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Authors
Jain, Preetesh
Thompson, Philip A
Keating, Michael
et al.

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Long-term Outcomes for Patients with Chronic Lymphocytic Leukemia (CLL) who Discontinue Ibrutinib

Preetesh Jain, M.D., D.M., PhD[*,1], **Philip A Thompson, M.B.B.S.**[*,1], **Michael Keating, M.D.**[1], **Zeev Estrov, M.D.**[1], **Alessandra Ferrajoli, M.D.**[1], **Nitin Jain, M.D.**[1], **Hagop Kantarjian, M.D.**[1], **Jan Burger, M.D., PhD**[1], **Susan O'Brien, M.D.**[2], and **William G. Wierda, M.D., PhD**[1]

[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas

[2]Chao Family Comprehensive Cancer Center, UC Irvine

Abstract

Introduction—Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor, approved for the treatment of patients with chronic lymphocytic leukemia in frontline and relapsed-refractory settings. We previously reported poor outcomes for patients discontinuing ibrutinib; however, long term outcomes were not reported.

Methods—We retrospectively analyzed data for 320 patients treated with ibrutinib on clinical studies between 2010–15 at M.D. Anderson Cancer Center.

Results—We report long-term outcomes for CLL patients after discontinuing ibrutinib. Ninety patients discontinued ibrutinib from a total of 320 patients (28%) treated with ibrutinib-based regimens. Eighty patients were relapsed/refractory and 10 were treatment-naïve. The median time to discontinuation was 15 months (range 1.2–54). After a median follow up of 38 months from initiating ibrutinib, 40 patients (44%) were alive. Major reasons for ibrutinib discontinuation were intolerance, n=29 (32%); miscellaneous n=28 (31%); progression, n=19 (21%); and Richter's Transformation (RT), n=9 (10%). Median survival was 33 months for ibrutinib intolerance; 11 months for miscellaneous causes, 16 months for progressive CLL and: 2 months for RT. Among the 19 patients with progressive CLL, 42% responded to subsequent therapy.

Conclusions—Ibrutinib discontinuation is observed during therapy. Patients with disease transformation have especially poor outcomes, while patients who develop progressive disease on ibrutinib therapy have a median survival of <1.5 years. Survival was associated with reason for discontinuation; patients with progressive CLL had better survival compared to disease

Corresponding Author: William G. Wierda, MD, PhD, Professor, Department of Leukemia, Unit 428, 1515 Holcombe Boulevard, Houston, TX 77030; PO Box 301402, Houston, TX 77230-402, USA. Phone +1-713-563-1487 or (713) 792-1865; FAX +1-713-794-4297, wwierda@mdanderson.org.

*Equal Contribution

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Authorship Contributions

P.J., P.T. and W.W. designed the study.
P.J., P.T. and W.W. analyzed results.
P.J., P.T., M.K., W.W., J.B., N.J., S.O.B. wrote and reviewed the paper.
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All authors reviewed and gave the final approval for the paper.

transformation. Effective salvage strategies for patients with CLL who progress on ibrutinib therapy is of critical importance.

