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ORIGINAL ARTICLE

Reduced Dose Ibrutinib Due to Financial Toxicity in CLL

Deepesh P. Lad[1] · Pankaj Malhotra[1] · Alka Khadwal[1] · Gaurav Prakash[1] · Arihant Jain[1] · Subhash Varma[1]

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Abstract Ibrutinib is the only approved novel agent that is available for the treatment of relapsed-refractory and treatment-naive chronic lymphocytic leukemia patients with deletion 17p or TP53 mutation in India. The cost of ibrutinib is still prohibitive for most Indian CLL patients. We report here for the first time dose reductions due to the patient preference of financial toxicity. We prospectively followed up patients of CLL receiving ibrutinib at a tertiary referral center in India. The period of study was from April 2016 to April 2018. Reduced dose ibrutinib was defined as a sustained ($\geq$ 12 months) dosing at $<$ 420 mg/day, either at treatment initiation or within 3 months from starting therapy. Progression free survival was compared using Kaplan–Meier analysis. There were a total of three patients on reduced dose and twelve patients on standard dose ibrutinib. Two patients discontinued standard dose ibrutinib due to adverse events. The patient age, cytogenetics, number of prior therapies and follow-up were not significantly different between the two groups. The rate of $\geq$ grade3 adverse events was significantly different between the two groups. The overall response rate and median PFS were also not significantly different between the two groups. In the limited patient numbers and follow-up period we show that outcomes of reduced dose ibrutinib are comparable to standard dose ibrutinib but with fewer adverse events. This study provides a proof of concept that a subset of patients might do well on reduced dose ibrutinib.

✉ Deepesh P. Lad
deepesh.kem@gmail.com

[1] Clinical Hematology, Department of Internal Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Keywords CLL · Ibrutinib · Reduced dose · Financial toxicity

Introduction

Ibrutinib is approved for the treatment of all lines of chronic lymphocytic leukemia (CLL) [1]. The US FDA approved Ibrutinib in 2013, and the Indian Central Drugs Standard Control Organization approved it in 2015. Ibrutinib covalently binds Bruton's tyrosine kinase (BTK) and inhibits the B cell receptor downstream signaling pathway [2]. Five-year follow-up studies of ibrutinib have shown impressive results with a 92% progression-free survival (PFS) and overall survival (OS) when used as first line and 43% PFS, 57% OS when used in relapsed-refractory CLL [3]. However, the discontinuation rates in these studies have been to the tune of 5% at 5 years, mostly due to disease progression (33%) and ibrutinib intolerance (21%). Real world studies have confirmed the same finding [4]. European CLL experts recommend against dose reductions of ibrutinib without clinically important reasons. Ibrutinib dose reductions are to be made only for the second and subsequent occurrence of grade $\geq$ 3 non-hematological toxicity, grade $\geq$ 3 neutropenia with infection or fever, or grade 4 hematological toxicities [5]. This recommendation is based only on a single clinical trial (RESONATE) reporting inferior PFS in patients missing ibrutinib for $\geq$ 8 days versus those who adhered to continuous ibrutinib [6]. On the contrary, there is only one report of comparable outcomes of CLL patients treated with reduced dose ibrutinib [7]. Current costs of ibrutinib are prohibitive $2000 per month and out of reach of most patients in India. We describe here our small experience of reduced dose

ibrutinib due to patients preference of financial toxicity [8]. The is the first such report to the best of our knowledge.

Patients and Methods

This was a prospective study following up patients of CLL receiving ibrutinib at a tertiary referral center in India. The period of study was from April 2016 to April 2018. All patients consented to participating in the study. Institutional review committee approved the study. The demographic data, clinical presentation, prognostic factors, treatment indication, treatment lines, response, survival outcomes and adverse events were recorded prospectively. Response was as defined in the 2018 guidelines [9]. Progression- free survival (PFS) was defined as the time from treatment initiation until objective disease progression or death. Time to next treatment (TTNT) was defined as the time from treatment initiation to next treatment or death of any cause. Treatment interruptions and re-dosing were as per ibrutinib package insert suggestions. Patients were encouraged to continue ibrutinib till disease progression. Young, fit patients were also counseled about the option of allogeneic hematopoietic cell transplantation (HCT) as other novel agents are currently unavailable in India. Reduced dose ibrutinib was defined as a sustained ($\geq$ 12 months) dosing at $<$ 420 mg/day, either at treatment initiation or within 3 months from starting therapy [7]. Survival was compared using Kaplan–Meier analysis using GraphPad Prism software version 5. A p value of $< 0.05\%$ was used for statistical significance. In this study we focus on the outcomes of the three patients on reduced dose ibrtuinib and compare it with the outcomes of patients on standard dose ibrutinib.

