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ORIGINAL RESEARCH

Have we really demonstrated the safety of Ibrutinib on standard dose? Rethinking the dose of Ibrutinib in CLL

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Abstract:
Ibrutinib is usually used as 420mg standard dose for treatment of CLL (Chronic Lymphocytic Leukemia). It is suggested that ibrutinib can be lowered after the first cycle of ibrutinib with good acceptability. To test the phenomenon, a clinical study was designed to use lower dose of Ibrutinib(280mg and 140mg) daily and clinical, haematological parameters along with adverse effects were compared. It was observed that such dose reduction would lower cost, lesson untowards toxicity and facilitate rationale dose schedule.

Introduction:
Ibrutinib has emerged as a leading targeted therapy for chronic lymphocytic leukemia (CLL) and is an approved agent for previously untreated and relapsed / refractory disease. The standard ibrutinib dose for CLL is 420mg/day, which was selected from a phase 1 study of ibrutinib in patients with relapsed/refractory B-cell malignancies[1]. Although ibrutinib is well tolerated but major bleeding and atrial fibrillation were observed in a significant minority of patients[2].
Importantly, the frequency of incidenceof arterial fibrillation reported in the randomized controlled registration trials of ibrutinib (6.5%) markedly underestimates the frequency observed in unselected patients in a "real-world" setting (13% in a recent study of 582 patients)[3,4]. Furthermore, serious infections have been reported in patients receiving ibrutinib therapy[5-7].
Intolerance and adverse events (AEs) are major causes of discontinuation of ibrutinib[8-11]. In addition to the issues of safety and tolerability, the cost of ibrutinib is also of concern.
Lowering the dose of ibrutinib has clear potential to reduce the toxicities of ibrutinib and treatment failure, as well as the economic burden of CLL management. The standard ibrutinib dose for CLL is 420mg/d. Even though at least 97% BTK occupancy was achieved at the 2.5 mg/kg/d dose level, which roughly corresponds to 175mg/d.
In addition to occupancy data, BTK expression data in B cells provides further rationale for dose reduction[12]. Lower doses would also result in decreased levels of free drug in plasma and reduced binding to off-target kinases, potentially resulting in decreased incidence of AEs such as atrial fibrillation and bleeding manifestations. To test our hypotheses a clinical study on dose of ibrutinibwas planned.

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 04, 2022

Material & Methods:

Inclusion Criteria:

1. Patients with a diagnosis of CLL (any stage) with ALC>/= 20 x 109/l, requiring therapy.
2. Age >/= 18 years.
3. Patients should have discontinued any and all other therapy for CLL >/= 48 hours prior to start of study therapy.
4. Able to understand and sign the IRB-approved informed consent document for this trial.

Exclusion Criteria:

1. Previous treatment with ibrutnib.
2. Active, uncontrolled infection.
3. History of hypersensitivity to ibrutinib
4. Pregnancy or lactation.

Adults with CLL and absolute lymphocyte counts of at least 20 x 10^9/L who were candidates for ibrutinib therapy were eligible for the study.
10 numbers of patients were randomly prescribed 420 mg/d, 280 mg/d and 140 mg/d as three different dose treatment plans. Monthly clinical and haematological parameters were assessed and adverse effects and tolerability issue were assessed. Summary statistics were provided in the form of frequency and percentages for categorical data, and continuous variables were summarized using mean, SD, and median with range. The change in measured values was evaluated using the Wilcoxon signed rank test. All tests were 2-sided and $p<0.05$ was considered statistically significant. Statistical analysis was carried out using SPSS ver 15.0.

Results:
Base line characteristics were observed in (Table 1).The patient characteristics are shown in Table 2. Most of patients did not have deletion 17p, this occurred purely by chance. The somatic hypermutation status of IGHV gene was unmutated in four, while the remaining patients were having mutated IGHV. On standard dose i.e. 420mg/day,three patients continue, one patients drop out due to adverse effect. On 280mg and 140mg continue treatment for six months without any significant adverse effects. Hematological response was more or less similar with 420mg vs 280mg daily. Slow response was seen with 140mg daily. Initially increase in lymphocyte count was seen in all categories but after 6 months good response was seen hematologically and regression in lymph node size was seen. Adverse effects were common with standard dose (Table 3).

Table 1: Baseline Characteristics of 3 different arms of treatment in CLL

Parameters		WBC	ALC	Neutrophils	Hb	Platelet	Lymphedanopathy	Hepatomegely	Splenomegely	Symptoms
Arm 1	1	177000	130000	40000	11.3	188000	+++	+	+	B +
	2	91000	79000	11000	12.5	210000	+++	+	+	No
	3	64000	58000	7000	11.9	240000	++	+	+	No
	4	81000	66000	13000	11.7	310000	+++	+	+	No

ISSN: 0975-3583, 0976-2833 VOL13, ISSUE 04, 2022

Arm 2	5	96000	88000	7000	11.2	280000	++	+	+	B +
	6	74000	67000	6000	12.4	190000	+++	+	+	No
	7	91000	84000	6500	10.5	170000	+++	+	+	No
	8	68000	61000	6200	12.7	180000	++	+	+	No
Arm 3	9	73000	66000	5800	12.1	220000	++	+	+	No
	10	60000	54000	4500	11.8	190000	++	+	+	No
	11	108000	92000	12500	7.6	160000	+++	+	+	B +
	12	94000	84000	87000	9.9	240000	+++	+	+	No

