Clinical Trial Brief Report

Clinical Cancer Research

Long-term Follow-up of Treatment with Ibrutinib and Rituximab in Patients with High-Risk Chronic Lymphocytic Leukemia

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Abstract

Background: Ibrutinib is an active therapy with an acceptable safety profile for patients with chronic lymphocytic leukemia (CLL), including high-risk patients with del17p or with *TP53* mutations. Ibrutinib is broadly indicated for the treatment of patients with CLL and specifically including those with 17p deletion. The optimal use of ibrutinib in combination with other agents remains controversial.

Experimental Design: We report the long-term outcome [median follow-up of 47 months (range, 36–51 months)] of 40 patients with high-risk CLL, treated on the first ibrutinib combination trial with rituximab (IR). The majority of patients (36/40) were previously treated.

Results: Median age was 65 years, and 21 patients (52%) had 17p deletion. Median duration on treatment was 41 months (range, 2–51 months), and median number of treatment cycles was 42 (range, 2–49). Overall response rate was 95%, and 9 patients (23%) attained a complete remission. Twenty-one patients discontinued treatment, 10 due to disease progression, 9 for other causes, and 2 due to stem cell transplantation; the remaining 19 patients continue on ibrutinib. Median progression-free survival for all patients was 45 months, which was significantly shorter in the subgroup of patients with del17p ($n = 21$, 32.3 months, $P = 0.02$). Fourteen patients (35%) died, five from progressive disease, five from infections, and four from other causes. Median overall survival has not been reached.

Conclusions: IR combination therapy leads to durable remissions in high-risk CLL; the possible benefit from the addition of rituximab is currently explored in a randomized trial. *Clin Cancer Res; 23(9); 2154–8. ©2016 AACR.*

Introduction

Ibrutinib is a Bruton tyrosine kinase (BTK) inhibitor with clinical activity in several B-cell malignancies, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and Waldenstrom macroglobulinemia (1). A series of clinical trials demonstrated a major improvement in progression-free (PFS) and overall survival (OS) in patients with CLL treated with ibrutinib in the first-line (2, 3) and the relapse-refractory (4, 5) disease setting. The advent of ibrutinib is especially significant for high-risk CLL patients, such as patients with 17p deletion, who generally do not achieve durable responses with chemo-immunotherapy. Three-year follow-up of a clinical trial with single-agent ibrutinib in relapsed-refractory and in treatment-naïve patients (age $\geq$ 65 years) demonstrated durable responses and an acceptable safety profile with continued long-term therapy in the majority of patients (6). However, with ibrutinib single-agent use, most patients, even after long-term therapy, achieve partial remissions, and complete remissions remain the exception. Therefore, ibrutinib combination therapy has been pursued in a number of clinical trials. We previously reported the results of a phase II trial of the combination of ibrutinib with rituximab (IR) in patients with high-risk CLL (7), which was the first trial to report ibrutinib combination therapy data. In this trial, we demonstrated that the addition of rituximab attenuated the redistribution lymphocytosis observed in studies with single-agent ibrutinib in patients with CLL, which often results in partial remission (PR) with lymphocytosis, and consequently, patients achieved remissions within a shorter time. However, the long-term impact of IR on survival, response, immunologic parameters, and the toxicities in patients with high-risk CLL has not been characterized (8). In this report, we describe the long-term follow-up data of IR in patients with high-risk CLL.

Patients and Methods

This single-arm phase II study in high-risk patients with CLL ($n = 40$) treated with ibrutinib and rituximab (IR) was developed by the investigators in collaboration and supported by Pharmacyclics, Inc. and was approved by The University of Texas MD Anderson Cancer Center Institutional Review Board. Informed consent was obtained in accordance with institutional guidelines and the Declaration of Helsinki. Patients with high-risk CLL

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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included patients with the presence of a 17p deletion, *TP53* mutation, and/or 11q deletion and patients with short remission durations of <36 months after first-line treatment with chemoimmunotherapy. Details of the inclusion, exclusion criteria, study design, follow-up, and response assessment were reported previously (7). Treatment consisted of ibrutinib (420 mg orally daily) combined with weekly rituximab (375 mg/m^2) for weeks 1 to 4 (cycle 1), then monthly rituximab until cycle 6, followed by single-agent ibrutinib continuously. Patients remained on ibrutinib treatment until disease progression or toxicities or complications precluded further therapy. The primary endpoint was to assess the activity of ibrutinib and rituximab in high-risk CLL, measured as overall response rate (ORR) and PFS. Statistical analyses were conducted using GraphPad Prism Version 6.00 for Windows (GraphPad Software). Survival or time to progression function was estimated using the Kaplan–Meier method. Toxicity was reported by the type, frequency, and severity.