Keywords

Ibrutinib; CLL; chronic lymphocytic leukemia

Introduction

Ibrutinib is a BTK (Bruton's tyrosine kinase) inhibitor currently used as first-line and salvage therapy in patients with CLL. Combinations of ibrutinib with chemotherapy, anti-CD20 monoclonal antibodies[1] or with venetoclax and other novel agents are in clinical trials. Several studies[2–5] have shown that 10–20% of patients receiving ibrutinib (frontline or RR), discontinued therapy after a median follow-up of 1 year, due to either intolerance, disease progression, transformation or other causes. Few groups have previously reported that the survival of patients who discontinue ibrutinib due to disease transformation or early disease progression are poor. [2, 3, 6] Patients with BCL6 abnormalities or complex karyotype had increased risk of disease progression on ibrutinib.[2] Survival after ibrutinib was associated with the reason for discontinuation, being very short in patients who discontinued ibrutinib due to CLL transformation and 18 months or longer in patients who discontinued for disease progression.[2] The median follow up of patients reported in these studies was <2 years. Development of progressive CLL is frequently associated with *BTK* mutations,[7, 8] most commonly C481S or activating mutations in phospholipase-gamma-2 (*PLCγ2*).[9] Rarely ibrutinib resistant sub-clones were detectable in patient samples prior to ibrutinib.[7] Additionally, clones with del(8p), mutations in *EP300*, *MLL2* and *EIF2A* and SH2 domain mutation (*BTKT316A*) have also been identified in resistant patients.[7, 10] Ibrutinib resistance[8] is a growing concern as more patients receive this treatment. In this report, we will present the long-term outcome of CLL patients who discontinued ibrutinib.

Methods

We reviewed the charts of 90 patients who discontinued ibrutinib from a total of 320 patients who were treated with ibrutinib-based regimens on various clinical trials from 2010–15 at M.D. Anderson Cancer Center (Supplemental Table-1). Treatment protocols and informed consents were approved by the Institutional Review Board (IRB) and trials were conducted in accordance with the declaration of Helsinki. Survival analysis was performed using the Kaplan-Meier method and comparison of groups performed using Cox Regression. The cumulative incidence method was used to calculate time to ibrutinib discontinuation, taking into account competing risks.

Results and discussion

Overall, 90 (28%) patients discontinued ibrutinib following first-line (n=10/68) or salvage ibrutinib therapy (n=80/252). Forty-seven patients (52%) received ibrutinib monotherapy; 31 patients (34%) received ibrutinib in combination with rituximab; and 12 patients (13%) received ibrutinib with bendamustine and rituximab. Overall median time to discontinuation of ibrutinib was 15 months (range 1.2–54), 19 months (5–47) for the previously untreated

patients and 14.5 months (1.2–54) for R/R patients. Reasons for and median time to discontinuing ibrutinib were: intolerance/toxicity [n=29, 32%; 16 months], miscellaneous (9 stem cell transplantation (SCT), 8 other cancers, 2 sudden death, 6 sepsis and previous comorbidities, 3 unknown), [n=28, 31%; 10.4 months] progressive CLL [n=19, 21%; 22.3 months], disease transformation [n=9, 10%; 13.2 months (7 diffuse large B cell lymphoma, 1 histiocytic sarcoma and 1 plasmablastic lymphoma)] and transition to commercial supply (n=5; 26 months). Among the 9 patients who discontinued for SCT, 4 were in complete remission (CR) and remained under observation after SCT and remained in CR. Reasons for discontinuation after first-line ibrutinib (n=10) were: disease transformation [n=2]; intolerance [n=6; 3 atrial fibrillation and arrhythmias, 2 bleeding and 1 pneumonia]; transition to commercial supply (n=1) and death due to unknown cause (n=1). Reasons for discontinuation in R/R patients (n=80) were: disease transformation [n=7]; intolerance/ toxicities [n=23; 7 diarrhea, 5 atrial fibrillation, 4 bleeding, 1 pneumonia and 6 miscellaneous toxicities]; disease progression [n=19], miscellaneous reasons [n=27] and transition to commercial supply in [n=4] patients. Clinical characteristics of patients who discontinued ibrutinib for intolerance and CLL progression/transformation are summarized in Table-1. In Table-2, we have summarized the clinical data at progression, survival outcomes and causes of death in 28 patients who discontinued ibrutinib due to CLL progression (n=19) and/or disease transformation (n=9). On first-line ibrutinib, 2 patients developed Richter's Transformation (RT) while none had progressive refractory CLL. Both patients who developed RT on first-line ibrutinib had *IGHV*-UM, (one VH3 and another VH1-69) Rai stage-I disease, overexpression of CD38 and Zap-70, and del(17p) by FISH, prior to starting ibrutinib. Overall, the majority of patients had high-risk features prior to starting ibrutinib (91% *IGHV*-UM, 41% with del(17p) by FISH, 35% with a complex karyotype and advanced Rai stage disease (55%).