Table 2: Characteristics of 12 patients with CLL enrolled in 24 weeks pilot trial, along with different dose schedule

Subject No.	Age	Sex	CLL grade	Year since diagnosis	ALC	FISH	IGHV	Dose of Ibrutinib
1	70	M	III	3 years	66000	Del (17p) -ve	Unknown	140
2	56	M	III	5 years	54000	-ve	Mutated	140
3	55	F	IV	2 years	92000	Del (13q) Positive Del 17 negative Trisomy12 -ve	Unmutated	140
4	57	F	III	1 year	88000	Negative	Mutated	280
5	54	F	III	2 years	67000	Negative	Mutated	280
6	55	M	IV	4 years	61000	Negative	Mutated	280
7	60	M	III	7 years	130000	Negative	Mutated	420
8	55	F	IV	2 years	79000	Negative	Unmutated	420
9	75	M	III	5 years	58000	Negative	Mutated	420
10	67	M	III	8 years	71000	Negative	Unmutated	140
11	71	M	IV	6 years	84000	Positive	Unmutated	280
12	69	F	III	5 years	66000	Negative	Mutated	420

Table 3: Adverse events in different dose of Ibrutinib

Adverse events		**420 mg**	**280 mg**	**140 mg**
Hematological	Anemia			
	Thrombocytopenia			
	Neutropenia			
Diarrhea		2	1	0
Arthrelgia		1	0	0
Haemorrhage		1	0	0

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Artrial Fibrillation	1 stopped and switch on lower dose		

Discussion:

The clinical and haematological responses were compared for 6 months (6 cycles) 2.5 mg, 5 mg and 12.5 mg/kg resulted more or less similar clinical response as standard dose. The clinical response was fast with 420 mg/d but after 6 months similar response was observed. In US multicentre retrospective analysis of 197 patients with CLL during a 5-year period found that reducing the ibrutinib dose did not affect progression-free survival (PFS) or overall survival (OS)[13]. The UK CLL forum reported similar findings in 26% of 315 patients in whom dose reduction was required. The disease-free survival (90% for both) and the OS (905 vs 92%) were similar in the reduced-dose and standard-dose cohorts[14]. Likewise, a study in Sweden reported no difference in PFS or OS between patients who had ibrutinib dose reductions lasting longer than 3 months and patients whose dose was not changed, or was only briefly reduced[15].

Furthermore, reducing the ibrutinib dose, mainly because of AEs, did not negatively affect outcome in 165 patients in a Polish study[16]. Our trial data are in line with these reports, and after 1 year poststudy, 8 of 9 patients have been maintained at ibrutinib doses lower than 420 mg/d, with 7 being at 140 mg/d and 1 at 280 mg/d. Collectively, these real-world studies demonstrate that globally, ibrutinib intolerance results in dose reduction by physicians and patients without negatively affecting PFS and OS. It is important to note that although dose reduction appears not to have a deleterious effect on OS and PFS, drug interruptions for more than 8 days affect clinical outcomes adversely[13-17].Ibrutinib-bound BTK is irreversibly inactive; however, longer interruptions may likely result in new synthesis of BTK protein not bound by ibrutinib. Reduced doses may be sufficient to bind to any newly synthesized BTK molecules.

Our results provide the scientific basis for equivalent survival outcomes at lower doses of ibrutinib. This study concentrated only on CLL , and because ibrutinib is also approved for other malignancies such as mantle cell lymphoma and Waldenstrommacroglobulinemia, as well as for chronic graft versus host disease, our results may also be relevant in those settings. Lower doses may mitigate AEs in patients taking ibrutinib, reducing the financial burden associated with treatment, and may provide more avenues for laboratory-based rational combination strategies.

Lisa S. Chen, PhD, of the department of experimental therapeutics at The University of Texas and colleagues had previously shown a decrease in BTK protein levels in CLL cells after one cycle of ibrutinib, suggesting that ibrutinib dose could be lowered after completion of the first cycle without a loss of effect.

Chen and colleagues enrolled 11 patients and initiated treatment with one cycle of 420 mg per day ibrutinib. The dose was then reduced to 280 mg per day for cycle 2, and again to 140 mg per day for cycle 3. Nine patients completed all three cycles. The researchers evaluated for pharmacokinetics, BTK occupancy, and pharmacodynamics at the different doses. Chen and colleagues found that plasma and intracellular levels of ibrutinib were dose dependent. However, even the 140 mg per day dose was sufficient to occupy on average more than 95% of BTK protein. In addition, BTK downstream signalling inhibition was maintained at the lowest dose.

Also similar were reduction in plasma chemokine CCL3 and CCL4 levels, considered biomarkers of drug response.

Dose reduction are desirable because of the possibility of indefinite administration of the drug in patients who respond, along with financial toxicity related to the cost of the drug and CLL management and associated adverse events.

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Our study does have several limitations among that is small sample size and short follow-up. Further, because patients with higher-risk genomic characteristics were not evaluated in this study,it is unknown whether the results are generalizable to this subset of patients with CLL.

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