Results

Patients and treatment

Previously untreated ($n = 4$, all with del17p) and previously treated ($n = 36$) patients were included in the study. The clinical characteristics of the patients are described in Table 1. Eleven patients (27%) were over the age of 70 years. Twenty-one patients had del17p FISH cytogenetic aberration, and 12 patients had del11q. Thirty-three patients had unmutated immunoglobulin heavy chain variable region genes (IGHV), one patient had mutated IGHV, and six patients had inconclusive IGHV status. Median follow-up of the patients was 47 months (range, 36–51 months). At the time of last follow-up, 19 patients (47%) remained on treatment (6 with del17p), and 21 (52%) had discontinued treatment, 10 due to disease progression, 9 due to other complications, and 2 patients underwent stem cell transplantation in response. Causes of treatment discontinuation, death, and clinical characteristics are detailed in Table 2. Of note, among the four previously untreated patients with CLL with del17p, two patients are still continuing on study, and two discontinued treatment, one due to complicated ear infections and ear bleeding and another due to significant arthralgias, enthesitis, and bruising. Among these four patients, three were alive, and one died from disease progression approximately 2 months after discontinuation of ibrutinib. Among the 10 patients who discontinued due to disease progression, 2 patients developed Richter transformation, both with del17p. Thirteen patients (46%) had complex karyotype, and disease progression was more frequent within this subgroup (in 7/13 or 54% of these patients). Overall, the median number of cycles received by the patients was 42. The majority of patients (38/40 or 95%) received $\geq$6 cycles of therapy. The median dose of ibrutinib was 420 mg daily. Median duration of ibrutinib therapy was 41 months (range, 2–51 months). Among the 21 patients who came off therapy, the median survival after treatment discontinuation was 8 months. The best ORR was 95%, with 28 patients (72%) achieving a PR, 9 (23%) a complete remission (CR), 2 patients did not respond, and 1 patient was not evaluable. Of the 9 patients with CR, 2 patients achieved a minimal residual disease (MRD) negative CR. The CR rate improved from 4 patients (10%) reported initially (7) to 9 patients (23%) with the longer follow-up, which is consistent with the single-agent ibrutinib experience and longer follow-up (6). Among the 21 patients with del17p, 18 of 21 responded (86%), 5 achieved a CR (24%), and 13 a PR (62%). Among the four patients who were previously untreated and had del17p, three (75%) achieved a CR (two were MRD negative), and one patient a PR. The toxicities that were considered to be likely related to IR treatment are displayed in the Supplementary Table S1. Overall, we noted that 16 patients (40%) developed clinically significant infections, requiring therapy, involving the upper respiratory tract and/or the lungs. Overall, 14 patients died, 5 while being on study, 3 due to complicated infections, 1 had a sudden death without antecedent illness, presumed cardiac, and 1 patient from metastatic non–small cell lung cancer. Figure 1A–D shows the PFS and OS. Overall, the median PFS was 45 months, and the median OS was not reached. The number of events and deaths were higher in patients with del17p, resulting in a significantly shorter PFS and shorter OS in patients with del17p (PFS, $P = 0.02$; OS, $P = 0.24$; Fig. 1B–D). The median PFS of patients with del17p was 32.3 months. Similarly, patients with complex karyotype abnormalities, which constitutes another high-risk subset of patients, had shorter PFS or OS (Fig. 2A and B); however, these differences did not reach statistical significance. In a subset analysis, among the patients with del17p ($n = 21$), the PFS and OS were not significantly different according to the presence ($n = 11$) or absence of complex karyotype ($n = 4$) (Supplementary Fig. S1). This could be due to smaller number of patients in each group and require large dataset for the analysis.

