JPSIM Journal of Pakistan Society of Internal Medicine

Original Article

Comparing Imatinib and Nilotinib in the Treatment of Newly Diagnosed Chronic Myeloid Leukemia in Patients of Sandeman Provincial Hospital, Quetta, Pakistan

Afia Haque, Syed Khalid Shah, Humaira Rahim, Abdul Wahid

Department of Internal Medicine, Sandeman Provincial Hospital, Quetta

Abstract

Objective: To compare the effectiveness of Imatinib and Nilotinib as first-line drug in the treatment of chronic myeloid leukemia.

Methods: The study was conducted at Medicine Unit III, S.P.H, Quetta, from April 2019 to 2020. Study was commenced after taking approval from ethical committee of the institute. Newly diagnosed, treatment naïve, chronic myeloid leukemia patients visiting Medical OPD, Emergency and Medicine ward fulfilling the inclusion criteria. Exclusion criteria was strictly followed to control confounder and bias in the study. Patients were randomly divided into two groups, one started on Imatinib and other Nilotinib, were followed up at 3, 6 and 11 months with CBC and molecular response by bcr-abl PCR on blood or bone marrow. Informed consent was taken from all the patients prior to the commencement of the study and thpeir information was kept confidential.

Results: Of the 149 patients in Imatinib group, 99 showed response to treatment with 36% achieving MMR in 9 to 12 months, while 130 patients on Nilotinib showed drug effectiveness with 52% achieving MMR within 9 to 12 months, mainly at 9 months of treatment.

Conclusion: The study endorses that Nilotinib is better than Imatinib in the treatment of CP-CML, and hence can be used as first line therapy.

Keywords: CP-CML, Imatinib, Nilotinib, MMR, CCyR.

How to cite this:

Haque A, Shah SK, Rahim H, Wahid A. Comparing Imatinib and Nilotinib in the Treatment of Newly Diagnosed Chronic Myeloid Leukemia in Patients of Sandeman Provincial Hospital, Quetta, Pakistan. J Pak Soc Intern Med. 2022;3(1):36-40

Corresponding Author: Afia Haque

Email: dusk786@hotmail.com

DOI: https://doi.org/10.70302/jpsim.v3i1.2207

Introduction

Chronic Myeloid Leukemia (CML) is a hematogenous disease defined by increased number of different stages of myeloid cells that are present in the blood. There is a specific chromosomal abnormality (i.e. Philadelphia chromosome) and a specific molecular abnormality (i.e. bcr-abl gene) in CML resulting in a novel protein that is different from the routine abl gene as it possess tyrosine kinase activity.[1] In CML a stem cell dysfunction resulting from genetic mutation results in a corresponding balanced translocation between the long arms of chromosomes 9 and 22, t(9;22) (q34;q11.2), cytogenetically detected as the Philadelphia chromosome (Ph). The natural course of the disease may be biphasic or triphasic, with an initial insidious or chronic phase, later usually an accelerated phase and a final blast crisis.

CML comprises 15% of all leukemias with modest male predominance (male: female ratio 1.6:1). The average age of diagnosis is 55–65 years, its occurrence rate is 1.5 cases per 100,000 individuals per annum. Prior to the advent of TKIs, CML had a grave prognosis with a median survival of only 3-7 years and ≤30% of 10-year survival rate. With the introduction of TKIs in 2000, the treatment, natural course and progression of CML has totally changed. Now, the 10-year survival rate is approximately 85%, with the use of imatinib mesylate, the earliest BCR-ABL1 TKI licenced for CML treatment, and the yearly mortality rate of CML has dropped to just 2% rather than 10-20%. And hence, the allogenic stem cell transplantation (SCT), a therapeutic but high risk treatment option, is now used as a second- or third-line option after the failure of TKIs.[2]

Hence tyrosine kinase inhibitors are generally highly effective in treating CML and its use has likely more impact on the lifespan of patients with CML especially in Balochistan, Pakistan, where the disease presentation is at a younger age and very few resources are available for bone marrow transplantation.

