Ibrutinib in Patients with Chronic Lymphocytic Leukaemia

A Case-Series Study in Mosul City

Sandy Gorgis Ayou Gorgis FIBMS, **Khalid N M Al-Kheroo** CABM FRCP

ABSTRACT

Background: Chronic lymphocytic leukaemia is a malignant lymphoid neoplasm that is characterized by the accumulation of a population of small mature B cells. It is one of the most common types of leukaemia in the Western world but it significantly less frequent in Asia. Chronic lymphocytic leukaemia and other low-grade B-cell malignancies treatment changed significantly over the past 10 years, Bruton's tyrosine kinase is the most vulnerable B-cell receptor kinase exploited therapeutically; its absence results in a predominantly B-cell deficient phenotype and predisposition to select viral and bacterial infection. Pharmacologic inhibition or genetic knockout of Bruton's tyrosine kinase prevents or effectively controls the disease in preclinical murine models.

Objectives: To assess the effect and adverse effects of Bruton's tyrosine kinase inhibitor (ibrutinib) in chronic lymphocytic leukaemia patients.

Methods: A case-series study that was conducted at haematology division at Ibn Sina Teaching Hospital in Mosul from the 1st of March to 1st of September 2021. Thirteen patients were included, five of them have deletion in the short arm of chromosome 17 alone, one patient have tumor protein P53 mutation alone, three patients have both deletion in the short arm of chromosome 17 with tumor protein P53 mutation, and four patients have failure of up to three lines of treatment. Pretreatment for those who had failure of treatments consisted of fludarabine plus cyclophosphamide plus rituximab, bendamustine plus rituximab, chlorambucil plus rituximab for two patients, and one patient recieved fludarabine plus cyclophosphamide plus rituximab with chlorambucil, and another one received fludarabine plus cyclophosphamide without rituximab due to allergic reactions. Patients received ibrutinib monotherapy orally 140 mg capsule three capsules at once a total dose 420 mg daily and re-evaluation was carried out one month after treatment and then every two months until reaching the response whether complete remission, partial remission, relapses or progressive disease.

Results: The total number of patients were thirteen, the median duration of follow up was 4 months. The median age was sixty years. Eight of them were males and five were females. The results showed that two patients were stage 4, four patients were stage 3, and four patients were stage 2 according to Rai staging system. Bruising with rash was the most common side effect of the drug occurred in 5 out of 13 patients, with anaemia occurred in four patients. Five patients had complete remission with another five had a partial remission with lymphocytosis and all were male gender and two of them was stable disease. The median lymphocytes percentage was declined from 75% to 58% in comparison between pre and post treatment with ibrutinib. In addition, there was grade ≥3 neutropenia occurred in 7.7% of the patients.

Conclusions: Ibrutinib is a preferred treatment option in relapsed disease and those with cytogenetic detection in high-risk group; it has an acceptable safety profile with high and promising overall response rate.

Keywords: **Ibrutinib, Mosul City, Chronic Lymphocytic Leukaemia.**

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Chronic lymphocytic leukaemia (CLL) is a malignant lymphoid neoplasm that is characterized by the accumulation of a population of small mature B cells. The diagnosis of CLL requires the presence of at least 5000 circulating B cells/μL with clonality demonstrated by flow cytometry according to International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) criteria[1].

Ibrutinib a once daily, orally bioavailable inhibitor of Bruton's tyrosine kinase (BTK), was first introduced to clinical trials in February 2009 and represented a novel compound for treating B-cell malignancies and drug development. By virtue of the cysteine 481 residue on BTK, ibrutinib binds covalently, thereby inhibiting kinase activity[2,3]. Ibrutinib therapy is associated with exacerbation of lymphocytosis frequently (>70%) due to redistribution that does not affect the response to therapy, usually peaks one month after therapy and subsequently slowly declines. The median time to resolution of lymphocytosis on ibrutinib therapy is 19 weeks, but prolonged lymphocytosis up to 124 weeks has been seen in patients with ongoing treatment responses[4]. Clinically durable responses to ibrutinib are observed regardless of high-risk genomic features, such as complex karyotype; chromosome 17p deletion referred to hereafter as del (17p) and mutated *TP53*[5].

Side effects of ibrutinib in the short-term have been well characterized and include gastrointestinal symptoms, rash, infection, ocular symptoms, and hypertension, the impact of long-term treatment continues to be investigated.