Results

A total of 17 patients were enrolled on ibrutinib over a period of 2 years. Out of these 17 patients, two (11.7%) patients died due to progressive disease on standard dose ibrtuinib, two (11.7%) patients discontinued ibrutinib due to intolerable, recurrent grade 3 diarrhea despite dose reduction. Three patients (17.6%) requested dose reduction citing financial burden and are continuing dose reduced ibrutinib without disease progression till the last follow-up period. Rest 10 patients continue taking standard dose ibrutinib. None of the patients went on to receive allogeneic HCT. We describe here the three patients on reduced dose ibrutinib (Table 1).

Patient 1. Mrs. HK is a 56-year-old homemaker diagnosed with CLL, Rai I/Binet B with del(11q) in 2010. She was previously treated with chlorambucil and bendamustine-rituximab (BR) sequentially with time to next treatment (TTNT) of less than 3 and 2 years respectively. She received ibrutinib 420 mg as the third line. Within a month she had grade 2 diarrhea and bleeding episodes. Unable to continue affording ibrutinib she reduced her dose of ibrutinib to 280 mg. She had no adverse events on this dose. She had redistribution lymphocytosis which resolved by 12 months. She has been on ibrutinib 280 mg for 2 years now without any progression.

Patient 2. Mr. HS is a 76-year-old retired professor diagnosed with CLL in 2013, Rai stage II/Binet B with bulky lymphadenopathy and trisomy 12. His previous treatment included BR regimen. On relapse after 44 months he had del(17p). Citing financial burden, he requested a reduced dose of ibrutinib. He attained a PR with 280 mg of ibrutinib without any adverse events. He

Table 1 Disease and treatment details of patients on reduced dose ibrutinib

Patient no.	Age/gender	FISH panel	Previous therapies	TTNT (months) with previous therapies	Ibrutinib starting dose (mg)	Dose reduced at time point	Current ibrutinib dose (mg)	Follow-up (months)	Response	Adverse events on standard dose ibrutinib, none on reduced dose ibrutinib
1	56/F	del 11	Clb BR	33 24	420	1 month	280	24	PR	Gr 2 diarrhea and bleed
2	76/M	del 17, trisomy 12	BR	42	280	–	280	12	PR	None
3	60/M	del 11	BR FCR	22 16	420	3 months 16 months	280 140	18	PR	Gr 4 neutropenia, gr 3 diarrhea, gr 2 anemia, thrombocytopenia infection and bleed

Clb chlorambucil, *BR* bendamustine, rituximab, *FCR* Fludarabine, cyclophosphamide, rituximab

has completed one-year without any progression till the last follow-up.

Patient 3. Mr. RS is a 60-year-old businessman, diagnosed with CLL with del(11q) and bulky abdominal lymphadenopathy in 2012. He previously received BR and FCR regimen with the TTNT of 22 and 16 months respectively. He received the ibrutinib 420 mg as the third line. He had grade 3 diarrhea but was restarted on full dose ibrutinib after transient interruption of 1 week. However, in the 3rd month, he developed grade 4 neutropenia with an infection. After that he was unwilling to try the full dose of ibrutinib, also cited financial difficulty and went on to get 280 mg ibrutinib daily. At 16 months he has further reduced the dose to 140 mg daily. He had no adverse events after that and remains in PR one and a half year later.

