosphamide, and rituximab (FCR) is frequently used for initial treatment and is also active in relapsed/refractory patients [5,6].

Recently, significant progress in the better characterization and understanding of the biology and prognosis of CLL has provided new opportunities for the development of innovative, more effective therapies of this disease. In particular, the use of B-cell antigen receptor (BCR) signal transduction inhibitors ibrutinib (PCI-32765) and idelalisib (GS-1101, CAL-101) is a promising new strategy for targeted CLL treatment (Figure 1). These drugs are available in oral preparations and are given as continuous treatment. They seem to be active in traditionally poor risk disease groups, including fludarabine-refractory patients

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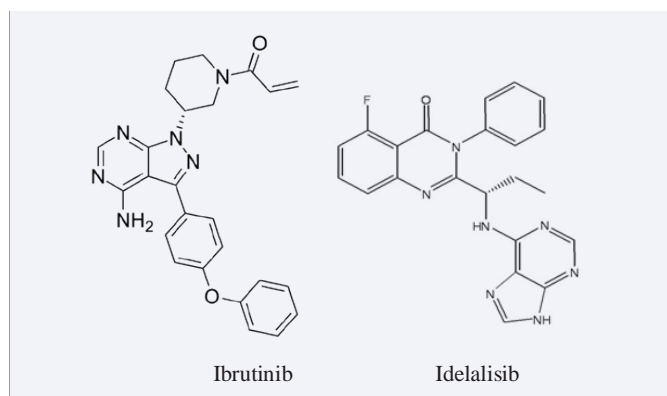


Figure 1 Chemical structure of ibrutinib and idelalisib.

and patients with bulky lymphadenopathy. These agents induce rapid resolution of lymphadenopathy and a transient increase of lymphocytosis due to mobilization of CLL cells into the peripheral blood. However, after several months of continuous therapy, response can be achieved in a substantial number of patients [7,8].

IBRUTINIB

Burton's tyrosine kinase (BTK) is a critical enzyme in the BCR signaling pathway that is essential for B-cell proliferation, survival, migration, and tissue homing. Ibrutinib is a first-in-class selective, irreversible, covalent inhibitor of BTK under development for the treatment of B-cell malignancies [9,10]. Because of covalent binding to cys-481 of BTK, ibrutinib has a sustained pharmacodynamics effect [11]. In a Phase 1b/2 study ibrutinib demonstrated rapid absorption and elimination at doses of 420 and 840 mg/day. Ibrutinib can be dosed once daily despite a relatively rapid clearance. Initial reports on the use of ibrutinib as a single agent found that it was well-tolerated and particularly active in patients with refractory/relapsed CLL patients, thus justifying its further testing in ongoing trials (Table 1) [12,13]. Farooqui et al. reported the early results of a phase II trial using ibrutinib 420 mg daily on 28-day cycles

in 26 treatment-naïve and previously-treated patients older than 65 years and/or patients with 17p deletion [14]. Fourteen patients (54%) had a partial response (PR) and 62% achieved a reduction in lymphadenopathy greater than 50%. The increase in lymphocytosis peaked within the first 2 months followed by a slow decline. More pronounced relative increases in lymphocytosis were observed in treatment-naïve patients and the most dramatic increase occurred in patients with a lower starting absolute lymphocyte count. In addition, treatment-naïve patients responded more rapidly than previously-treated patients.

Ibrutinib is associated with a high frequency of durable remissions in patients with relapsed or refractory CLL, including patients with high-risk genetic lesions. Byrd et al. conducted a phase 1b-2 multicenter study to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of ibrutinib in 85 patients with relapsed or refractory CLL or small lymphocytic lymphoma [15]. The patients received ibrutinib orally once daily; 51 received 420 mg, and 34 received 840 mg. The overall response (OR) rate was 71% in the group that received 420 mg and the group that received 840 mg. An additional 20% and 15% of patients in the respective groups demonstrated a PR with lymphocytosis. The response was independent of clinical and genomic risk factors present before treatment, including advanced-stage disease, the number of previous therapies, and the 17p13.1 deletion. At 26 months, the estimated PFS rate was 75% and the rate of OS was 83%. In a recent update, the OR rate among thirty-one previously untreated patients aged ≥65 years was 71%, and the most common adverse effects were diarrhea, fatigue and rash [16]. Toxic effects were predominantly grade 1 or 2 and included transient diarrhea, fatigue, and upper respiratory tract infection; thus, patients could receive extended treatment with minimal hematologic toxic effects. The results of this trial suggest that ibrutinib could be a reasonable choice of treatment for older, treatment-naïve patients with CLL.

Ibrutinib in combination with rituximab is also an effective and well-tolerated regimen for high-risk CLL patients. A recent study showed that 40 high-risk patients treated with ibrutinib

Table 1: Ibrutinib in clinical trials in CLL.