Atrial fibrillation is an important complication of ibrutinib therapy (~10%) that could be the result of the inhibition of BTK and related kinases. Ibrutinib therapy is frequently complicated by minor bruising. Severe hemorrhage is less common, and patients on anticoagulant and antiplatelet therapy are at the highest risk of these complications. Ibrutinib therapy should be stopped 3-7 days before and after surgical procedure due to risk of bleeding, concomitant use of moderate or strong CYP3A inhibitors require ibrutinib dose reduction[6].

The aim of this study is to assess the effect and adverse effects of Bruton's tyrosine kinase inhibitor (ibrutinib) in chronic lymphocytic leukaemia patients.

Methods

A case-series study that was conducted at haematology division at Ibn Sina Teaching Hospital in Mosul from 1st of March to1st of September 2021. Thirteen patients were included, five of them have deletion in the short arm of chromosome 17 alone, one patient have tumor protein P53 mutation alone, three patients have both deletion in the short arm of chromosome 17 with tumor protein P53 mutation, and four patients have failure of up to three lines of treatment. Pretreatment for those who had failure of treatments consisted of fludarabine plus cyclophosphamide plus rituximab, bendamustine plus rituximab, chlorambucil plus rituximab for two patients, and one patient received fludarabine plus cyclophosphamide plus rituximab with chlorambucil, and another one received fludarabine plus cyclophosphamide without rituximab due to allergic reactions. Patients received ibrutinib monotherapy orally 140 mg capsule three capsules at once a total dose 420 mg daily and re-evaluation was carried out one month after treatment and then every two months until reaching the response whether complete remission, partial remission, relapses or progressive disease. The patients have preserved renal function with no cardiovascular comorbid conditions, not taking any form of antiplatelet nor anticoagulant drugs. Exclusion criteria include patients refusal to participate in the study, patients with cardiovascular or renal disease and transformed disease.

The data were collected directly for each patient with the stage of the disease at starting the drug (ibrutinib), number of lines of treatment used for the patient, were gained from files saved for each patient. Renal function was done at the beginning of the study as a base-line measurement, then at an interval of three months. Cardiovascular assessment was done by baseline echocardiography and ECG, then as indicated by physical examination.

Adverse events were assessed by history, examination, complete blood

picture and symptoms mentioned by the patients.

After a thorough explanation of the study objectives to the patients, a written consent was obtained from each one of them to participate in the study through their full choice. The patients were given a pledge that all the information taken will be reserved strictly confidential, and would not be used by anyone other than the researchers, and for any purpose other than research work.

The data collected during the study were summarized in sheets of Microsoft Excel 2007. The statistical analysis performed by using IBM-SPSS 26. The normality of these data tested by Shapiro-Wilk test, and the nonparametric tests were decided to be chosen. Frequencies, medians, and ranges were calculated. The Wilcoxon Signed Ranks Test used to calculate the difference between the two-paired groups. P-value ≤ 0.05 considered as significant.

——————————Results

The study sample according to gender demonstrates that eight patients were males representing 61.5% while females were five constituting 38.5%.

The proportion of ibrutinib prescriptions shows that 38.5% were due to 17p del, and 30.5% were due to failure of more than three lines of treatment, and 23% were due to TP53+17p del and only 8% were due to TP53 mutation, (Table 1).

About the distribution of study sample according to age groups and gender demonstrates that female was dominating at younger age (20-30 years) and male was dominating at older age (40 to 70 years), (Table 2).

The response to treatment among study sample showed that five patients get complete remission, five patients get partial remission with lymphocytosis, two patients were stable disease, one patient was partial remission, and no one was progressive disease[7], (Table 3).

The numbers and proportions of Rai staging[8] among study sample reveals that stage 1 represent 23.07% while stage 2 and 3 comprises 30.75% for each among study sample, while stage 4 represent 15.43%, (Table 4).

The percentages of side effects among the study sample reveals that bruising and rash are present in five patients representing (38.4%). Anaemia, fatigue, and dizziness present in four patients and constitute (30.7%). Atrial fibrillation is present in three patients (23%). Hypertension, headache, vomiting, diarrhoea, Dyspepsia and oedema comprise (15.3%) occurring in only two patients. Chest infection, dyspnoea, nausea, constipation, muscle spasm, neutropenia and death presented merely in one patient, (Table 5).

About the distribution of study sample according to outcomes with the initial Rai staging system reveals that five patients got complete remission with (2, 3, 4, 2, 1) Rai staging. Also, partial remission plus lymphocytosis occurred in five patients of different Rai staging. Partial remission occurred in one patient having Rai staging of 2. Stable disease occurred in two patients having Rai staging 3, (Table 6).

About the distribution of study sample according to outcomes with gender revealed that all five patients with partial remission with lymphocytosis were males, two patients were with stable disease were females, one patient with partial remission was female, with five patients were in complete remission three of them were males and two of them were females, (Table 7).

