Original Article

A Study of Disease Outcome following Tyrosine Kinase Inhibitor Therapy in Patients with Chronic Myeloid Leukemia, from a Tertiary Care Center of North Bengal

Debasis Chakrabarti[1], Arka Mukhopadhyay[2], Pasang Lahmu Sherpa[3], Dipanjan Bandyopadhyay[4]

Background and Objectives : Chronic Myeloid Leukemia (CML) remains one of the very few malignancies with excellent prognosis following the advent of Tyrosine Kinase Inhibitors (TKIs). Apart from Imatinib, there are several novel TKIs which can be used as first line therapy with even better clinical outcomes like faster clinical response, less evidences of recurrence and lesser adverse effects like cytopenia.

Materials and Methods : A hospital based observational, descriptive and prospective study was designed to follow up patients being diagnosed with CML in chronic phase and were started on TKIs, Imatinib or Nilotinib and they were followed up with records of baseline blood counts, bone marrow examination, BCR-ABL studies and their blood counts were recorded over 3rd and 6th months of therapy.

Results : Most of the patients had an excellent clinical response by 3rd month. Still, 14.89% (n=7) patients had leukocyte count >12000/mm^3 whereas 4.25% (n=2) patients had leukocytopenia with counts <4000/mm^3. Hemoglobin trend was steadily increasing whereas platelet count remained within normal limits. For those patients treated with Nilotinib had comparatively better cytological response by 3rd and 6th months compared to Imatinib, with a slightly higher increase in hemoglobin level and lesser evidence of cytopenia over the course of 6 months.

Interpretation : TKIs have resulted excellent cytological response although issues like cytopenia remains an important concern.

Conclusion : TKIs remain the cornerstone while treating CML patients. Among the TKIs, Nilotinib can garner faster cytological response while have lesser chance of having cytopenia compared to Imatinib.

[*J Indian Med Assoc* 2025; **123(1):** 24-8]

***Key words* : Chronic Myeloid Leukemia, TKI in CML, Cytopenia, Imatinib *versus* Nilotinib, Tyrosine Kinase Inhibitors.**

Chronic Myeloid Leukemia (CML), one of the most common type of hematological malignancies[1], is also among the best treatable malignancies[2]. Since the advent of Tyrosine Kinase Inhibitors (TKI), treatment of CML has been revolutionized with excellent prognosis altogether increasing the life expectancy similar to that of general population[3,4]. Imatinib has been used as a first line TKI for treating CML for almost 2 decades. In recent years, Nilotinib is also being considered as a first line therapy[4]. Although several studies compared Imatinib to Nilotinib for treatment efficacy and adverse effects from around the world in recent days, there are very few Indian literature for the comparison[5-7]. We aim at analyzing the baseline blood parameters to that of 3rd month and 6th month changes through this prospective study.

Editor's Comment :

- CML can be present at a very young age, even in the second decade.
- TKI therapy reduces the blood count dramatically, but they are prone to cause cytopenia which remains a major concern.
- Nilotinib, compared to Imatinib, has a faster response, yet less propensity to cause cytopenia, whereas Imatinib remains better tolerated, at least as a first line therapy.

Aims and Objectives

(1) To observe the baseline hematological parameters in patients of CML

(2) To document the disease outcomes over 3 and 6 months following treatment with TKIs

(3) To compare the blood count changes over 3rd and 6th month between Imatinib and Nilotinib

Materials and Methods

This is an observational, prospective and a descriptive hospital-based study. Place of study were Medicine Outpatient Departments (OPD) and

Department of Medicine, North Bengal Medical College & Hospital, Sushruta Nagar, Siliguri, West Bengal 734012
[1]MD (Medicine), Associate Professor and Corresponding Author
[2]MD (Medicine), Senior Resident
[3]MD (Medicine), Associate Professor
[4]MD, Professor and Head

Received on : 31/03/2023
Accepted on : 12/05/2023

Inpatient Departments (IPD) of North Bengal Medical College and Hospital situated in the Darjeeling district in the state of West Bengal. Study population includes all the patients attending medicine OPD and IPD with the diagnosis of CML. The duration of this study was January, 2018 to December, 2019, a total of 2 years. Ethical committee approval has been taken before starting the study. Patients were chosen in to the study based on the inclusion and exclusion criteria, described as follows:

Inclusion Criteria :

All the newly diagnosed patients with CML.