Study	Treatment	Disease characteristics	N	Median age	CR	OR	PFS
Advani et al. [12]	Ibrutinib 420 mg	Relapsed/refractory, median 3 previous treatments	16	65	2/16 (14%)	11/16 (79%)	13.6 months*
Byrd et al. [15,16]	Ibrutinib 420/840 mg	Relapsed/refractory median 4 previous treatments	61	71	3%	50%	22 month PFS -76%
Byrd et al. [16]	Ibrutinib 420/840 mg	Treatment naïve	31	64	10%	71%	22 month PFS -96%.
Byrd et al. [16]	Ibrutinib 420/840 mg	High risk, median 4 previous treatments	24	68	0	67%	22 month PFS -76%
Byrd et al. [15]	420 mg/ day or 840 mg/ day	Relapsed or refractory CLL, majority with high-risk diseases	85	68		71%	Estimated PFS at 26 months- 75%
Farooqui et al. [14]	Ibrutinib 420 mg/ day	Treatment naïve and previously treated >65 years old and with del 17p	26	NR	0	14 (54%)	NR
Burger et al. [17]	Ibrutinib 420 mg/ day + Rituximab	Treated or untreated high-risk CLL	20	65	NR	85%	NR
Brown et al. [19]	Ibrutinib 420 mg/day + Bendamustine + Rituximab	Relapsed/refractory CLL with median 2 (1-3) prior regimens	30	62 (41-82)	10%	90%	Estimated 11-m PFS - 90%.
Jagłowski et al. [20]	Ibrutinib 420 mg/ day + Ofatumumab	Two or more prior therapies	27	66 (51-85)	1 pt	100%	100% with median follow-up of 9.8 m

Abbreviations: OR- overall response rate; CR – complete response rate; OS –overall survival; PFS – progression free survival; NR- not reported; m- months

plus rituximab had high OR rate of 85% [17]. At a median follow up of 4 months, 38 of 40 patients continued on therapy without disease progression. Out of 20 patients evaluable for response assessment at 3 months, 17 patients achieved a PR and 3 achieved a PR with persistent lymphocytosis. Interestingly, in this study, re-distribution lymphocytosis peaked earlier and the duration was shorter than with single-agent ibrutinib. Similar results were achieved in a phase Ib/II trial of ibrutinib in combination with bendamustine and rituximab in patients with relapsed and refractory CLL [18,19]. A total of 30 patients were enrolled, of whom 37% were refractory to a PNA-containing regimen and 13% refractory to bendamustine. The treatment regimen consisted of ibrutinib 420 mg/day administered continuously in combination with bendamustine 70 mg/m² on days 1–2 with rituximab 375 mg/m² in cycle 1 escalating to 500 mg/m² in cycles 2–6. The overall response rate was 93%, with 13% of patients achieving a CR with no morphologic evidence of CLL. With a median follow up of 8.1 months only two patients were found to have progressive disease. The estimated 11-month PFS was 90%. The toxic effects consisted of diarrhea, nausea, fatigue, and skin rash. Grade 3 hematologic toxicity was present in 17% of patients and grade 4 in 10% and consisted mainly of neutropenia. Two patients developed tumor lysis syndrome. No discontinuations for adverse events were reported.

Jagłowski et al. reported interim data from a phase Ib/II trial investigating ibrutinib in combination with ofatumumab [20]. A total of 27 patients, including 24 with CLL and prolymphocytic leukemia (PLL), and 3 patients with Richter transformation, were included. Patients with relapsed/refractory CLL who have received two or more prior therapies were treated with ibrutinib at a dose of 420 mg daily until disease progression, followed by concomitant ofatumumab with continued ibrutinib until progression. Ofatumumab was administered over eight cycles: a dose of 300 mg on day 1 and then 2000 mg on days 8, 15, and 22 of cycle 2; on days 1, 8, and 15 of cycle 3; on day 1 in cycles 4–8. For the CLL/PLL patients the OR rate, and PFS, was 100%, with a median follow-up of 9.8 months. The combination was well tolerated and highly active in patients with heavily pretreated relapsed/refractory CLL. Grade 3 to 4 side effects included anemia, pneumonia, and urinary tract infection. Recently, a randomized, multicenter, open-label, phase III study of ibrutinib

versus chlorambucil in patients 65 years or older with treatment-naïve CLL/SLL (RESONATE-2) has been initiated [21].