With the launch of tyrosine kinase inhibitor Imatinib in 2001, the treatment aspects of chronic myeloid leukemia has changed alot and is being used since very long, but due to the grave side effects and resistance, there is a need for newer agents to improve health related quality of life . However with the advent of new drugs the side effect and resistance profile has greatly improved. Studies have shown Nilotinib to be more effective as compared to Imatinib in newly diagnosed chronic phase, Philadelphia chromosome positive CML.[3]

There are side effects seen with TKIs but that too is comparatively lower with Nilotinib as compared to imatinib, as is supported by many studies. The incidence rate of the adverse events was either significantly lower for Nilotinib than Imatinib or not different between the two drugs.[4]

The present practice of CML treatment in our hospital is Imatinib as first line, however newer agent Nilotinib is available and is recommended by the literature to be the first-line treatment in CML. Keeping in view the economic burden of CML treatment and the need of tyrosine kinase inhibitors as the only treatment option for CML in Balochistan, where there is no Bone Marrow Transplant facility, this study will compare the efficacy of Imatinib and Nilotinib. The drug which will be found to be of higher efficacy will be selected as front-line treatment for CML, decreasing the incidence to switch on to other agents in case of disease progression, side effects or resistance to any one of the drugs, so that the people of Balochistan suffering from CML with limited resources can also have better quality of life.

Methods

A randomized controlled trial was conducted at Medicine Unit III, Sandeman Provincial Hospital, Quetta, spanning over a period of 13 months from April 2019 to April 2020. Taking cytogenetic response at 12 months for Nilotinib to be 78% and that for Imatinib to be 65%, keeping confidence level of 95% and power of test to be 80%, the estimated sample size was 149 patients in each group.[5] Total n = 298 patients. A non probability consecutive sampling technique was used and the patients who best fulfilled the inclusion criteria were chosen i.e., patients with chronic myeloid leukemia between 16yrs to 55yrs including both males and females, diagnosed on bone marrow trephine biopsy with Philadelphia chromosome positive and positive bcr-abl immunophenotyping on either bone marrow or blood. Other types of hematological malignancies including acute leukemias and chronic lymphocytic leukemia were excluded to control effect modifier and avoid bias in the study. All the newly diagnosed CML patients visiting Medical OPD, Emergency Department and those admitted in the Medicine ward of S.P.H. Quetta, who were treatment naïve were included in the study. Diagnosis of CML was as per history and examination, and confirmed on the basis of complete blood count, ESR, ultrasonography and bone marrow trephine biopsy and Ph with bcr-abl PCR. Study was commenced after taking approval from ethical committee of the institute. Once diagnosed, the participants were subdivided into two groups randomly, group A having patients started on Imatinib 400mg OD and group B, including those patients who were given Nilotinib 300mg OD. The patients were regularly followed up at 3, 6 and 12 months. At 3 months CBC was repeated, at 6 months cytogenetic response checked by Ph chromosome level in bone marrow and at 12 months of follow up molecular response was evaluated by bcr-abl PCR on blood or bone marrow sample. The patients were given description of the whole study protocol so that their confidence could be gained and they come for consultation in between the set follow up dates in case of any adverse events. Privacy regarding details of the participants was observed. Authorization from all the participants was sought prior to the commencement of the research. Statistical analysis was done by Statistical Package for Social Sciences (S.P.S.S) for Windows, version 21.0 Frequency distribution and percentages were calculated for gender and efficacy. Mean and standard deviation of age, duration of treatment, WBC count, Hb and platelet count was calculated. Chi square test was applied to compare the two drugs for efficacy. p value ≤ 0.05 was considered significant.

Results

A total of 298 participants were incorporated in the research, divided randomly in two groups of 149 patients. One group including those given Imatinib 400mg OD orally and the other group including those who were given Nilotinib 300mg BD per oral. Patients under study who expired during treatment and those who lost to followup were excluded from the study.

The study sample included patients from 16 years to 55 years, including both males and females. Of the 298 patients, 174 were males (58.4%) and 124 were females (41.6%).

The mean age at presentation was 38.93±11.769 years.

Out of 149 patients in Imatinib group, 99 showed drug efficacy in terms of Ph/BCR-ABL improvement, while 130 out of 149 patients in Nilotininb group showed response, as shown in table I.

Table 1: *Effectiveness of Both Drugs*

Drug Used Vs Drug Efficacy Cross tabulation						
			Drug Efficacy		Total	P Value
			No	Yes		
Drug Used	Imatinib	Count	50	99	149	Less than 0.05
	Nilotinib	Count	19	130	149	
Total		Count	69	229	298	

Chi square test was applied

p value ≤ 0.05 is considered significant

All the patients were subjected to BCR-ABL 1 transcripts level by PCR after 9 to 12 months of the treatment and the levels were measured. The data demonstrated that out of 99 patients giving response on Imatinib, 36 patients (36.3%) showed MMR, while out of 130 patients in Nilotinib group, 68 patients (52.3%) demonstrated MMR, hence favouring Nilotinib as more effective drug in CML-CP.