We then analyzed survival outcomes for patients after they discontinued ibrutinib. After a median follow up of 38 months, 40 patients (44%) were alive at the time of last follow up. The median overall post ibrutinib survival time was 20.6 months (Figure-1A). Survival according to the cause of discontinuation is shown in Figure-1B. Median survival of patients was 33 months for patients who discontinued ibrutinib because of intolerance/toxicities, 11 months for those who discontinued for miscellaneous reasons, 16 months in those with progressive disease, and 2.3 months in patients who developed CLL transformation ($P<0.0001$). Patients with progressive CLL had superior survival than patients who developed RT (Hazard ratio 6.7; $P<0.0003$). Survival of patients did not differ significantly according to prior treatment status Figure-1C. The cumulative incidence of discontinuation of ibrutinib according to reason for discontinuation is shown in Figure-1D. We also assessed the response to subsequent therapies among the 19 patients who developed progressive disease on ibrutinib treatment. Eight of 19 patients (42%) responded to subsequent therapy. Among the 8 responders, 5 (62%) achieved a partial response (PR) on venetoclax-based therapy (3/5 also failed idelalisib prior to commencing venetoclax); 2(25%), responded to ofatumumab monotherapy and one patient was treated (12%) with idelalisib with rituximab. Evaluation for *BTK* and *PLCγ2* mutations was performed in 2 patients at the time of CLL progression: one patient had a *BTK* mutation (C481S) after disease progression; another

patient who progressed on both ibrutinib and venetoclax had *BRAF*, *TP53* and *FBXW7* mutations; however, pre-treatment mutational profile was not available for this patient.

