Comparison of Response to Treatment with Imatinib Versus Nilotinib in the Initial Three Months in Chronic Myeloid Leukaemia

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ABSTRACT

BACKGROUND

Chronic myeloid leukemia (CML) accounts for 15 - 20 % of leukemia in adults worldwide. At present, the three tyrosine kinase inhibitors (TKI) imatinib, dasatinib, or nilotinib are accepted as the standard first-line treatment in chronic phase (CP). Nilotinib is a second generation TKI having faster and deeper response compared to imatinib. We wanted to see if the response achieved with nilotinib in the first three months could be translated into long term benefits when imatinib was given after 3 months.

METHODS

Newly diagnosed CML-CP patients were randomized into two arms. The patients on the first arm were given imatinib and in the second arm nilotinib was given for first 3 months. After three months nilotinib was switched over to imatinib. The molecular response was assessed in both arms at 3 months and 6 months.

RESULTS

Twenty-six patients in each arm were analysed. The optimal molecular response (QPCR <10 %) after 3 months was significantly higher in patients receiving nilotinib than imatinib (96.1 % vs 65.38 %; P < 0.0048). The optimal response after 6 months (QPCR < 1 %) was found to be more in the initial nilotinib arm than the initial imatinib arm (76.9 % vs 65.3 %; P - value = 0.35).

CONCLUSIONS

Patients on nilotinib arm did well even after switching to imatinib. It gives us an important platform for an economically backward country like India where the therapy with more potent drug like nilotinib is given in the initial three months or even six months.

KEYWORDS

Chronic Myeloid Leukaemia, Imatinib, Nilotinib, Optimal Response, Major Molecular Response

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DOI: 10.18410/jebmh/2021/376

How to Cite This Article:
Singh IA, Jain A, Devi PV, et al. Comparison of response to treatment with imatinib versus nilotinib in the initial three months in chronic myeloid leukaemia. J Evid Based Med Healthc 2021;8(24):2001-2005. DOI: 10.18410/jebmh/2021/376

Submission 05-01-2021,
Peer Review 15-01-2021,
Acceptance 28-04-2021,
Published 14-06-2021.

BACKGROUND

Chronic myeloid leukemia is a progressive and often fatal hematopoietic neoplasm. It accounts for 15 - 20 % of leukaemia in adults worldwide.[1] At present, the three tyrosine kinase inhibitors - imatinib, dasatinib, or nilotinib is accepted as the standard first-line treatment for patients with newly diagnosed chronic-phase CML (CML-CP).[2] Imatinib is a first generation TKI which has been the standard of therapy for patients with CML in all stages of the disease.[3] A complete cytogenetic response (CCyR) can be achieved in over 80% of those receiving imatinib as first-line therapy.[4] However, despite the excellent results with imatinib, resistance occur in some cases at an annual rate of approximately 4 % in newly diagnosed CML and even more in advanced disease.[5] As a result, second-generation TKIs, including nilotinib and dasatinib, have been developed to overcome the shortcomings of imatinib. Nilotinib is 30 times more potent at inhibiting BCR–ABL activity.[6] Nilotinib could reduce the BCR-ABL transcript faster than imatinib. The nilotinib had a better safety profile when compared to imatinib.[7] One of the main drawbacks of nilotinib is the higher cost and in a country like India majority of patients belong to the backward economic condition. Whereas imatinib is available as generic further reducing the cost. It will be very difficult for the patients to afford nilotinib for a longer duration. So, we gave nilotinib in one group of patients in the first three months of treatment and followed by imatinib maintenance. We wanted to see if the response achieved with nilotinib in the first three months could be translated into long term benefits. We reported interim response of our study at 3 and 6 months.

METHODS

The study was conducted at the Haematology Department, AIIMS, New Delhi from December 2015 to May 2017. All newly diagnosed cases of chronic myeloid leukemia in chronic phase (CML-CP) were eligible for the study. Previously treated CML-CP, accelerated phase (AP), blast crisis (BC) and not signing the consent were excluded from the study. The study was an open-label, cross-over randomized control trail. A randomization table was generated before the patients were enrolled for the study.