Blood variables difference between pre and post treatment of significant concerning was the lymphocytes which show declining from 75.5 to 58.0, (Table 8).

Table 1: The proportion of ibrutinib prescription.

Ibrutinib indications	Number of patients	Percentage
17p del	5	38.5
failure>3Rx	4	30.5
TP53+17p del	3	23
TP53	1	8.00%
Total	**13**	**100%**

Table 2: The distribution of study sample according to age groups and gender.

Age (years)	*Males*	*Females*
20-30	0	1
31-40	0	0
41-50	2	1
51-60	3	1
61-70	2	1
More than 70	1	1
Total	**8**	**5**

Table 3: The response to treatment among study sample.

Outcome of disease	**Number of patients**
Complete remission	5
Partial remission	1
Partial remission + lymphocytosis	5
Stable disease	2
Progressive disease	0
Total	**13**

Table 4: Numbers and proportions of Rai staging among study sample.

Rai staging	Numbers	Percent
1	3	23.07
2	4	30.75
3	4	30.75
4	2	15.43

Table 5: The side effects percentage among study sample.

Patient side effects	*Number of patients*	*Percentage*
Bruising	5	38.4
Rash	5	38.4
Anaemia	4	30.7
Fatigue	4	30.7
Dizziness	4	30.7
Atrial Fibrillation	3	23
Hypertension	2	15.3
Vomiting	2	15.3
Dyspepsia	2	15.3
Diarrhoea	2	15.3
Oedema	2	15.3
Headache	2	15.3
Pneumonia	1	7.7
Dyspnoea	1	7.7
Constipation	1	7.7
Muscle spasm	1	7.7
Nausea	1	7.7
Neutropenia	1	7.7
Death	1	7.7

Table 6: Distribution of study sample according to outcomes with initial Rai staging.

Complete remission	Partial remission	Partial remission plus lymphocytosis	Stable disease	Progressive disease
Rai	Rai	Rai	Rai	Rai
2	2	4	3	
3		2	3	
4		1		
2		3		
1		1		

Table 7: Distribution of study sample according to outcomes with gender.

Complete remission	Partial remission	Partial remission plus lymphocytosis	Stable disease	Progressive disease
Gender	Gender	Gender	Gender	Gender
M	F	M	F	
M		M	F	
F		M		
F		M		
M		M		

(M)=Male (F) =Female

Table 8: The comparison of blood variables between pre and post treatment.

Blood variables	Pre-treatment		Post-treatment		Z	p-value*
	(Median)	(Range)	(Median)	(Range)		
WBC (x 10^3/µL)	14.80	3.01	13.50	1.80	-0.910 [b]	0.363
Neutrophil (x 10^3/µL)	4.25	7.65	3.20	6.75	-2.168 [b]	0.030
Lymphocytes (%)	75.50	63.0	58.00	67.0	-2.482 [b]	0.013
Hb (g/dl)	10.55	6.90	11.65	6.70	-1.727 [c]	0.084
Platelets (x 10^3/µL)	173.0	262.0	160.50	226.0	-0.848 [b]	0.397

* Wilcoxon Signed Ranks Test. b Based on positive ranks. c Based on negative ranks.

Discussion

The median age were 60 years with eight of patients were males (61.50%); while five of them were females (38.50%), this is in agreement with Cantú ES, et al[9], study was compatible with this finding. The median age was 62 years with 61% of patients were males; while 39% of them were females.

In this study results revealed that six patients (46.18%) were in stage 3 or 4 of Rai staging system. Four patients were stage 3 and two patients were stage 4. The rate of del (17p) was observed 38.50%, however a study by Göçer M, et al[10] that was conducted at nearby Turkey on eleven patients with refractory CLL showed that seven patients about (63.6%) of total patients had stage 3 or more (at diagnosis), but in agreement with the rate of del (17p) that was 36.4% among their sampled patients.

In this study, the incidence of pneumonia was 7.7%, clinical trials investigating BTKi (ibrutinib) in patients with B cell malignancy revealed an increased rate of infection, particularly with pneumonias caused by opportunistically characteristic pathogens. This higher frequency of infection could be attributed to, at least in part, to the recipe of ibrutinib-mediated inhibition of BTK and ITK (expressed in T cells), which together modify innate and adaptive immune function[3].