Exclusion Criteria :

(1) Morbidly ill patients not eligible for chemotherapy and follow up.

(2) Patients not giving consent to this study.

History of the chosen patients were taken relevant to the illness. Data collected from the history were demographic data like age, sex, address, presenting complaints. Clinical examinations were done for signs like pallor, jaundice, pedal edema, ascites, hepatosplenomegaly, any sign of hemorrhage. Complete blood count recorded at baseline, then repeated at 3rd and 6th month of follow up. CML was confirmed by BCR-ABL (FISH) study. A case record form was used to keep all these data charted.

Statistical Analysis :

All the data were collected and tabulated in a master chart, followed by assortment with standard statistical tools. Standard statistical analyses made using dedicated computer software SPSS, version 27.

Result and Analysis

We recorded total of 47 patients' data during the study.

Baseline counts: Hemoglobin level at presentation mostly was below 10 g/dL with (81.25%) with a mean of 8.738 g/dL. Three patients had hemoglobin level below 6 g/dL at presentation.

All the patients presented with a high leucocyte count as the mean value was 268.43 thousand/dL. 72.92% (n=35) of the patients having a count ranging from 1.5-3.5 x 10^3 /dL.

Neutrophil with band form count was distributed maximally within 40-50% of total cells in 77.78% of male patients and 61.9% of female patients in this study with a cumulative total 70.83% patients (n=34). All the patients were found to have lymphocyte count under 10% among which a maximum of 19 patients (39.58%) were having lymphocyte count of 3%.

Platelet count was distributed ranging from 165 to 800 thousand/dL with a high mean count of 425.44 thousand/dL. Most of the patients have platelet count between 300-600 thousand per dL in 34 patients (70.83%).

Blood Counts after 3 Months of TKI Therapy :

Hemoglobin at 3rd month was placed mostly within the range of 8-12 g/dL with a total 76.6% patients (n=36) and mean hemoglobin increased to 10.513 g/dL overall.

Leucocyte count after 3 months of TKI treatment ranged 6000-10000/dL for 53.19% of patients (n=25), although 14.89% patients (n=7) had a leucocyte count >12000/dL whereas 4.25% patients (n=2) had a leucocyte count <4000/dL.

Platelet count at 3rd month was mostly distributed across the range of 200-400 thousand/dL of patients whereas 17.02% patients (n=8) had platelet count below 150 thousand/dL.

Blood Counts after 6 Months of TKI Therapy :

Hemoglobin level at 6th month was placed mostly within the range of 12-14 g/dL with 72.34% of patients (n=34) and the mean value was 11.294 g/dL.

Total WBC count was found to be ranged between 4000-6000 cells/dL in maximum of 31 patients (65.95%). However, 4 patients (8.51%) had total WBC count below 4000 cells/dL among which 2 had a count <2000 cells/dL.

Platelet count was found with a range of 250-300 thousand/dL in 14 patients (29.78%). However, 11 patients (23.4%) were found to have platelet count below 150 thousand/dL at 6th month.

Comparison among Mean Counts over Baseline, 3rd and 6th Months:

Mean hemoglobin had an increasing trend from a baseline mean of 8.738 g/dL to 10.513 d/dL at 3rd month, followed by 11.294 d/dL in the 6th month (Fig 1).

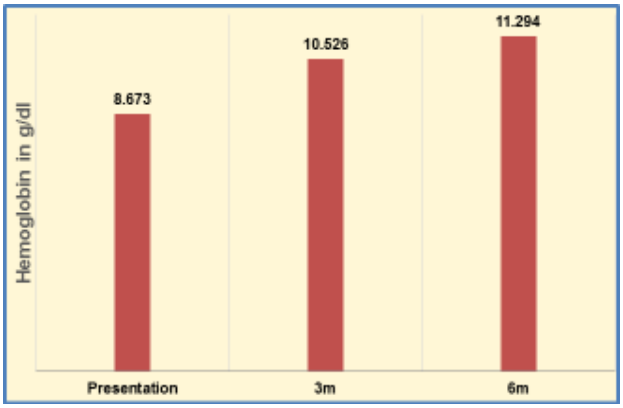

Fig 1 — Mean Hemoglobin in g/dL Trend

While extrapolating leucocyte count over 6 months of TKI therapy, average WBC count was found to be 268.678 thousand cells/dL in the baseline, which reduced to 9.2 thousand cells/dL in 3rd month, followed by 5.315 thousand cells/dL in 6th month (Fig 2).

