Idelalisib (Zydelig)

Hien C. Tang, PharmD, James YC Shen, MD, and Betty M. Chan, PharmD, BCOP

Abstract

In 2015, newly diagnosed chronic lymphocytic leukemia (CLL) is estimated to reach 14,620 cases, with 4650 deaths in the United States. First-line options typically include chemoimmunotherapy; however, in patients who relapse or are refractory, oral agents offer a new and safe alternative. Idelalisib is the first agent to target the phosphatidylinositol-3-kinase (PI3K) pathway, and the second oral agent approved by the US Food and Drug Administration (FDA), in July 2014, for the treatment of relapsed/refractory CLL. In addition, idelalisib was granted accelerated approval for treatment of relapsed follicular B-cell non-Hodgkin lymphoma (FL) and relapsed small lymphocytic lymphoma (SLL). In a phase III study of idelalisib in combination with rituximab in 220 patients with relapsed CLL, the overall response rate (ORR) was 81%, with a statistically significant overall survival (OS) of 92% versus 80% at 12 months ($P = .02$). In a phase II study in patients with indolent non-Hodgkin lymphoma, the median duration of response was 12.5 months, median overall survival was 20.3 months, and 1-year survival was 80%. The most common adverse events (≥10%) reported in clinical trials included fever, chills, nausea, cough, infusion reaction, and gastrointestinal symptoms. The FDA-approved labeling of idelalisib includes black box warnings for fatal and/or serious diarrhea or colitis, gastrointestinal perforation, pneumonitis, and hepatotoxicity.

Key words: idelalisib review, CLL, FL, SLL, toxicity management

Introduction

In 2015, newly diagnosed chronic lymphocytic leukemia (CLL) is estimated to reach 14,620 cases, with 4650 deaths occurring in the United States.[1] The age-adjusted annual incidence rate in 2007 to 2011 was 4.4 per 100,000 in all age groups, and reaching 25.3 per 100,000 in those 65 years or older. The 5-year survival of patients younger than 65 years reached 89.7% compared with 74.5% for those age 65 years or older.[2]

The most current guideline published by the National Comprehensive Cancer Network (NCCN) recommends chemoimmunotherapy for patients younger than age 70 years, and who do not have significant comorbidities. The combination of chemoimmunotherapy for these patients includes fludarabine, cyclophosphamide, and rituximab as the first-line option. In relapsed/refractory patients, the next line of treatment is dependent on length of response to initial treatments. For patients able to maintain a long response, retreatment with first-line therapy is recommended until short response. In those with short responses to chemoimmunotherapy, the NCCN recommends use of oral agents. One potential option is the use of idelalisib in combination with rituximab.[3]

In July 2014, idelalisib was approved by the US Food and Drug Administration (FDA) for the treatment of relapsed CLL in combination with rituximab after failure of 2 prior therapies. In addition, it was granted accelerated approval for treatment of relapsed follicular B-cell non-Hodgkin lymphoma (FL) and relapsed small lymphocytic lymphoma (SLL). The FDA-approved dose and schedule for idelalisib is 150 mg orally twice daily for patients with FL/SLL and in combination with rituximab for patients with CLL.[4]

CLL, Relapsed

An initial phase I, dose-ranging trial evaluated 54 patients with relapsed/refractory CLL treated with idelalisib (GS-1101, CAL-101) at dosages of 50 mg to 350 mg once daily or twice daily. Treatment with idelalisib demonstrated an overall response rate (ORR) of 72%, with 39% of patients with partial responses (PRs; International Workshop on Chronic Lymphocytic Leukemia 2008 criteria[5]) and 33% with PRs in the presence of treatment-induced lymphocytosis.[6] For those patients who responded, the median time to response was 1 month, with a median duration of response of 16.2 months. The median progression-free survival (PFS) for all patients was 15.8 months.[7]

A phase III, multicenter, double-blind, placebo-controlled study randomized patients (N = 220) to idelalisib 150 mg twice daily in combination with rituximab (375 mg/m^2 once, then 500 mg/m^2 every 2 weeks for 4 doses, then every 4 weeks for 3 doses, for a total of 8 doses; **Table 1**). There was a statistically significant longer rate of PFS at 24 weeks: 93% in the treatment group versus 46% in the control group (P <.001). The median duration of PFS in the treatment group was not reached at the time of analysis compared with 5.5 months in the control group. The