Hematological Trends on Reduced Dose Ibrutinib

Figure 1 demonstrates the trend of hemoglobin, absolute lymphocyte counts and platelet counts in the three patients. All three patients had a transient dip in the hemoglobin. The hemoglobin recovered to normal in all three patients by 1 year. Similarly, all three patients had a dip in their platelet counts. The platelet counts also recovered to more than 100×10^9/mcl in all three patients by 1 year. The redistribution lymphocytosis was seen in all three patients. The redistribution lymphocytosis took 12 months to normalize in these patients. Only patient 3 had grade 4 neutropenia on the standard dose of ibrutinib, but none on reduced dose ibrutinib. These trends highlight that blood counts eventually normalize by 1 year and may be longer than the time taken with the standard dose of ibrutinib. There were fewer treatment interruptions on the reduced dose due to fewer adverse events.

Table 2 compares the data between patients taking reduced dose ibrutinib and standard dose ibrutinib excluding the patients who discontinued ibrutinib due to adverse events. This table shows that the patient age, cytogenetics by FISH, median number of previous therapies and median follow-up were not significantly different between the two groups ($p > 0.1$). However, as expected the rate of $\geq$ grade3 adverse events was significantly different between the two groups ($p < 0.0001$). The overall response rate and median PFS were also not significantly different between the two groups. The median PFS was not reached in both the groups (Fig. 2).

Discussion

Ibrutinib is one of the only few novel agents that work in CLL patients with deletion 17p or TP53 mutation. The other drugs idelalisib and venetoclax are not yet available in India and their import costs are prohibitive (Rs. 15 lakhs/month for standard dose venetoclax). Ibrutinib was launched as Imbruvica by Janssen in India at a much lower price than the western countries. With monthly price of ₹275,000 and a patient assistance program of 1 month free drug, the cost of ibrutinib is around ₹ 137,500

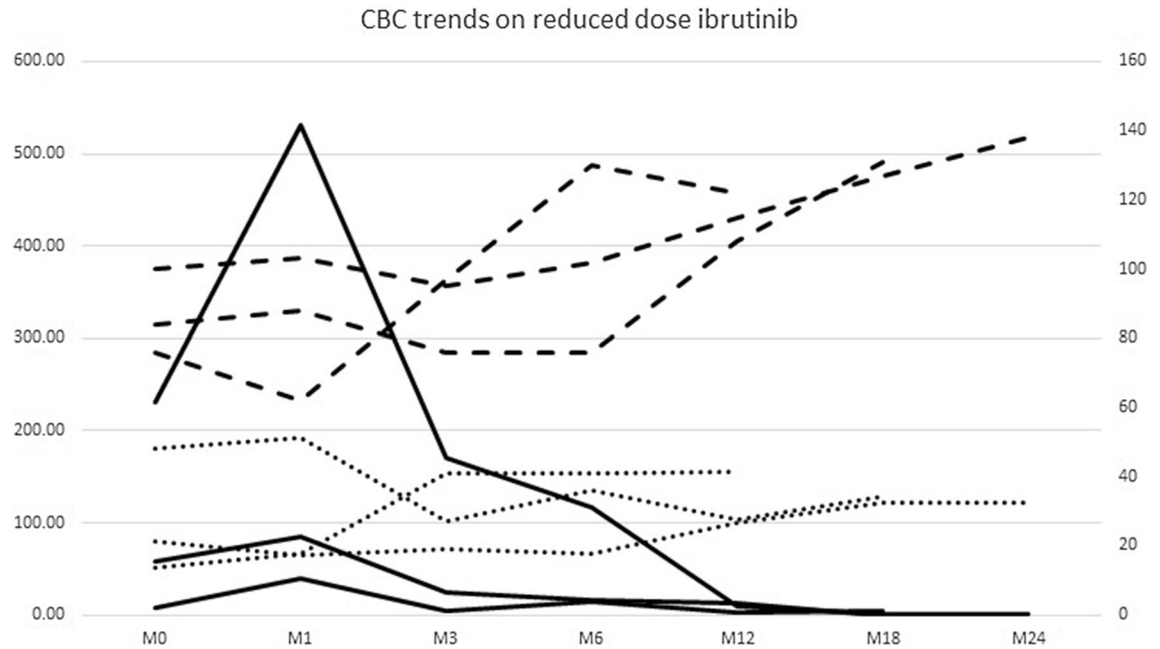

Fig. 1 Complete blood count (Hemoglobin (g/L)- dashed line, absolute lymphocyte counts ($\times 10^9$/L- solid line, platelet counts ($\times 10^9$/L)- dotted line) trends in three patients on reduced dose ibrutinib. (M = month)