Improvements in CBC by both the drugs are demonstrated in table II.

Table 2: *Improvement in Complete Blood Counts*

		WBC Count			Hemoglobin Level			Platelet Count		
		Yes	No	Total	Yes	No	Total	Yes	No	Total
Drug Used	Imatinib	111	38	149	91	58	149	114	35	149
	Nilotinib	127	22	149	117	32	149	124	25	149
Total		238	60	298	208	90	298	238	60	298

The descriptive statistics of improvements in WBC counts, Hb and Platelet counts by both the drugs are shown in Figures 1, 2 and 3 respectively.

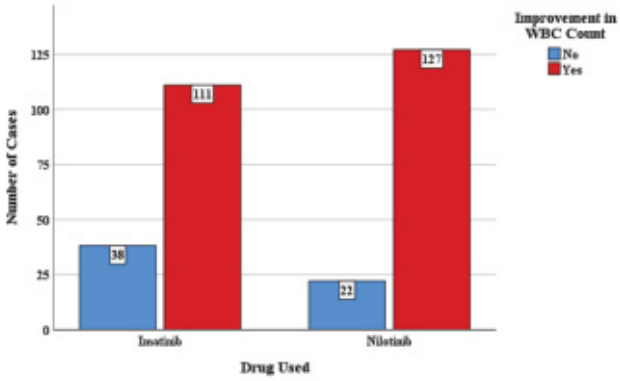

Figure 1: *Descriptive Statistics of Improvement in WBC Count with both the Drugs*

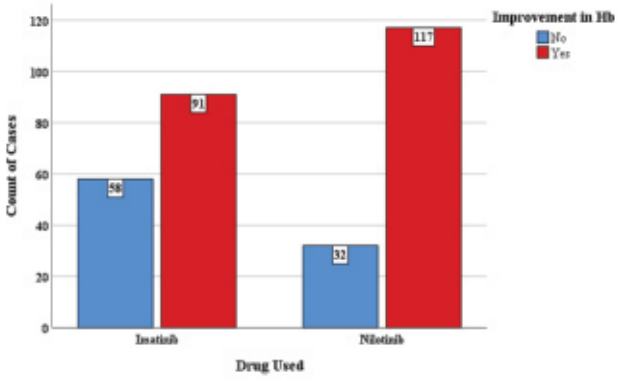

Figure 2: *Descriptive Statistics of Improvement in Hemoglobin Level with both the Drugs*

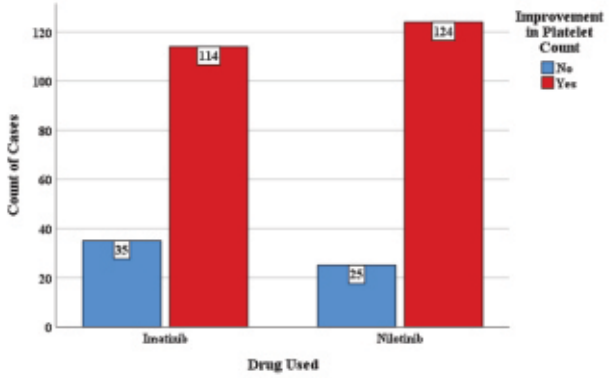

Figure 3: *Descriptive Statistics of Improvement in Platelet Counts*

The duration of treatment and response by each drug is also monitored and the results are represented in figure 4.