Only one patient developed a secondary cancer after starting treatment, a squamous cell cancer of the lungs, diagnosed 2 years after starting IR therapy. Patterns of change in other disease-associated parameters, absolute lymphocyte count (ALC), absolute neutrophil count, platelet count, and serum β2 microglobulin (β2M) levels, are shown in Supplementary Fig. S2. Serum immunoglobulin levels (IgG, IgM, IgA) and absolute T-cell subsets were analyzed and are summarized in the Supplementary Material (Supplementary Figs. S3 and S4). There was no

Table 1. Initial patient characteristics ($N = 40$)

Patients ($N = 40$)	
Median age (range)	65 (35–82)
Female	14 (35%)
Male	26 (65%)
Del (17p)[a]	21 (52%)
Del (11q)	12 (30%)
Del (13q)	5 (12.5%)
FISH negative	2 (5%)
Mutation status IGVH (immunoglobulin heavy chain variable region)	Unmutated (33), not done (6), mutated (1)
	Median (range)
Prior treatments	2.0 (0–8)
Cycles completed	42 (2–49)
Median follow-up time of alive patients (months)	47 (36–51)
Hemoglobin (g/dL)	11.7 (6.7–15.6)
Platelets (10^3/μL)	91.5 (36–242)
White blood cell count (10^3/μL)	22.4 (2.2–297.8)
Absolute lymphocytes (10^3/μL)	19.9 (0.4–277)

[a]Overall, among the 40 patients, 21 were del17p by FISH, of which only 3 were del17p alone, and the distribution of other FISH abnormalities in the remaining 18 patients was as follows: 1 with del11q, 1 with 11q and trisomy 12, 2 with trisomy 12, 6 with del11q and del13q, and 8 with del13q. Similarly, there were 12 patients with del11q (without del17p), of which only 4 were del11q alone and 8 were del11q with del13q.

Table 2. Summary of causes of discontinuation of ibrutinib with rituximab (IR) with patient characteristics ($n = 21$)

Patient characteristics												
Age (y)	Gender	FISH	#IGHV mutation status	Cause of discontinuation	Type of complication	Duration of ibrutinib (months)	Salvage treatment	Survival status	On study death (Y/N)	Post-IR survival (months)	Causes of death	Disease transformation (Y/N)
65	Male	Neg.	UM	Stem cell transplant	None	12.6	Unknown	Dead	N	4.5	Disease progression	No
63	Female	17p	UM	Stem cell transplant	None	14.9	None	Alive	N	23.4	—	No
62	Male	17p	UM	Complications	Ear infections	16.8	—	Dead	Y	0.0	Pulmonary complications	No
67	Male	11q	UM	Complications	Unknown, found dead in his sleep	16.4	—	Dead	Y	0.0	Unknown	No
61	Male	17p	UM	Complications	Pulmonary infections	9.5	—	Dead	Y	1.5	Pulmonary infections	No
68	Male	11q	UM	Complications	Diarrhea, subdural hematoma	21.5	Restarted ibrutinib	Alive	N	14.8	—	No
72	Male	11q	UM	Complications	Progressive lung cancer	31.8	On ibrutinib	Dead	Y	0.0	Lung cancer	No
76	Male	17p	UM	Complications	Multifocal aspergillosis	2.1	—	Dead	Y	0.2	Pneumonia, brain abscess	No
57	Female	17p	M	Complications	Mucositis	6.0	OFAR, ibrutinib restarted	Dead	N	18.5	Sepsis	No
82	Male	17p	UM	Complications	Comp-CHF, COPD	8.4	—	Dead	N	3.9	CHF, COPD	No
61	Female	17p	UM	Complications	Toxicity-arthritis	45	Planning	Alive	N	0	—	No
73	Female	17p	UM	Disease progression	—	14.4	Rituximab	Died	N	1.4	Resistant disease	No
58	Male	17p	UM	Disease progression	—	34.3	Idelalisib + rituximab	Alive	N	4.2	—	No
52	Male	13q	UM	Disease progression	—	21.4	ABT-199, HCVAD, idelalisib	Died	N	15.8	Resistant disease with TP53 acquisition	No
35	Female	11q	UM	Disease progression	—	6.8	—	Died	N	2.1	Pneumonia	No
76	Female	17p	UM	Disease progression	—	45.1	Ibrutinib with BR	Alive	N	0.0	—	No
65	Female	17p	UM	Disease progression	—	13.1	R-MP then IPI-145	Died	N	2.5	Progressive disease	Yes
73	Female	17p	UM	Disease progression	—	32.3	Expt. agents	Died	N	8.6	Infections	No
73	Female	17p	UM	Disease progression	—	21.9	ABT-199	Died	N	3.1	Progressive disease	Yes
78	Female	17p	UM	Disease progression	—	22.5	Ofatumumab	Alive	N	20.0	—	No
65	Male	17p	ND	Disease progression	—	47.1	Venetoclax	Alive	N	2.9	—	No

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HCVAD, hyper-CVAD (cyclophosphamide, vincristine, adriamycin, and dexamethasone); M, mutated; ND, not detected; OFAR, oxaliplatin, fludarabine, cytarabine, and rituximab; UM, unmutated.