Mean platelet count at the time of diagnosis recorded at 427.170 thousand/dL, which was down to 256.936 thousand/dL after 3 months of TKI, a slight reduction further after 6 months at 227.489 thousand/dL (Fig 3).

Additionally, in comparative analysis of differential counts between 3rd and 6th month, it was found that neutrophil count was reduced from 64% at 3rd month to 58% in 6th month, whereas lymphocyte count was increased from 30% at 3rd month to 35% in 6th month. Eosinophil count increased from 3% at 3rd month to 5% in 6th month. And monocyte count was reduced from 3% at 3rd month to 2% at 6th month. Mean basophil count remained at 0% in both 3rd and 6th month data (Table 1).

Comparison between Imatinib *versus* Nilotinib :

On the basis of Blood Counts over baseline, after 3 months and after 6 months (Table 2).

Discussion

This study was conducted to observe the hematological parameters in CML patients at baseline and at 3 and 6 months of receiving standard care as per international protocols at a Tertiary Care Hospital in Sub-Himalayan West Bengal, India. 41.67% of patients presented with a hemoglobin <8 g/dL and the mean hemoglobin at presentation remained 8.74 g/dL. Mean leucocyte count at presentation remained at 268.678 thousand/dL. In the differential leucocyte count most dominant type was neutrophil with band form with mean count of 42.73%. Basophil count requires particular mention as it ranged from 2% to 25% where the mean count was 9.42% which establishes the trend of higher basophil count in CML patients[8]. Platelet count was mostly on the higher side with mean being 425.44 thousand/dL.

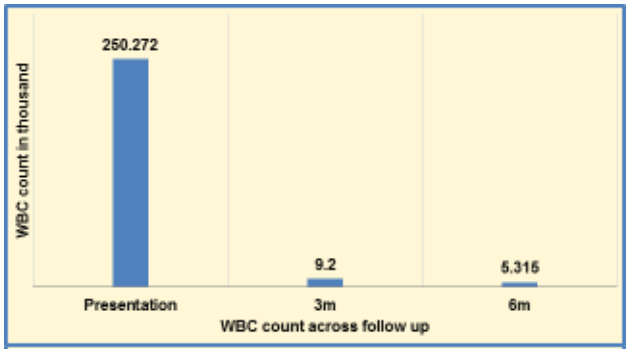

Fig 2 — Mean Leucocyte Count in thousand/dL Trend

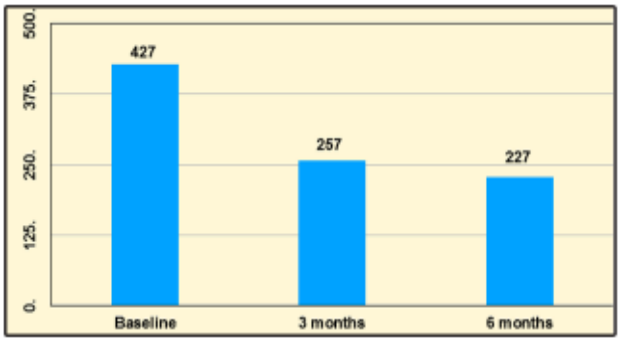

Fig 3 — Mean Platelet Count in thousand/dL Trend

After 3 months of TKI therapy, mean hemoglobin was raised to 10.513 g/dL. Total leukocyte count was reduced to a mean count of 9200/dL with only 14.89% patients having a count more than 11000/dL. None of the patients had blast cell in the peripheral smear. Mean platelet count was reduced to 256.94 thousand/dL with only 17.02% patients having a count <150 thousand/dL. As we already know, TKI therapy does reduce cell count, but predisposes the patient to a cytopenia as early as 3 months, as for our study, it manifested as thrombocytopenia.