Ibrutinib has significantly improved outcomes for patients with CLL. Nevertheless, there continue to be challenges with this treatment since most patients achieve partial remission as the best response, treatment is continuous and indefinite, and some patients must discontinue treatment owing to resistance or intolerance/toxicity. In prior reports, early ibrutinib discontinuation was associated with a poor outcome and subsequent survival correlated with the reason for discontinuation; patients with disease transformation had very poor outcomes[2, 3], while patients who developed progressive CLL had a median survival of 17 months[2]. Similar to previous publications[2], we have shown that RT occurs relatively early during ibrutinib therapy, with the risk decreasing significantly after 12–18 months on treatment; in contrast, there is an ongoing incidence of CLL progression and cessation of treatment due to toxicity during long-term follow-up.[11] The outcomes for patients who develop CLL progression remain poor; approximately 70% of patients who progressed on ibrutinib will respond to venetoclax[12]; however, the durability of these responses is not clear and other salvage options are currently limited. Furthermore, the outcome of patients who develop Richter's transformation while on ibrutinib remains very poor.[2] Therefore, development of effective salvage strategies for patients with progression/Richter's transformation on ibrutinib therapy is of critical importance. Ideally, these strategies should be guided by the knowledge of the molecular mechanisms of resistance in an individual patient.[8] Several molecular mutations associated with ibrutinib resistance have been identified, but whether these specifically predict for response to subsequent salvage therapy is unclear and should be systematically studied in future. It is likely that the subclonal architecture in such patients is complex[7, 13, 14] and that sequential monotherapy with other targeted agents after development of ibrutinib resistance will also see outgrowth of resistant subclones. For this reason, we and other groups are developing combination strategies for treatment of high-risk CLL patients. Additionally, the increasingly likelihood of treatment discontinuation for toxicity over time and poor outcomes after discontinuation for intolerance argue for the importance of developing time-limited, combination therapy in all patients, rather than relying on indefinite, ibrutinib monotherapy. In this study, there were 2 patients who developed Richter's transformation on first-line ibrutinib and they had poor outcomes with salvage therapy. It is unclear whether RT occurring during ibrutinib therapy is molecularly distinct from RT occurring *de novo* or after chemoimmunotherapy. It is also unclear whether *BTK* and/or mutations play any role in development of RT, as there is limited data on sequencing performed from lymph node specimens taken at the time of transformation. In summary, as the use of ibrutinib treatment continues to increase in patients with CLL; it is essential to delineate the pattern of mutations and dynamics of clonal evolution in patients who are discontinuing ibrutinib due to disease progression/transformation and identify pathways for therapeutic targeting to improve the survival outcomes for these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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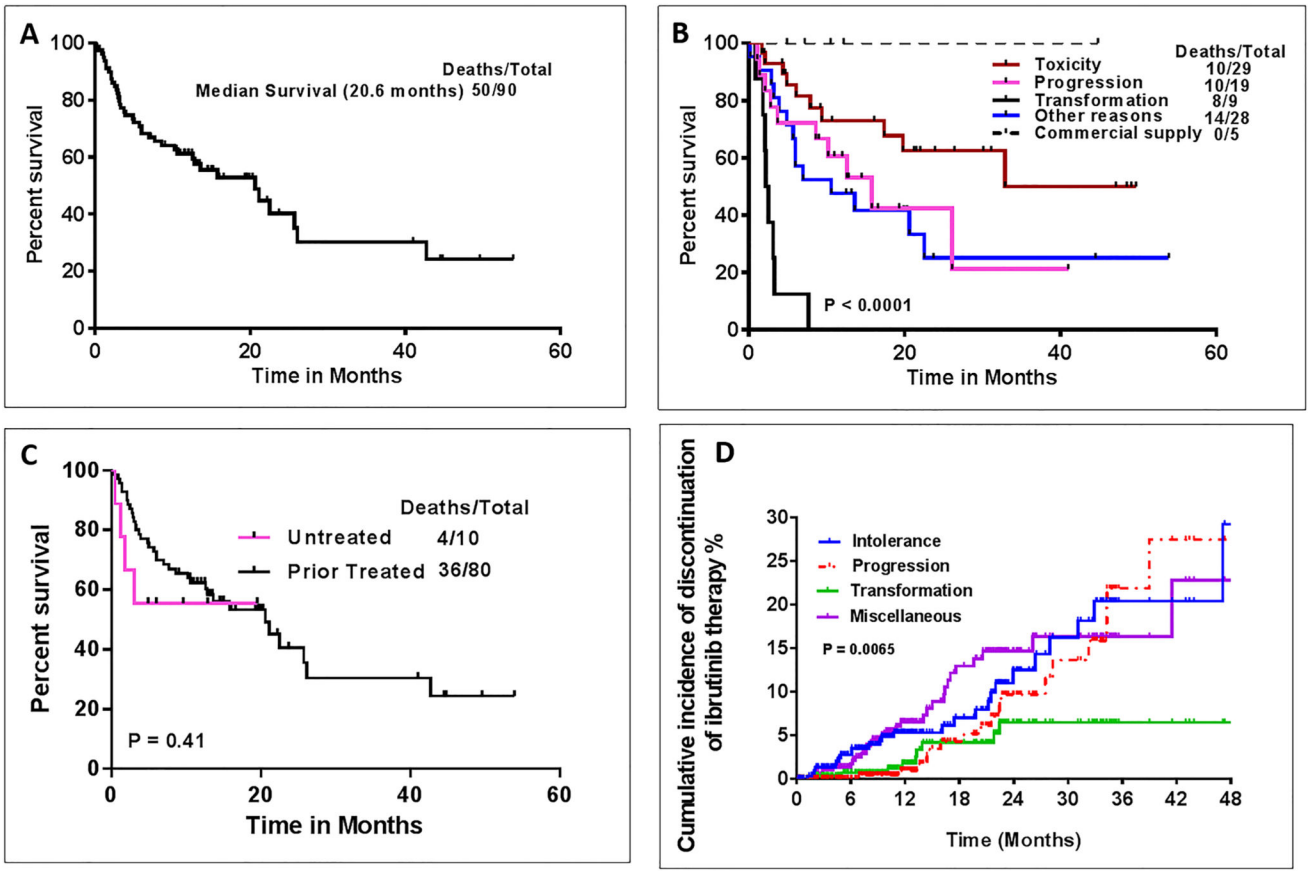