TABLE 1. Pivotal Published Trials

Trial	Phase	Study Design	Treatment	Results
Furman et al[8]	III	Multicenter, randomized, double-blind, placebo-controlled study in relapsed CLL (N = 220)	Treatment: Rituximab (IV 375 mg/m^2 x 1, then 500 mg/m^2 every 2 weeks for 4 doses, then every 4 weeks for 3 doses) + idelalisib 150 mg twice daily Control: Rituximab alone	PFS: Treatment vs control: not reached vs 5.5 months ORR: Treatment: 81% Control: 13% *P* <.001 CR: None OS at 12 months: Treatment: 92% Control: 80% *P* = .02
Gopal et al[10]	II	Multicenter, open label, single-group study in relapsed NHL (N = 125)	Idelalisib 150 mg twice daily	ORR: 57%, (CR, 6%; PR, 50%; minor response 1%) Time to response: median 1.9 months Duration of response: median 12.5 months PFS: median 11 months OS: median 20.3 months (at time of data analysis)

CLL indicates chronic lymphocytic leukemia; CR, complete response; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

ORR was 81% in the treatment group compared with 13% in the control group (*P* <.001); all responses were PRs. Overall survival (OS) at 12 months in the treatment group was 92% versus 80% in the control group (*P* = .02).[8]

Indolent Lymphoma, Relapsed

A phase I study of idelalisib evaluated 64 patients with relapsed indolent non-Hodgkin lymphoma (NHL) at dosages ranging from 50 mg to 350 mg once daily or twice daily.[9] Treatment with idelalisib resulted in an ORR of 47%, with 1 patient achieving complete response (CR). The median time to response for the 30 patients was 1.3 months, with a median duration of response of 18.4 months. The median PFS was 7.6 months in all patients.

In a phase II, multicenter, open-label study of 125 patients with relapsed indolent NHL treated with idelalisib 150 mg twice daily, the reported response rate was 57%, including 6% CRs (**Table 1**).[10] In addition, the median time to response was 1.9 months, with a median duration of response of 12.5 months. At 48 weeks, 47% of patients remained progression-free, with a median PFS of 11 months. Median OS was 20.3 months, and OS at 1 year was estimated at 80%.

Side Effects and Management of Toxicities

In patients being treated with idelalisib in combination with rituximab, the most common adverse events (AEs; ≥10%) reported in clinical trials included fever, chills, nausea, cough, infusion reaction, and gastrointestinal (GI) symptoms (**Table 2**). Grade 3 or higher serious AEs included fever, sepsis, pneumonitis, diarrhea, neutropenia, *Pneumocystis jiroveci* pneumonia, and febrile neutropenia. The AEs that led to discontinuation in the treatment group included GI and skin disorders. Laboratory abnormalities included neutropenia, hepatic transaminitis, and electrolyte disturbances. Although no patients discontinued idelalisib due to elevations in aspartate transaminase (AST) and alanine transaminase (ALT) in clinical trials, the FDA-approved labeling of idelalisib recommends interruption of therapy if AST/ALT reaches greater than 5 times the upper limit of normal (ULN).[8,11]

In indolent NHL where idelalisib is used as a single agent, common reported AEs included fever, fatigue, cough, dyspnea, GI symptoms, decreased appetite, weight loss, rash, insomnia, and night sweats. Serious AEs included fever, pneumonia, diarrhea, colitis, febrile neutropenia, acute renal failure, and pneumonitis. Laboratory abnormalities included hematological cytopenias and hepatic transaminitis.[10,11]

Black box warnings on the idelalisib approved label include fatal and/or serious diarrhea or colitis, GI perforation, pneumonitis, and hepatotoxicity. Severe diarrhea or colitis (grade ≥3) have been reported in clinical trials, with median onset of 1.9 months for any grade, 1.5 months for grade 1/2, and 7.1 months for grade 3/4. During clinical trials, 2 types of diarrhea