By 6 months of treatment, hemoglobin further increased to a mean of 11.294 g/dL. But what drew

Table 1 — *Comparison of differential counts at 3rd and 6th month (n=47)*

	Neutrophil	Lymphocyte	Eosinophil	Monocyte	Basophil	Total
3rd month	64	30	3	3	0	100
6th month	58	35	5	2	0	100

Table 2 — *Imatinib versus Nilotinib on the basis of Blood Cell Counts*

Parameters	Overall (n=47)	Imatinib treated (n=37)			Nilotinib treated (n=10)		
	Baseline	Baseline	3 months	6 months	Baseline	3 months	6 months
Hemoglobin	8.74 g/dL	8.62 g/dL	10.49 g/dL	11.08 g/dL	9.17 g/dL	10.6 g/dL	12.07 g/dL
Total Leukocyte Count	268.68 thousand/dL	266.24 thousand/dL	9429.73 /dL	5181.08 /dL	277.67 /dL	8350 /dL	5810 /dL
TLC <4000	-	-	10.81% (n=4)	10.81% (n=4)	-	0%	0%
Total Platelet Count	427.17 thousand/dL	431.92 thousand/dL	252.89 thousand/dL	209.41 thousand/dL	409.60 thousand/dL	271.9 thousand/dL	294.4 thousand/dL
Platelet ≤150 thousand/dL	-	-	18.92% (n=7)	24.32% (n=9)	-	10% (n=1)	20% (n=2)

our attention was 2 patients with hemoglobin of 7.8 g/dL. Mean total leukocyte count further dropped to 5314.89/dL. Again, 8.51% patients had a count of <4000/dL. Similarly, mean platelet count dropped to 227.49 thousand/dL, and more importantly 23.4% patients experienced a platelet count below 150 thousand/dL. Although our patients did not have any hemorrhagic complication during the study, thrombocytopenia is quite usual and hemorrhagic manifestations have been recorded in the literature[8].

We treated our patients Imatinib (n=37) and Nilotinib (n=10) (as feasible as per hospital supply). It has been proven in literature that Nilotinib was more effective to bring the total leukocyte count to a normal range[10]. Mean leukocyte count at 3 months was 8350 /dL for Nilotinib compared to 9429.73 /dL for Imatinib. But when we compared leukocyte count on baseline, 3rd month and 6th month in between Imatinib and Nilotinib treated patients, this reduction in leukocyte count was statistically insignificant. What drew our attention was the fact of Imatinib having more propensity to cause cytopenia both for leukocyte and platelets. Even though mean leukocyte count was lower in Nilotinib treated patients, still there were 10.81% Imatinib treated patients who had leukocyte count less than 4000/dL compared to none for Nilotinib. Even after 6 months of TKI therapy, there were no patient with leukopenia in Nilotinib treated patients. Platelet count reduction was higher for Imatinib, and there were 18.92% patients with platelet count ≤150 thousand/dL for Imatinib compared to 10% for Nilotinib at 3 months of TKI therapy and 24.32% for Imatinib compared to 20% for Nilotinib at the end of 6 months of TKI therapy which was reflected as a statistically significant data while comparing platelet counts on 6th month (paired 't' test, one sided p=0.009) as reduction in platelet count was higher in Imatinib treated patients. When we look for hemoglobin trends, it was increasing over 6 months. Again, for Nilotinib mean hemoglobin was higher at 10.6g/dL at 3 months, 12.07 g/dL at 6 months compared to 10.49 g/dL at 3 months and 11.08 g/dL at 6 months for Imatinib. Change in hemoglobin trend did not yield any statistical significance.

Although there are published literature comparing between Imatinib and Nilotinib elsewhere in the World, to best of our knowledge, there is no such study in Indian context and we believe our study is a first of its kind in this country for comparing these two TKIs[10,11].

Conclusion

With significant progress made over last 2 decades, CML remains arguably the blood cancer with best prognosis. TKIs have revolutionized the CML treatment and it was quite evident. Most dramatic was the reduction of leukocyte count mostly to normal counts within 3 months. Hemoglobin level consistently increased and reached a normal population level by 6 months. What drew our attention was the cytopenia both for leukocytes and platelets. None of the patients had any cytopenia related complications.