The diagnosis was done by qualitative reverse transcriptase PCR for BCR-ABL (RT-PCR for BCR-ABL). Bone marrow examination was also performed whenever there was a suspicion of AP/BC. But it was not mandatory for all the cases. LAP score, routine biochemical analysis, viral markers, electrocardiogram and radiological investigations were done as routine policy. Risk stratification was done using the Sokal score at baseline. The patients on the first arm were given imatinib 400 mg once daily after meal throughout the study and in the second arm nilotinib 300 mg twice daily was given for 3 months. After completion of three months of therapy, nilotinib was switched over to imatinib 400 mg. Complete hemogram was repeated after 15 days and 30 days to look for any haematological response and toxicity. Then every one month in the first three months. Thereafter three monthly hemograms were done. The complete haematological response was defined as white blood cell count < 10,000/microL with no immature granulocytes and < 5 percent basophils on differential platelet count < 450,000/microL and spleen not palpable. Quantitative real-time PCR for BCR-ABL (RQ-PCR for BCR-ABL) was done at 3, 6 months as per standard of care to see the response of therapy. All the values were in an international scale. Response was defined as per ELN 2013 guidelines. The optimal response was defined as RQ-PCR for BCR-ABL transcript levels of ≤ 10 % at 3 months, < 1 % at 6 months. The warning was defined as RQ-PCR for BCR-ABL transcript levels > 10 % after 3 months and > 1 % and < 10 % after 6 months. Treatment failure was defined as RQ-PCR for BCR-ABL transcript was more than 10 % after 6 months of treatment. Major molecular response (MMR) was defined as RQ-BCR-ABL1 < 0.1 %. The accelerated phase and blast crisis were defined as per the world health organization (WHO) definition. Those patients having accelerated or blast crisis were defined as disease progression. The side effects of the treatment were monitored. During the treatment, supportive treatment as per standard guidelines was given.

All statistical tests were performed using STATA 13.0 software. Statistical analysis included chi 2, Fisher's exact and two-sample test of proportions where applicable. P - value of less than 0.05 was considered significant.

RESULTS

Sixty newly diagnosed CM-CP were enrolled in the study and randomised to two arms equally. Twenty-six patients in each arm could be analysed at the end of six months. Baseline characteristic was similar in both the arms and shown in the table. No. 1. The Sokal risk score was slightly higher in the nilotinib arm but not statistically significant (P - value = 0.52).

Characteristics	Imatinib 400mg (N = 26)	Nilotinib 300mg (N = 26)	P-Value
Median age (range)- years	31(15-76)	30(18-65)	0.93
Male sex – no (%)	15 (57.7)	22 (84.6)	0.03
Median to diagnosis (range)-days	60 (30-365)	60 (30-240)	1.0
Pallor – no (%)	10 (38.46)	9 (34.62)	0.76
Fever – no (%)	6(23.08)	8 (30.77)	0.5
Awareness of LUQ mass – no (%)	21 (80.77)	23 (88.40)	0.4
Splenomegaly >10cm BLCM	13 (50)	16 (61.54)	0.42
Fatigue – no (%)	20 (76.92)	18 (69.23)	0.57
Median Hb (range)-g / dl	10.1(6.9-14.6)	9.75(6.3-12.1)	0.9
Median TLC (range)- 10^9 / L	119 (13.6-453)	231 (23-608)	0.28
Median platelets (range) - 10^9 / L	284 (120-980)	324 (145-909)	0.75
Sokal risk group – no (%)			
Low	10 (38.4)	6 (23)	0.24
Intermediate	11 (42.3)	12 (46.5)	0.77
High	5 (19.2)	8 (30.7)	0.35

Table 1. Baseline Characteristics

Characteristics	Imatinib 400mg (N = 26) (%)	Nilotinib 300mg (N = 26) (%)	P Value
Optimal response (QPCR < 10 %)	17 (65.38)	25 (96.15)	0.0048
Warning (QPCR > 10 %)	9 (34.62)	1 (3.8)	0.0036
Major molecular response (QPCR < 0.1 %)	0	4 (15.38)	0.04

Table 2. Response at 3 Months

SOKAL Score	RQ-PCR for BCR ABL1<10%(IS) Imatinib 400mg	Nilotinib 300mg	P-Value
Low	7 / 10 (70)	6 / 6 (100)	0.13
Intermediate	7 / 11 (63)	11 / 12 (91.6)	0.10
High	3 / 5 (60)	8 / 8 (100)	0.005