TABLE 2. Adverse Events With Idelalisib

Treatment Group[8,10,11] Adverse Events and Serious Adverse Events							
Rituximab + Idelalisib (CLL) N (%)				Idelalisib (NHL) N (%)			
AE		SAE		AE		SAE	
Pyrexia	32 (29)	Pneumonia	7 (6)	Diarrhea	54 (43)	Pyrexia	13 (10)
Fatigue	26 (24)	Pyrexia	7 (6)	Nausea	37 (30)	Pneumonia	9 (7)
Nausea	26 (24)	Febrile neutropenia	5 (5)	Fatigue	37 (30)	Diarrhea	9 (7)
Chills	24 (22)	Sepsis	4 (4)	Cough	36 (29)	Colitis	5 (4)
Infusion reaction	17 (15)	Pneumonitis	4 (4)	Pyrexia	35 (28)	Dehydration	4 (3)
Cough	16 (15)	Diarrhea	3 (3)	Decreased appetite	22 (18)	Febrile neutropenia	4 (3)
Constipation	13 (12)	Neutropenia	3 (3)	Dyspnea	22 (18)	Acute renal failure	3 (2)
Decreased appetite	13 (12)	PJP	3 (3)	Abdominal pain	20 (16)	Pneumonitis	3 (2)
Vomiting	13 (12)	Neutropenic sepsis	3 (3)	Vomiting	19 (15)		
Dyspnea	12 (11)	Dyspnea	1 (1)	URTI	18 (14)		
Night sweats	11 (10)	Cellulitis	1 (1)	Weight decreased	17 (14)		
Rash	11 (10)			Rash	16 (13)		
				Asthenia	14 (11)		
				Night sweats	14 (11)		
				Pneumonia	14 (11)		
				Peripheral edema	13 (10)		
				Headache	13 (10)		
Lab abnormalities				**Lab abnormalities**			
Neutropenia	60 (55)			AST/ALT elevation	103 (82)		
Hypertriglyceridemia	62 (56)			Neutrophils decreased	78 (53)		
Hyperglycemia	59 (54)			Hemoglobin decreased	41 (28)		
AST/ALT elevation	38 (35)			Platelets decreased	38 (26)		
GGT increased	29 (26)			Alkaline phosphatase elevation	28 (22)		
Anemia	28 (25)			Bilirubin elevation	13 (10)		
Thrombocytopenia	19 (17)						
Lymphocyte decrease	22 (20)						
Lymphocyte increase	27 (25)						
Hypoglycemia	12 (11)						
Hyponatremia	22 (20)						

Any grade (≥10%) or serious adverse events;
AE indicates adverse event; AST/ALT, aspartate aminotransferase/alanine aminotransferase; GGT, gamma-glutamyl transferase; PJP, *Pneumocystis jiroveci* pneumonia; SAE, serious adverse event; URTI, upper respiratory tract infection.

were observed. The first was a self-limiting type that occurs within 8 weeks of idelalisib initiation, which was typically mild or moderate and responsive to common antidiarrheal medication. The second type of diarrhea observed typically occurred late in treatment and responded poorly to antimotility medications and empiric antibiotics. Corticosteroids were used in some cases to manage this toxicity in clinical trials, with enteric budesonide used most commonly. If severe idelalisib-associated diarrhea or colitis is suspected (≥7 stools/day over baseline), initiation of budesonide and interruption of idelalisib is recommended un-

til complete resolution of diarrhea. Recommended dosage of budesonide is 9 mg orally once daily or prednisolone 1 mg/kg orally or intravenously (if unable to tolerate oral), with tapering when diarrhea returns to grade 1.[11,12]

Fatal cases of pneumonitis have occurred in patients treated with idelalisib. The FDA-approved labeling of idelalisib recommends prompt evaluation for symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates, or oxygen saturation decrease of more than 5%. Idelalisib therapy should be interrupted for suspected pneumonitis, and if confirmed, corticosteroids should be initiated, as appropriate.[11]