IDELALISIB

Idelalisib is a first-in-class, selective, oral inhibitor of phosphatidylinositol 3-kinase P110δ (PI3Kδ) that reduces proliferation, enhances apoptosis, and inhibits homing and retention of malignant B cells in lymphoid tissues. Idelalisib used in monotherapy has shown substantial clinical activity and a favorable safety profile in heavily pretreated, refractory and high risk patients with CLL (Table 2). In a Phase I study, patients with relapsed/refractory CLL were treated continuously with oral idelalisib as a single agent at 50 mg/dose (QD or BID) [22]. Recently final results of this study were reported [23]. Fifty-four patients with relapsed/refractory CLL were treated continuously with single-agent oral idelalisib from 50-350 mg/dose (QD or BID). ORR was 56% including 2 CR and 28 PR. The median time to first response was 1.9 (0.9-12.9) months and median PFS was 17 months. Most common Grade ≥ 3 adverse events (AEs) included fatigue, diarrhea, pyrexia, rash, upper respiratory tract infection and pneumonia. In a more recent report, idelalisib was administered with rituximab at a dose of 375 mg/m² given weekly for 8 doses, and/or 90 mg/m² bendamustine given on days 1 and 2 of each cycle for 6 cycles. These combinations used in relapsed/refractory CLL was associated with improved OR rates of 78%, 82%, and 87% for idelalisib and rituximab, idelalisib and bendamustine, or idelalisib, rituximab and bendamustine combinations, respectively [24]. Almost all evaluable patients demonstrated reductions in lymphadenopathy. With a minimum follow-up of 40 weeks, 1-year PFS rates were 74%, 88% and 87%, respectively. A favorable safety profile and lack of overlapping toxicities was also observed. In a more recent report Barrientos et al. updated the results of a phase I study of idelalisib in combination with rituximab and/or bendamustine in patients with relapsed or refractory CLL [25]. The OR rate was 81%, including a CR in one patient. The median time to response was 1.9 month, and the 2-year PFS and OS were 62% and 85%, respectively. Most common Grade ≥ 3 AEs were pyrexia, diarrhea, cough, fatigue and nausea. These results indicate that combination of idelalisib with rituximab and/or bendamustine is tolerable and highly active in patients with relapsed or refractory

Table 2: Idelalisib in clinical trials in CLL.

Study	Treatment	Disease characteristics	N	Median age	CR	OR	PFS
Furman et al. [29] Coutre et al. [22]	Idelalisib 150 mg/day	Relapsed/ refractory, median 5 previous treatments	37	65	0	33%	Not reached
Coutre et al. [24]	Idelalisib 150 mg/ day +/- Rituximab +/- Bendamustine	Relapsed/ refractory	51	38-84	NR	78% - 87%	1-year PFS 74%
Brown et al. [23]	Idelalisib 50-350 mg/dose	Relapsed/ refractory, median 5 prior therapies	54	NR	2 pts	56%	Median - 17 months
O'Brien et al. [26]	Idelalisib 150 mg bid for 48 weeks + Rituximab 375 mg/m ² weekly x 8	Treatment-naïve ≥65 years	50	71 yrs (65- 89)	NR	96%	91% at 24 m
Barrientos et al. [25]	Idelalisib 150 mg BID + Rituximab 375 mg/m ² weekly x 8 + Bendamustine 70 or 90 mg/m ² x 2, every 4 wks x 6	Relapsed or refractory	52	64 (41-87)	1pt	81%	2-year PFS - 62%

Abbreviations: OR- overall response rate; CR – complete response rate; OS –overall survival; PFS – progression free survival; NR- not reported; m- months

CLL. Phase III trials evaluating the efficacy of idelalisib in combination with these two antileukemic drugs are ongoing in CLL patients.

O'Brien et al. recently reported the results of the up-front therapy with idelalisib and rituximab in patients over 64 years old with CLL or small lymphocytic lymphoma (SLL) [26]. They were treated with rituximab given at a dose of 375 mg/m² weekly x 8 and idelalisib 150 mg bid continuously for 48 weeks. Patients completing 48 weeks of treatment without progression continued to receive idelalisib on an extension study. The ORR was 96% for the first 50 of the 64 enrolled patients and PFS was 91% at 24 months. Of note, all six patients with del (17p) responded, including one with a CR, and there have been no on-study relapses. A phase III, randomized study evaluating the efficacy and safety of idelalisib in combination with bendamustine and rituximab for previously treated CLL was initiated in June 2012 [27]. A phase III, randomized, controlled study evaluating the efficacy and safety of idelalisib in combination with ofatumumab for previously treated CLL has also been initiated [28].

CONCLUSIONS

Ongoing clinical trials will help to determine if ibrutinib and idelalisib need to be combined with chemotherapy to achieve maximum effect and to establish optimal drug combinations. Combinations with monoclonal antibodies and/or cytotoxic drugs are likely to shorten the time to remission and increase the depth of responses. A recent report indicates that idelalisib combined with rituximab and/or bendamustine offers major and rapid reductions in lymphadenopathy and durable tumor control. Early clinical studies have demonstrated that BCR signaling inhibitors are well tolerated and have an excellent safety profile in patients with refractory CLL. However, data concerning the safety of ibrutinib and idelalisib, especially in long-term applications, are at this time unknown and will likely become an area of research within the next few years, once these agents are longer and more widely used. Particularly, more information is needed about tolerability, duration of response, mechanisms of resistance, interactions with other drugs and the differences between both drugs. Moreover, additional clinical trials are ongoing to establish the role of these drugs as optimal treatments in previously untreated and refractory/relapsed patients with CLL. Their results should confirm whether these agents are effective and safe ways of achieving therapeutic goals for patients with this disease.

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