Table 3. Optimal Response Based on Sokal Score at 3 Months

Characteristics	Imatinib 400mg (N= 26) (%)	Nilotinib 300mg (N = 26) (%)	P - Value
Optimal response (QPCR < 1 %)	17 (65.3)	20 (76.9)	0.35
Warning (QPCR > 1 %, < 10 %)	7 (26.9)	2 (7)	0.06
Failure (QPCR > 10 %)	2 (7.6)	3(15)	0.38
Major molecular response (QPCR< 0.1 %)	6 (23)	9(34.6)	0.35

Table 4. Response at 6 Months

	RQ-PCR for BCR-ABL1 (IS) (Range)		P Value
3 months	Imatinib 400 mg (N = 26) 2.06 % (0.18 - 98.18%)	Nilotinib 300 mg (N = 26) 1.122 % (0.02 - 25.14 %)	0.11
6 months	Imatinib 400 mg Imatinib 400 mg (N = 26) 0.3 % (0.01-13%)	Nilotinib 300 mg Imatinib 400 mg (N = 26) 0.1 % (0.008 -18.77 %)	0.07

Table 5. Kinetics of Median RQ-PCR for BCR-ABL1 at 3 Months and 6 Months

Characteristics	Imatinib 400mg (N = 26) (%)	Nilotinib 300mg (N = 26) (%)	P - Value
Gastritis	7 (26.92)	1 (3.89)	0.05
Nausea	6 (23.08)	0	0.023
Pruritus	5 (19.23)	1 (3.89)	0.19
Myalgia	1 (3.85)	1 (3.85)	1.00
Diarrhoea	0	0	
Oedema	2 (7.69)	0	0.49
Anaemia	8 (30.77)	4(15.38)	0.32
Neutropenia	0	0	
Thrombocytopenia	0	0	
Pancreatitis	0	0	
Cardiac complications	0	0	
Deranged LFT	0	0	
Deranged KFT	0	0	

Table 6. Adverse Events and Newly Occurring or Worsening Haematological Complications

Molecular Response at 3 Months

The optimal molecular response (QPCR < 10 %) after 3 months were significantly higher in patients receiving nilotinib than imatinib (96.1 % vs 65.38 %; P < 0.0048). The warning response (QPCR > 10 %) after 3 months was seen in (3.8 %) case in nilotinib arm while in 9 (34.62 %) cases in imatinib arm (P - value = 0.0036). At the end of 3 months, major molecular response (QPCR < 0.1 %) was seen in 4 (15.53 %) of patients receiving nilotinib while none was seen in the imatinib arm (P – value = 0.042). (Table no.2)

In the low Sokal score, the optimal response of imatinib arm was 70 % while that of nilotinib arm was 100 % (P - value = 0.1). In the intermediate Sokal score, the patients in imatinib arm had achieved 63 % optimal response while the patients in nilotinib arm had achieved 91 % (P - value = 0.1).

Whereas when the high Sokal score was analyzed, patients in nilotinib achieved 100 % optimal response while patients in the imatinib arm achieved 60 % optimal response (P - value = 0.005). So, the optimal molecular response after 3 months was more in nilotinib arm in all the three Sokal risk score and statistically significant in the high Sokal score. (Table no 3)

Molecular Response at 6 Months

The optimal response after 6 months (QPCR < 1 %) was found to be more in the initial nilotinib arm than the initial imatinib arm (76.9 % vs 65.3 %; P - value = 0.35). The warning response after 6 months (QPCR > 1 % and < 10 %) was lower in the patients with nilotinib than nilotinib (7 % vs 26.9 %; P - value = 0.06). The treatment failure after 6 months (QPCR > 10 %) was found in 4 patients who were on initial nilotinib while 2 patients were on initial imatinib (15 % vs 7.6 %; P - value = 0.35). The major molecular response (QPCR < 0.1 %) occurred in 15 patients of the study population at the time of analysis after 6 months. Out of 15 patients who achieved MMR, 9 (34.6 %) patients were on nilotinib and 6 (23 %) patients on imatinib. The difference was not statistically significant (P - value = 0.35). (Table no 4)