Elevations of AST/ALT greater than 5 times ULN have occurred and were typically observed within 12 weeks of initiating therapy. Interruption of idelalisib therapy results in transaminase normalizations; however, hepatotoxicity may recur when rechallenging with reduced dosages. The FDA-approved labeling of idelalisib recommends monitoring liver function tests (LFTs) weekly for those with AST/ALT greater than 3 to 5 times ULN or bilirubin greater than 1.5 to 3 times ULN, until AST/ALT and/or bilirubin is 1 or less times ULN. Temporary interruption of idelalisib is recommended for AST/ALT greater than 5 to 20 times ULN or bilirubin greater than 3 to 10 times ULN. Liver function should be monitored weekly until AST/ALT and/or bilirubin is 1 or less times ULN, at which time therapy may be reinitiated at 100 mg twice daily. Idelalisib should be discontinued permanently if AST/ALT is greater than 20 times ULN, bilirubin is greater than 10 times ULN, or if the patient develops recurrent hepatotoxicity.[11]

Renal excretion of idelalisib is 14%. In patients with renal impairment, no dosage adjustment is necessary in patients with creatinine clearance (CrCl) greater than or equal to 15 ml/min. Renal adjustment data are not available in patients with CrCl less than 15 ml/min.[11]

Place in Therapy

Currently, first-line therapy for the treatment of CLL includes a combination of chemotherapeutic agents and monoclonal antibodies that target cell-surface antigens. In patients with treatment-naïve CLL, the combination of fludarabine, cyclophosphamide, and rituximab (FCR) results in ORR greater than 90% and complete responses of 44% to 70%.[13,14] However, if patients have relapsed/refractory disease and are unable to tolerate additional courses of chemotherapy, idelalisib offers an alternative, effective, and safe treatment option secondary to ibrutinib. Ibrutinib, an irreversible inhibitor of Bruton's tyrosine kinase (BTK), is an alternative agent recently approved by the FDA for patients with previously treated CLL. Ibrutinib was initially granted accelerated approval for the treatment of relapsed mantle cell lymphoma (MCL) in November 2013; in February 2014, the FDA granted accelerated approval of ibrutinib for the treatment of patients with CLL that has recurred after at least 1 prior therapy.[15] In July 2014, ibrutinib gained expanded approval for the treatment of CLL in patients with chromosome 17p deletion, based on a phase III study of 391 patients.[16] In this multicenter, open-label study of ibrutinib compared with ofatumumab in patients with previously treated CLL, ibrutinib significantly improved PFS (not reached vs median 8.1 months; P <.001) and OS rates (42.6% vs 4.1%; P <.001).[17] At 12 months, the OS rate was 90% with ibrutinib compared with 81% with ofatumumab. A total of 63% (122/195) PRs were seen in the ibrutinib group versus 4% (8/196) in the ofatumumab group. In addition, a subgroup analysis of patients with chromosome 17p13.1 deletion showed similar results with ibrutinib.

Similarly, in patients with FL, first-line treatment options include the use of chemotherapy with rituximab, such as bendamustine plus rituximab (BR); cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab (R-CHOP); or cyclophosphamide, vincristine, prednisone plus rituximab (RCVP). In addition to relapsed CLL/SLL indications, idelalisib has also obtained accelerated approval for relapsed FL. Currently, the use of idelalisib is limited to second-line treatment of FL after failure of 2 prior therapies, including rituximab and an alkylating agent.

Preclinical data in MCL have shown that specific BTK mutations that led to ibrutinib resistance also enhanced PI3K dysregulation.[18] PI3K inhibition in the same ibrutinib-resistant model was able to restore the cell-line cytotoxicity. In a separate experiment, ibrutinib in combination with idelalisib produced strongly synergistic inhibition of the lymphoma cell line.[19] The likely rationale for the synergistic effect is because ibrutinib and idelalisib both target the B-cell receptor signaling through different mechanisms. These data taken together suggest that in ibrutinib-resistant patients, idelalisib may still prove to be an effective therapy, and that combination idelalisib-ibrutinib might be explored in the future.