The most interesting finding was found while comparing Imatinib to Nilotinib as first line therapy. Nilotinib treated patients reached a normal leukocyte count faster than Imatinib and they had higher increase in hemoglobin level as well. On the contrary, none of the Nilotinib treated patients had leukopenia even after 6 months of treatment compared to Imatinib where one tenth of the patients had leukopenia. Reduction in the platelet count was roughly similar both for Nilotinib and Imatinib but higher proportion of Imatinib treated patients reported a thrombocytopenia. There is a tendency of having cytopenia with TKI therapy and it remains the major concern globally flagging up to stop the treatment. A longer follow up and blood count monitoring is warranted to further address the issue in a wider prospect.

Despite having better clinical response, during the course of treatment we found that Nilotinib was less tolerated for about one fifth of the patients, mostly as restlessness, headache, palpitation, anxiety which are similar to the already reported publications[11]. Imatinib was way better tolerated with not a single adverse effect complained by the patients. Lack of adequate literatures, along with being more expensive hold back Nilotinib for wider uses as a first line therapy for CML.

There are very few studies Worldwide comparing Imatinib and Nilotinib as first line treatment modality. We hope this study highlighted key factors and would pioneer further larger and multi-centric studies as we progress to superior treatment options in the future.

Limitations :

(1) Smaller study population may have resulted hospital bias.

(2) This hospital serves a smaller geographic area which may not represent the overall epidemiology.

(3) This was a single centre study. Multicentre study should delineate the parameters better.

(4) Shorter follow up of only 6 months leaves us hankering after a way longer follow up, at least for years.

(5) Molecular analysis was not performed either at baseline or follow up.

(6) Mutational analysis was not performed before selection of TKI.

(7) Higher treatment expenses and limited hospital supplies

Conflict of Interest : None.

References

1 Smith A, Howell D, Patmore R, Jack A, Roman E — Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. *Br J Cancer [Internet]* 2011 [cited 2022 Feb 11]; **105(11):** 1684-92. Available from: https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC3242607/

2 Pulte D, Jansen L, Brenner H — Changes in long term survival after diagnosis with common hematologic malignancies in the early 21st century. *Blood Cancer J [Internet]* 2020 [cited 2022 Feb 11]; **10(5):** 56. Available from: https://www.nature.com/articles/s41408-020-0323-4

3 Bower H, Björkholm M, Dickman PW, Höglund M, Lambert PC, Andersson TM — Life expectancy of patients with chronic myeloid leukemia approaches the life expectancy of the general population. *J Clin Oncol* 2016; **34:** 2851-7.

4 Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, *et al* — European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia* 2020; **34:** 966-84.

5 Kantarjian HM, Hughes TP, Larson RA, Kim D-W, Issaragrisil S, le Coutre P, *et al* — Long-term outcomes with frontline nilotinib *versus* imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. *Leukemia [Internet]* 2021 [cited 2022 Feb 12]; **35(2):** 440-53. Available from: https://www.nature.com/articles/s41375-020-01111-2.

6 Nakamae H, Fukuda T, Nakaseko C, Kanda Y, Ohmine K, Ono T, *et al* — Nilotinib vs. imatinib in Japanese patients with newly diagnosed chronic myeloid leukemia in chronic phase: long-term follow-up of the Japanese subgroup of the randomized ENESTnd trial. *Int J Hematol [Internet]* 2018; **107(3):** 327-36. Available from: http://dx.doi.org/10.1007/s12185-017-2353-7.

7 Saglio G, Kim DW, Issaragrisil S, Le Coutre P, Etienne G, Lobo C, *et al* — Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *New England Journal of Medicine* 2010; **362(24):** 2251-9.

8 Kantarjian H, Cortes J — Chronic myeloid leukemia. In: Jameson JL, Kasper DL, Longo DL, Fauci AS, Hauser SL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 20th Ed. USA: McGraw-Hill Education; 2018. 748-57.

9 Song KW, Rifkind J, Al-Beirouti B, Yee K, McCrae J, Messner HA, *et al* — Subdural hematomas during CML therapy with imatinib mesylate. Leukemia & lymphoma. 2004 Aug 1;45(8):1633-6.

10 Saglio G, Kim DW, Issaragrisil S, Le Coutre P, Etienne G, Lobo C, *et al* — Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *New England Journal of Medicine* 2010; **362(24):** 2251-9.

11 Larson RA, Hochhaus A, Hughes TP, Clark RE, Etienne G, Kim DW, *et al* — Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. *Leukemia* 2012; **26(10):** 2197-203.