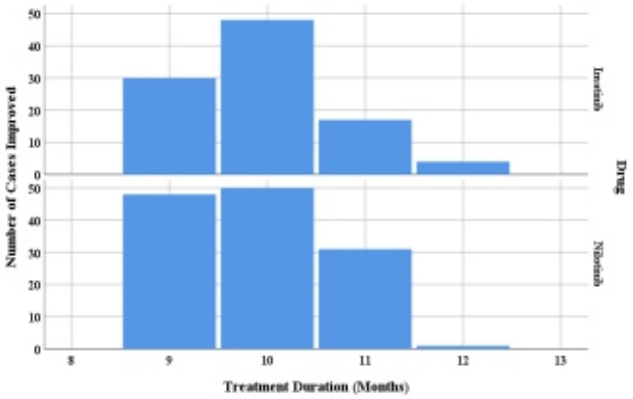

Figure 4: *Duration of Treatment and Response to Drugs*

Discussion

A number of prior studies done have shown that Nilotinib is better than Imatinib for the treatment of CML-CP in terms of response to the treatment, CCyR and MMR. However, this was a much needed study in our area i.e. Quetta, Balochistan where no study has been conducted prior to this and also the only treatment available here is these two drugs, the NIlotinib and Imatinib. We conducted this study to show that which of the two drugs is more effective in treating CML-CP so that patients can be started directly on the front line therapy with the effective drug, hence reducing duration of treatment and economic burden as well.

This study showed that the disease in our area is more common in younger age group as opposed to the general view, CML commonly occurs, around 70% in adults of 40 years or above and is rare in children.[6] The mean age at presentation as shown by our study was 38.9 years with SD of 11.76.

This disease is shown to have a slight predilection in males, and the same was demonstrated by our study. Out of 298 patients, 174(58.4%) are males and 124 (41.6%) are females with a ratio of male to female 1:1.4.

Our study demomstrated that Nilotinib is better than Imatinib in patients with CML-CP. Out of 149 patients on Nilotinib, 130 patients (43.62%) showed effectiveness in drug and only 19 patients (6.38%) showed no response. However, in case of Imatinib 99 patients (33.22%) out of 149 showed response while 50 patients (16.78%) out of 149 showed no response. Chi square test was applied and the p value came out to be less than 0.05, hence favoring the set hypothesis that Nilotinib is better than Imatinib in the treatment of CML-CP, as is favoured by previuos studies, which show that the NG-TKIs as first-line medicines for CML demonstrated better efficacy with regards to MMR as well as in preventing progression of the disease to accelerated phase or blast crisis.[7]

The complete cytogenetic response (CCyR) is taken as BCR-ABL1 level <1% at 6 months and <0.1% at 12 months and after, with BCR-ABL1 level below 0.1% representing -3log reduction or deep molecular response (MR3). With Imatinib the CCyR was seen in 63 out of 99 oatients i.e. 63% cases showed CCyR, while MR3 was seen in 36/99 cases i.e. 36% patients showed deep molecular response. However, in case of Nilotinib 62 out of 130 patients i.e. 47.6% showed CCyR and 68/130 cases i.e. 52.3% cases showed deep molecular response (MR3). The same is supported by the statistics of the phase III ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients) trial that Nilotinib can be used as a likely newer standard in first line treatment of newly diagnosed chronic phase CML patients. Nilotinib showed higher efficacy in comparison to imatinib with regards complete cytogenetic response and MMR, and also had lesser chances of progress to advanced disease.[8] And also by another study which showed that MMR was 86% with Nilotinib and deep molecular response with Nilotinib was 39%.[9]

The response to drug therapy and duration of treatment was also measured as shown in figure 7, which demonstrated that Nilotinib showed early response rate as compared to Imatinib. Majority of the cases taking Nilotinib showed response in 9 months (48/130 cases) and 10 (50/130 cases) months of treatment, while with Imatinib, major response was seen in 10 months duration (48/99 cases). Hence proving that although Imatinib does show an early response for CML-CP patients, greater and earlier response is achieved with Nilotinib. Same findings are favoured by a recent study that Nilotinib showed greater CMR rate and also fewer disease progressions and deaths.[10] Another study conducted on Nilotinib revealed that the response rate was early and 96% patients showed CCyR in 3 months while 98% in 6 months.[11] Further studies also suggest the same that the second generation TKIs induce a persistent deep molecular response over a shorter period of time in comparison to Imatinib.[12]

Another finding of this study was improvement of different cell lines with Nilotinib, all the patients in both the drug groups had undergone complete blood count test at 3 months after commencing the drug therapy, and the improvement in overall CBC as well as in different blood lines was also checked, represented in figures 1-3. The study demonstrated that 111/149 patients (74.5%) in Imatinib group showed improvement in WBC at 3 months of treatment. While 25.5% showed no improvement. However, 127/149 cases (85.2%) on Nilotinib treatment showed improvement in WBC after 3 months of treatment, whereas 14.8% cases showed no improvement at 3 months.