Figure 1. (A–D) Outcomes of patients after discontinuing ibrutinib

A) Median overall survival was 20.6 months after discontinuation of ibrutinib (n=90) **B)** Survival of patients according to the cause of discontinuation is shown; median survival, toxicity 33 months; disease progression 16 months; disease transformation 2.3 months, other causes 11 months and commercial supply not reached **C)** Median survival is compared between patients who were previously untreated (not reached) vs those with R/R CLL (21 months) (p= 0.41) **D)** Cumulative incidence of ibrutinib discontinuation is shown. Most events occurred within first 2 years of ibrutinib therapy. Except transformation, incidence of other causes of discontinuation, progression, intolerance and miscellaneous reasons, continued to increase after 48 months (p=0.0065).

Table 1

Characteristics of patients at the time of ibrutinib discontinuation

Characteristic Measure/Category	Intolerance (n=29)	Progression (n=19)	Transformation (n=9)	Miscellaneous (n=28)	P value
Age, years Median (range)	67 (43–80)	66 (35–84)	66 (53–80)	67 (50–83)	0.52
Rai stage (0,1–2/3–4) (%)	96/4	58/42	28/72	36/64	0.0001
WBC $\times 10^9$/L Median (range)	9.3 (2.6–130)	14 (4.4–133)	6.5 (1.8–85)	21 (1.8–263)	0.06
ALC $\times 10^9$/L Median (range)	3.03 (0.29–100)	7.3 (1.3–7.3)	1.2 (0.2–120)	20 (0.3–223)	0.01
Hemoglobin g/dL Median (range)	12.5 (5–17)	13 (8–16)	9.4 (8–15)	11.6 (8–15)	0.14
Platelets $\times 10^9$/L Median (range)	150 (48–276)	102 (7–262)	79 (15–212)	97 (19–184)	0.0008
β2M (mg/L) (</≥ 4 mg/L) (%)	75/25	72/28	43/57	50/50	0.08
IGHV mutation (M/UM) (%)	20/80	12/88	0/100	4/96	0.09
Prior therapy None/ previously treated (%)	21/79	0/100	22/78	4/96	0.04
Median number of prior therapies (range)	2 (0–7)	2 (1–6)	2 (0–5)	2 (0–6)	N.S.

Table–2

Patients who progressed and/or transformed on ibrutinib therapy (n=28) – Survival after ibrutinib and patient characteristics