Kinetics of RQ-PCR for BCR ABL1 at the End of 3 Months and 6 Months

At the end of 3 months, median RQ-PCR for BCR ABL1 (IS) is shown in table no. It was 1.112 % (range 0.02% to 25.14 %) in nilotinib arm whereas 2.23 % (range 0.3 % to 98.18 %) in imatinib arm. At the end of 6 months, the median RQ-PCR for BCR ABL1 (IS) is shown in table no 6. It was 0.1 % (range 0.008 % to 18.77 %) in the nilotinib arm and 0.3 % (range 0.01 % to 13 %) in the imatinib arm. (Table no 5)

Adverse Effects and Safety Issues

Gastritis was more common in the imatinib arm in comparison to nilotinib arm (26.92 % vs 3.89 %; P - value = 0.5). Nausea was only in the imatinib arm (23.08 %; P - value = 0.023) Peripheral oedema and periorbital oedema was only seen in 2 (7.69 %) patients in the imatinib arm. There were two patients with myalgia one in each arm. There were no complaints of loose motion, vomiting, alopecia and cardiac problems. The haematological complication during the treatment occurred in the form of anaemia only. The incidence of anaemia was more in the imatinib arm compared to the nilotinib arm (30.7 % vs 15.3 %; P - value = 0.32). (Table no 6)

DISCUSSION

In the study the baseline characteristics were similar in both the groups. Jain et al. (2016) reviewed a total of 487 consecutive newly diagnosed CML-CP treated with four TKIs and majority of patients (70 %) had a low Sokal score.[8] Mishra et al. (2013) had also reported that 40 % of CML-CP in AIIMS had high-risk Sokal score.[9] In the present study overall low Sokal score was seen in 30.7 %, intermediate score in 44 % and high Sokal score was seen in 25 %. The majority of patients belong to intermediate risk group which is much higher in comparison to the western data. Mishra et al. (2013) had reported from AIIMS that all the patients achieved complete haematological response (CHR) within a period of 1 - 3months after starting imatinib.[9] In the present study, patients in both arms achieved complete

haematological response by 30 days (88 %). But the response was faster in the nilotinib group though not statistically significant (92.31 % vs 84.6 %, P - value = 0.37). This could have been due to smaller sample size.

Response at 3 Months

At the end of three months, the optimal response was seen in 25 (96.15 %) patients in the nilotinib group and 17 (65.3%) patients in the imatinib arm (P - value = 0.0048). The nilotinib arm had a higher rate of achieving optimal response and the difference was statically significant. When the optimal response was sub-analyzed based on the Sokal score, the patients with high Sokal score had a higher rate of optimal response in the nilotinib arm than imatinib arm (100 % vs 60 %, P - value = 0.005). The response was better in the low and intermediate risk group but the difference was not significant probably because of low sample size. So, more potent drug like nilotinib might be given in higher Sokal score to achieve optimal response. Jain et al. (2016) reviewed 487 consecutive patients with newly diagnosed CML-CP treated with four TKIs in Europe. They have reported a general trend for higher rates of optimal response at all times with imatinib 800, dasatinib and nilotinib compared to imatinib 400. Rates of optimal response at 3 months according to TKI modality were 75 % for imatinib 400, 90 % for imatinib 800, 89 % for dasatinib and 97 % for nilotinib.[8] In our study also the nilotinib achieved a similar response to that of European data at 3 months and slightly lower response in the imatinib arm. The lower response in imatinib arm in comparison to western data could be due to the use of generic imatinib. And moreover, the patients Jain et al. study had 70 % low Sokal score.

We found that 34.6 % patients in the imatinib arm were having warning response at the end of three months while 3.8 % patient were seen in the nilotinib group (P - value = 0.0036). Jain et al. (2016) in their study of four frontline TKIs in 487 patients they found higher proportions of patients who received imatinib 400 who met the criteria of warning at 3 months compared to nilotinib (15 % vs 1 %).[8] So the warning response in our study was similar to the above study.