The improvement in Hemoglobin was also shown to be more with Nilotinib than Imatinib at 3 months of treatment. In Imatinib group, 91/149 patients(61.1%) showed improvement in Hb, while 38.9% showed no improvement. On the other hand, 117/149 patients (78.5%) showed improved Hb levels at 3 months of treatment with Nilotinib whereas 21.5% cases didn't show improvement.

Similarly, the same pattern was seen with platelet count improvement i.e. higher counts correction with Nilotinib (124/149 patients – 83.2%) than with Imatinib (114/149 patients – 76.5%) at 3 months of drug therapy.

Conclusion

The novelty in this research is that it is conducted in

an area, i.e. Balochistan where there is no facility of bone marrow transplantation, and the only treatment option available is drugs, that also only Imatinib and Nilotinib, hence it was much needed to find out a best of the available options. Our study results conclude that Nilotinib is better than Imatinib for the treatment of CML-CP in terms of CCyR, MR3 and improvement in peripheral blood counts, and hence can even be used as a front-line therapy for CML-CP.

Conflict of Interest: None

Funding Source: None

References

1. Maxine A. Papadakis, Stephen J. McPhee MWR. Current medical diagnosis and treatment 2017. In: 56th Editi. Mc Graw Hill; 2017. p. 523–4.
2. Cortes HKJ. Chronic Myeloid Leukemia | Harrison's Principles of Internal Medicine, 19e | AccessMedicine | McGraw-Hill Medical. In [cited 2019 Dec 17]. Available from: [https:// accessmedicine. mhmedical.com/content.aspx?bookid=1130&sectionid=79731824]
3. Kantarjian HM, Hochhaus A, Saglio G, Souza C De, Flinn IW, Stenke L, et al. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. Lancet Oncol. 2011;12(9):841–51.
4. Guérin A, Chen L, Ionescu-Ittu R, Marynchenko M, Nitulescu R, Hiscock R, et al. Impact of low-grade adverse events on health-related quality of life in adult patients receiving imatinib or nilotinib for newly diagnosed Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase. Curr Med Res Opin. 2014;30(11):2317–28.
5. Saglio G, Kim DW, Issaragrisil S, Le Coutre P, Etienne G, Lobo C, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010;362(24):2251–9.
6. Chronic myeloid leukaemia (CML) - Leukaemia Foundation [Internet]. [cited 2022 Jan 4]. Available from: [https://www.leukaemia.org.au/blood-cancer-information/types-of-blood-cancer/leukaemia/chronic-myeloid-leukaemia/]
7. Yun S, Vincelette ND, Segar JM, Dong Y, Shen Y, Kim DW, et al. Comparative Effectiveness of Newer Tyrosine Kinase Inhibitors Versus Imatinib in the First-Line Treatment of Chronic-Phase Chronic Myeloid Leukemia Across Risk Groups: A Systematic Review and Meta-Analysis of Eight Randomized Trials. Clin Lymphoma, Myeloma Leuk. 2016;16(6):e85–94.
8. Erba HP, Pham DC, Zaiden R, Vu H, Tai S. Improving frontline treatment for chronic myeloid leukemia: emerging evidence for use of nilotinib and dasatinib. Clin Adv Hematol Oncol [Internet]. 2011 Oct [cited 2019 Dec 17];9(10):734–45. Available from: [http://www. ncbi.nlm.nih.gov/pubmed/22252576]
9. Zaidi U, Kaleem B, Borhany M, Maqsood S, Fatima N, Sufaida G, et al. Early and sustained deep molecular response achieved with nilotinib in high Sokal risk chronic myeloid leukemia patients . Cancer Manag Res [Internet]. 2019 Feb 15 [cited 2022 Jan 5];11:1493–502. Available from: [https:// www.dovepress.com/early-and-sustained-deep-molecular-response-achieved-with-nilotinib-in-peer -reviewed-fulltext-article-CMAR]
10. Kantarjian HM, Hughes TP, Larson RA, Kim DW, 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. Leuk. 2021; 35(2): 440–53.
11. Cortes JE, Jones D, O'Brien S, Jabbour E, Konopleva M, Ferrajoli A, et al. Nilotinib as front-line treatment for patients with chronic myeloid leukemia in early chronic phase. J Clin Oncol. 2010;28(3):392–7.
12. Annunziata M, Bonifacio M, Breccia M, Castagnetti F, Gozzini A, Iurlo A, et al. Current Strategies and Future Directions to Achieve Deep Molecular Response and Treatment-Free Remission in Chronic Myeloid Leukemia. Front Oncol. 2020;10(6):883.