Table 2 Comparison of patients taking a reduced dose and standard dose ibrutinib

	Reduced dose ibrutinib (n = 3)	Standard dose ibrutinib (n = 12)	*p* value
Age (years) median ± SD	60 ± 10.5	59.5 ± 10.1	NS
FISH (n)			NS
del. 17p	1	2	
del. 11q	2	3	
Others	0	7	
Median no. of prior therapies (range)	2 (1–3)	1.5 (0–4)	NS
Median follow-up (months)	12	10	NS
Adverse events (≥ grade3)	0	4/14 (28.5%)	< 0.0001
ORR	100%	91.6%	NS
Median PFS	NR	NR	NS

NR not reached, *NS* not significant

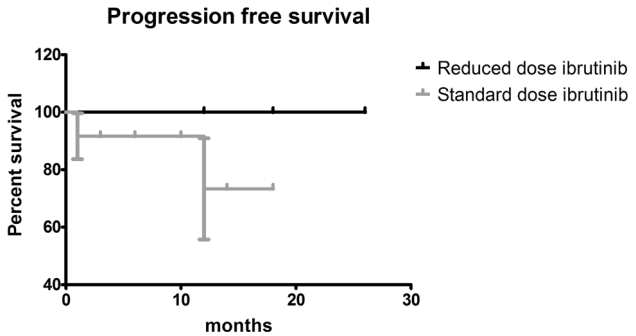

Fig. 2 Progression-free survival difference between patients on reduced dose and standard dose ibrutinib ($p = 0.4$)

(US$2000) per month. The gross national income per capita per year in India is US$1670 [10]. The estimated out of pocket expenditure for medical expenses is 65%, with only less than 20% of the population covered by some health insurance [11]. With an estimated prevalence of 25,000 CLL patients in India and a prevalence of deletion 17p/TP53 mutation of around 10%, there should be an estimated 2500 patients in need of this life saving drug [12]. Given the cost constraints patients are willing to try lower doses of such drugs even though against medical advice. The standard recommendations for dose reduction state that the drug needs to be held for any ≥ grade 3 hematological or non-hematological adverse event and reintroduced at the full dose after recovery. Only for the first or subsequent recurrences of adverse events is actual dose reduction recommended [5]. This is on the basis of the RESONATE clinical trial data which showed inferior PFS (10.9 months vs not reached) in patients with ≥ 8 days drug interruption versus those not interrupting ibrutinib [6]. Mato et al. have previously reported on comparable outcomes of reduced dose ibrutinib in CLL patients from a multicentre, retrospective study. In this study the indications for dose reductions were adverse events in 54% patients and physician preference in 46% patients. Five percent patients received concomitant CYP3A4 inhibitor which may have contributed to higher ibrutinib levels due to interactions [7]. Our study is the first study to the best of our knowledge to report on reduced dose ibrutinib due to patient preference and financial toxicity. Our study concurs with the results by Mato et al. that reduced dose ibrutinib has comparable outcomes in response rates, PFS but with significantly less adverse events in reduced dose ibrutinib. Whether this translates to better adherence and long-term outcomes needs to be seen. This study is limited by small patient numbers and a short follow-up and is not meant to displace the existing recommendations for dose reduction in event of adverse events. We do not recommend such dose reductions in clinical practice. We issue a caution to those patients compelled to reduce doses due to financial reasons that long-term data of safety and efficacy are unavailable. However, such studies should pave way to study reduced dose ibrutinib pharmacokinetic and pharmacogenetic studies to see if a subset of patients can benefit from such a strategy. One such clinical trial (NCT02801578) reported the pilot study outcomes of 11 patients receiving three consecutive monthly cycles of ibrutinib 420 mg, 280 mg and 140 mg and showed ≥ 98% BTK occupancy rates even with the lower doses of ibrutinib [13]. These two studies and our study provides proof of concept that lower doses of ibrutinib may be effective. This may have enormous impact on saving costs, improving adherence and access not only in resource-challenged settings but also in developed countries where economic burden is on the rise [14].

Compliance with Ethical Standards

Conflict of interest The authors report no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of

the institutional ethics committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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