Age (Yrs)	Gender	FISH	#IGHV Mutation Status	Cause of discontinuation	Disease Status[#]	Ibrutinib alone (Y/N)	Duration of Ibrutinib (Months)	Salvage treatment	Survival Status	Post IR survival (Months)	Cause of death
64	Male	Del11q	UM	Progression	RR	Y	39.0	Venetoclax	Dead	2.8	Disease progression, multiorgan dysfunction, infections
56	Male	Del17p	ND	Progression	RR	Y	34.3	3 Lines[*]	Dead	26.1	Disease progression, infections
56	Male	Del17p	UM	Progression	RR	Y	27.5	None	Dead	1.1	Disease progression and therapy related myelodysplasia, CNS bleed
52	Male	Del17p	UM	Progression	RR	Y	28.3	Venetoclax, anti-CD19	Dead	12.6	Disease progression and lost to follow up
83	Male	Del17p	UM	Progression	RR	Y	18.5	Ofatumumab	Alive	41.0	-
73	Female	Del13q	M	Progression	RR	Y	20.4	None	Dead	0.0	Disease progression, multiple comorbidities, sepsis
68	Male	Del17p	UM	Progression	RR	Y	11.4	Duvelisib, idelalisib	Dead	10.2	Fungal pneumonia
74	Female	Del17p	ND	Progression	RR	Y	22.4	Venetoclax, idelalisib	Alive	14.5	-
47	Female	Del13q	UM	Progression	RR	Y	14.7	Venetoclax	Alive	16.6	-
73	Female	Del17p	UM	Progression	RR	No	14.4	None	Dead	1.4	Progression, comorbidities, infections
53	Male	Del17p	UM	Progression	RR	No	53.3	3 Lines[¥]	Alive	11.0	-
58	Male	Del17p	UM	Progression	RR	No	34.3	3 Lines [**]	Alive	12.00	-
53	Male	Del13q	UM	Progression	RR	No	21.5	3 Lines [¥¥]	Dead	15.8	Complications of therapy
77	Male	Del17p	UM	Progression	RR	No	15.9	None	Dead	3.7	Disease progression, infection
35	Female	ND	UM	Progression	RR	No	6.9	None	Dead	2.1	Disease progression, infections, pneumonia
51	Male	Del17p	UM	Progression	RR	No	53.9	Idelalisib, venetoclax-obinutuzumab	Alive	9.0	-
73	Female	Del17p	UM	Progression	RR	No	32.3	Ofatumumab, idelalisib	Dead	8.6	Orbital cellulitis, multiple infectious complications
79	Female	Del17p	UM	Progression	RR	No	22.6	Obinutuzumab	Alive	19.3	-
65	Male	Del17p	M	Progression	RR	No	13.6	Venetoclax	Alive	12.8	-
66	Male	Del17p	UM	Disease Transformation	FL	Yes	10.1	HCVAD, OFAR	Dead	3.1	Richter’s transformation
80	Female	Del13q	UM	Disease Transformation	FL	Yes	11.7	None	Dead	1.8	Richter’s transformation
63	Female	Del17p	UM	Disease Transformation	RR	Yes	22.4	OFAR	Dead	2.2	Richter’s transformation
53	Male	Neg.	UM	Disease Transformation	RR	Yes	5.0	None	Dead	0.9	Richter’s transformation
57	Male	Del11q	UM	Disease Transformation[^]	RR	Yes	13.3	None	Dead	0.0	Sepsis and histiocytic sarcoma transformation

Age (Yrs)	Gender	FISH	#IGHV Mutation Status	Cause of discontinuation	Disease Status[#]	Ibrutinib alone (Y/N)	Duration of Ibrutinib (Months)	Salvage treatment	Survival Status	Post IR survival (Months)	Cause of death
73	Male	Del17p	UM	Disease Transformation	RR	Yes	1.9	OFAR	Dead	2.1	Richter's transformation
66	Female	Del11q	UM	Disease Transformation	RR	No	13.2	Duvelisib	Dead	2.5	Richter's transformation
73	Female	Del17p	UM	Disease Transformation	RR	No	21.8	Venetoclax	Dead	3.3	Unknown
66	Male	T12	UM	Disease Transformation	RR	No	13.9	HCVAD	Dead	7.7	Richter's transformation

[*] 3 lines – Duvelisib, idelalisib and obinutuzumab,

[#] First-line (FL) and relapsed refractory (RR),

[¥] 3 lines – Idelalisib, chimeric antigen receptor T cell therapy then venetoclax planned for stem cell transplant,

[**] 3 lines – Idelalisib with rituximab, obinutuzumab and venetoclax planned for stem cell transplant,

[¥¥] 3 lines – Venetoclax, ofatumumab-HCVAD then chimeric antigen receptor T cell therapy,

[^] CLL transformation to histiocytic sarcoma,