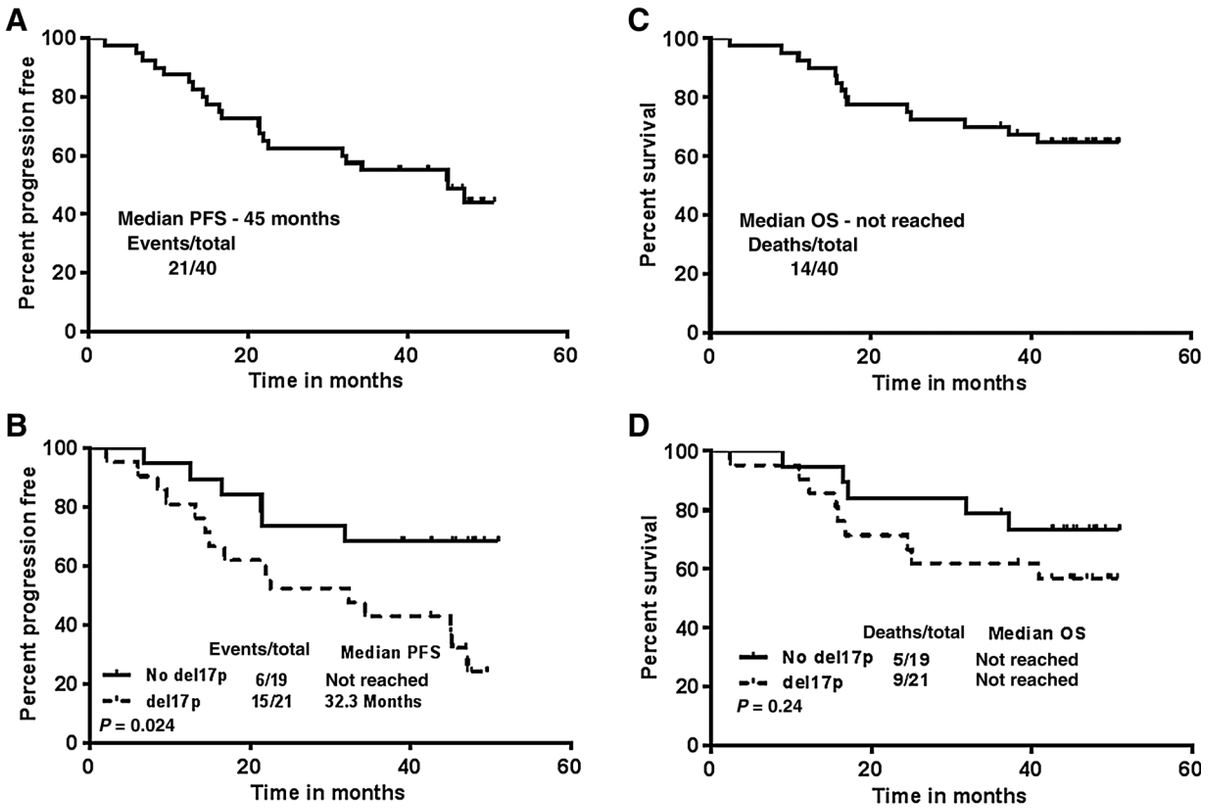

Figure 1.

Survival outcomes for patients treated with IR, PFS and OS after a median follow-up of 42 months. **A,** Median PFS in all patients was 45 months. **B,** PFS according to the presence or absence of deletion 17p; median survival not reached in patients without deletion 17p and median PFS 32 months in patients with deletion 17p ($P = 0.02$). **C,** Median OS in all patients was not reached. **D,** OS according to the presence or absence of deletion 17p; median survival not reached in both group of patients with/without deletion 17p ($P = 0.24$).

significant change in serum immunoglobulin levels over time, consistent with the ibrutinib single-agent experience. The ALC levels decreased and stabilized, and T-cell subset numbers and β2M levels decreased after starting IR treatment and stabilized over time when followed for up to 36 months.