Inhibitors of BTK have a unique and exclusive safety profile that comprises, relative to chemoimmunotherapy, an increase in rash, diarrhoea, arthralgia or myalgia, and cardiovascular and bleeding occasions. Although the causes of many of those side effects are unclear, and not understood; they are supposed to be associated with the inhibition of off-target cellular kinases, an important motivator for the development of next-generation BTK inhibitors[11].

In current study, regarding the side effects of ibrutinib, 23% of patients developed atrial fibrillation (AF), with 30.7% developed anaemia, 38.4% developed skin rash, 38.4% developed bruising, and 15.3% developed hypertension, These findings consistent with the results documented by Brown JR, et al[3], revealed that ibrutinib treatment is also associated with other side effects, including increased bleeding tendency, AF, hypertension (HTN), and arthralgia.; also risk of AF increase in patients with a history of AF and increased duration of treatment with ibrutinib[12-4].

Atrial fibrillation is a side effect of specific importance with BTK inhibitors, given that its management often comprises anticoagulants, which can exacerbate, and worsen the compromised hemostasis caused by the BTK inhibitors. In first-line trials, atrial fibrillation has been reported in CLL patients taking ibrutinib, up to 10-12%; higher rates had been reported in the real-world studies[15,16].

Although the mechanism of ibrutinib-induced AF is unclear, the off-target inhibition of PI3K in cardiac cells is a proposed model, with several *in vitro* and animal studies signifying the role of PI3K inhibition in cardiac arrhythmogenesis[17]. In this study, there were no changes in the diameter of cardiac chambers of the patients before ibrutinib therapy confirmed

by echocardiography. In one small prospective study, higher left atrial diameter and pre-existing cardiac comorbidity were shown to increase the risk of AF in patient taking ibrutinib[17].

Scoring systems was developed aiming to help predict the risk of incident AF in CLL patients. Shanafelt predictive model, which is based on atrial fibrillation risk factors (older age, male sex, valvular heart disease, and hypertension) identified from a retrospective study[18].

Hypertension is frequently observed in those patients receiving ibrutinib-based therapy, being in up to 20% of patients in clinical trials[19] and this is in agreement with this study that hypertension occurred in 15.3% of total patients.

In a retrospective study heralded by Dickerson T, et al[20] of 562 patients with B cell malignancies who were receiving ibrutinib-based therapy, development of new or worsened hypertension had been associated with a risk of other cardiac events; however, starting of antihypertensive agents was associated with a lower risk of major cardiovascular events. This finding, together with the observations that prevalence of hypertension increases during the course of ibrutinib, highlighted the significance of proper monitoring and management of this side effect. The mechanism of hypertension associated with ibrutinib therapy has not been clarified; however, indirect down-regulation of PI3K–P110α or of vascular endothelial growth factor has been postulated to contribute[21].

Regarding bleeding, in meta-analysis trials, minor bleeding and bruising are frequently reported in patients receiving ibrutinib (up to 50%)[22], moreover, this study show bruising occurred in 38.4% of total patients. Bleeding of any grade, most commonly occurs during the first year of treatment, although it can occur at substantial rate throughout the course of ibrutinib treatment[23]. Several mechanisms explained an increase in bleeding events with ibrutinib and other BTK inhibitors therapy compared with chemotherapy-based regimens. First, the BTKi inhibit both BTK and Tec, which are implicated in promoting platelet aggregation downstream of glycoprotein VI[24,25].

The results showed that complete remission was observed in five patients (38.46%) of the total thirteen patients. These findings consistent with results documented by Farooqui MZ, et al[26], illustrated that complete remission was observed in 23 out of 81 patients as 28.4% of total sample. Lymphocytosis may be observed in peripheral blood due to the rapid shrinkage of the lymph nodes during ibrutinib treatment. This is temporary and not associated with disease progression. It peaks at 2-4 weeks, and returns to normal within 6 months of treatment.

In this study, there was a decrease in WBC count and neutropenia after ibrutinib therapy, and showed grade ≥3 neutropenia occurred in 7.7% of the patients, moreover, a study done by Iris de Weerdt, et al[27], showed grade ≥3 neutropenia occurred in (10-17%) of the patients on ibrutinib monotherapy, usually in the initial months of therapy.

Limitations of our study were the small sample size, and a short duration of follow-up, recommend performing a large sample size studies.

In conclusion, ibrutinib is a preferred treatment option in relapsed disease and those with cytogenetic detection in high-risk group; it has an acceptable safety profile with high and promising overall response rate. Also, considered as frontline treatment for patients with CLL even without del (17p) or TP53 mutation. Ibrutinib, also, improve response rate and remission status with promising results, treatment with ibrutinib at an early stage decreases the burden of cytotoxic therapy in fragile patients leading to increased quality of life.

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