Mechanism of Action and Resistance

PI3K phosphorylation activates the serine/threonine kinase AKT, which then activates mammalian target of rapamycin (mTOR). PI3Kδ (isoform p110δ) is a central lipid kinase in the development and function of normal B cells. Overactive signaling of PI3Kδ has been shown to increase proliferation, survival, and migration of malignant B cells into lymphoid tissues.[20] Idelalisib is a selective small-molecule inhibitor of PI3Kδ compared with α, β, and γ isoforms.[11,21]

Better knowledge and familiarity with targeted therapy have led to increased understanding of the development of resistance. Idelalisib resistance has not yet been fully characterized, although research is currently under way to explore this subject. Proposed mechanisms include upregulation of alternative PI3K isoform enzymatic cascade through p110α,[22] activation of an "escape" oncogenic pathway such as RAS–RAF–MEK–ERK-MAPK cascade and amplification of MYC,[23] and increased upstream signaling

that overwhelms the competitive inhibition.[24] Rational combination therapy with agents of different mechanisms of action may ultimately be necessary to improve efficacy and overcome resistance. Future directions for overcoming resistance may also include patient selection using predictive biomarkers of response.

Dosing and Administration

Idelalisib is approved for relapsed CLL in combination with rituximab; for FL in patients who have received at least 2 prior systemic therapies; and for SLL in patients who have received at least 2 prior systemic therapies. The FDA-approved, recommended starting dosage is 150 mg orally twice daily without regard to food. Tablets should be taken whole and within 6 hours of scheduled dose if missed. If a dose of idelalisib is missed by more than 6 hours, patients should skip the dose and restart at the next scheduled administration time. Dosing of idelalisib should be adjusted for any toxicities, and permanently discontinued for anaphylaxis, life-threatening diarrhea, or other life-threatening toxicities that recur during rechallenging. Toxicities that require dosing adjustments or interruption of idelalisib include neutropenia or thrombocytopenia, diarrhea, symptomatic pneumonitis, or hepatotoxicity. Idelalisib should be stored in its original container at room temperature (68°F to 86°F) and away from the reach of children. In addition, idelalisib should not be cut, crushed, or altered.[11]

Idelalisib is a substrate of hepatic enzyme CYP3A, and concomitant administration should be avoided with strong CYP3A inducers, such as rifampin, phenytoin, St. John's wort, and carbamazepine. When administering with strong CYP3A inhibitors, closely monitor for signs of toxicity due to idelalisib. In addition, idelalisib is a strong CYP3A inhibitor, therefore avoid concomitant use of idelalisib with CYP3A substrates.

Conclusion

Idelalisib is the second oral agent approved for the treatment of relapsed/refractory CLL, and the first to target the PI3K pathway (in fact, the first in this class of drugs to be approved overall). Idelalisib in combination with rituximab offers an effective and safe alternative to chemotherapy in relapsed/refractory CLL, secondary to ibrutinib, especially in patients without 17p or 11q deletions. In addition, idelalisib is indicated for use in patients with FL who have failed 2 prior therapies. Ongoing studies registered at http://clinicaltrials.gov for treatment of newly diagnosed or treatment-naïve patients include registration numbers NCT01980888 (idelalisib in combination with bendamustine and rituximab) and NCT02044822 (idelalisib in combination with rituximab in patients with 17p deletion). However, until data are released for patients with untreated CLL, FDA indications for the use of idelalisib are limited to relapsed/refractory CLL, SLL, and FL.

Affiliations: Hien Chung Tang, PharmD, is adjunct assistant professor of Pharmacy Practice at the University of Southern California School of Pharmacy, USC/Norris Comprehensive Cancer Center & Hospital; James Yu Chang Shen, MD, is from the department of Internal Medicine, Jane Anne Nohl Division of Hematology, and a fellow in the Division of Hematology-Oncology, Keck School of Medicine of University of Southern California, Los Angeles; Betty M. Chan, PharmD, BCOP, is assistant professor of Clinical Pharmacy, residency program director, PGY2 Oncology Pharmacy Practice, and ambulatory pharmacy manager at USC/Norris Comprehensive Cancer Center & Hospital, University of Southern California School of Pharmacy, Los Angeles.

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Address correspondence to: Betty M. Chan, PharmD, BCOP, USC/Norris Comprehensive Cancer Center & Hospital, University of Southern California School of Pharmacy, Los Angeles, CA 90033. Email: betty.chan@med.usc.edu or bchan@usc.edu.

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