Discussion

In the current analysis, we present the long-term follow-up data of patients with high-risk CLL treated with a combination of ibrutinib and rituximab (IR). The majority of patients (36/40) were previously treated. This study demonstrated that IR in high-risk patients with CLL is well tolerated, active, and can induce durable remissions, including CR in patients with high-risk CLL. The improvement in long-term PFS in high-risk patients with CLL with ibrutinib-based therapy is a significant advance in treatment of CLL. Recently, the 3-year follow-up of single-agent ibrutinib was reported (6) and demonstrated that responses improve over time in treatment-naïve and in relapsed-refractory patients with CLL. In our study, with an extended follow-up of over 3 years, we demonstrated that patients with high-risk CLL treated with the IR combination have high response rates, which also further improve over time when compared with the original report (7). Median PFS and OS achieved after 3 years in our study (45 months and not reached) appear similar to single-agent ibrutinib data in relapsed-refractory patients, although cross trial comparisons are problematic. Nonetheless, as our study involved only patients with CLL who had high-risk disease, the achievement of median PFS of 45 months in patients with high-risk CLL constitutes a major improvement over previously reported data in patients with high-risk CLL with more conventional treatments (9, 10). Of note, in patients with del17p, the long-term follow-up data when using first-line chemo-immunotherapy with the FCR regimen showed a median PFS of 15 months (11). The fact that 21 patients came off study (10 were due to disease progression) and 14 patients died (5 deaths due to CLL) emphasizes that, despite the major improvement in outcome with ibrutinib-based therapy in high-risk CLL, there remains an urgent need for further improvement in these patients, which may come from cellular therapy approaches (allogeneic SCT, CAR-T cell therapy) and/or BCL2 antagonist, such as venetoclax. Furthermore, this dataset reemphasizes that outcomes of patients with CLL after they progress or develop disease transformation on ibrutinib-based treatment generally are poor (median survival, 2.8 months; ref. 12). Interestingly, with longer follow-up, serum immunoglobulin and T-cell numbers remained stable with IR therapy.

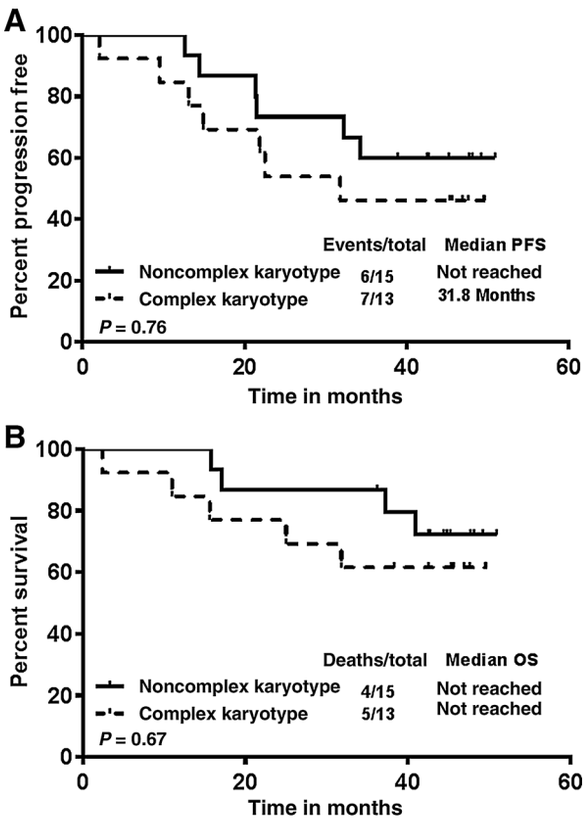

Figure 2.

Survival outcomes for patients treated with IR, complex versus noncomplex karyotype. **A,** Median PFS in patients with complex versus noncomplex karyotype was 31.8 months versus not reached ($P = 0.76$). **B,** OS according to the presence or absence of complex karyotype; median survival not reached in both group of patients ($P = 0.67$).

In summary, our data show that the combination of ibrutinib with rituximab is a potent treatment option for patients with high-risk CLL and can induce durable remissions in a majority of patients. However, data from the ongoing randomized study of IR versus ibrutinib single agent (Clinical trial identifier, NCT02007044) are required to determine the benefit from the addition of rituximab to ibrutinib in the treatment of patients with CLL.

Disclosure of Potential Conflicts of Interest

P.A. Thompson is a consultant/advisory board member for Pharmacyclics. Z. Estrov is a consultant/advisory board member for and reports receiving commercial research grants from Incyte. J. Burger is a consultant/advisory board member for Janssen and reports receiving commercial research grants from Gilead, GlaxoSmithKline, and Pharmacyclics. No potential conflicts of interest were disclosed by the other authors.

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