Four (15.38 %) patients had achieved a major molecular response in nilotinib arm after 3 months of treatment. Cortes et al. (2010) reported MMR of 40 % and 71 % at 3 and 6 months respectively on newly diagnosed CML-CP treated with frontline nilotinib 400mg.[10] Saglio et al. (2010) had reported that nilotinib had significantly higher MMR compared to the imatinib 400 mg at 12 months. During analysis at 3 months, the MMR was better in the nilotinib 300 mg or 400 mg compared to imatinib 400 mg (9 % vs 5 % vs 1 %) though not statistically significant.[11] Our data of MMR in 15.3 % patient at 3 months was higher than that of Saglio et al. and lower than that of Cortes et al.

Response at 6 Months

We found that optimal response after 6 months was still higher in the initial nilotinib arm than the imatinib arm (76.9% vs 65.3 %; p - value = 0.35). Jain et al. (2016) reported optimal response at 6 months for imatinib 400 mg, 800 mg, dasatinib and nilotinib as 41 %, 80 %, 86 % and 89 %.[8] In our study, the initial nilotinib arm even after switching to imatinib had achieved better optimal response in the patients who were treated with nilotinib initially. The optimal response after 6 months in imatinib arm in our study was better than that of the above report of 41 %. This could be due to small sample size of our study.

Jain et al. (2016) found higher proportions of patients in warning at 6 months who were on imatinib 400 mg compared to nilotinib (43 % vs 7 %). The rate of warning was higher in the imatinib arm than the initial nilotinib arm (26.9 % vs 7 %; P – value = 0.06). This finding suggests that optimal response achieved by the nilotinib in the initial nilotinib arm were able to provide the patients with lesser warning.

The MMR after 6 months was found to be still better in the initial nilotinib arm compared to the imatinib arm (34.6 vs 23 % P - value = 0.35). Saglio et al. had reported that at 6 months the MMR was more in the nilotinib 300 mg or 400 mg compared to imatinib 400 mg (33 % vs 30 % vs 12 %).[11] So, our data was comparable to the works of Saglio et al.

Jain et al. (2016) had reported that treatment failure at the end of 6 months was more in the imatinib arm than nilotinib arm (17 % vs 4 %).[8] Treatment failure at six month (QPCR > 10 %) was seen in 2 (7.6 %) patients on imatinib and 4 (15 %) patients on initial nilotinib arm (P - value = 0.38). The patients with treatment failure on initial nilotinib arm were given escalated dose of imatinib 600 mg. The treatment failure of Jain et al. study was calculated when the patients were still on nilotinib. While in our study the nilotinib had been already switched to imatinib. The treatment failure might have been reduced if the duration of nilotinib was longer than 3 months.

Complications

Both imatinib and nilotinib have got adverse effects reported by various authors.[12] In the present study, the common side effects were gastritis (26.9%), nausea (23.08%), pruritus (19.23), oedema (7.69%) and myalgia (3.8%) in imatinib arm. The nilotinib had mostly gastritis (3.8), myalgia (3.85) and pruritus (3.89%). So, the side effects were slightly lesser in our studies. We could see the similar adverse effects in our study also. We did not come across any cardiac complication in the nilotinib arm.

CONCLUSIONS

Overall, the nilotinib arm did well even after switching to imatinib. Optimal response 3 months and 6 months was better in the nilotinib arm. Warning at 3 months and 6 months was more in the imatinib arm. MMR at 3 months and 6 months were also better in the initial nilotinib arm except for a slight increase in treatment failure. It gives us an important platform for an economically backward country like India where the therapy with more potent drug like nilotinib is given in the initial three months or even six

months. By reducing the disease burden quickly, we could have achieved better long-term benefits. The primary aim of our study was to see the initial response. Further study is going on to see the long-term effect of the initial nilotinib in terms of overall survival, progression-free survival or even treatment free survival.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.
Authors acknowledge K.H. Jitenkumar Singh, Ph.D. Scientist-D, National Institute of Medical Statistics (NIMS), (ICMR), Dept. of Health Research, Ministry of Health & Family Welfare, Govt. of India.

REFERENCES

[1] Faderl S, Talpaz M, Estrov Z, et al. The biology of chronic myeloid leukemia. N Engl J Med 1999;341(3):164-172.
[2] Baccarani M, Castagnetti F, Gugliotta G, et al. A review of the European Leukemia Net recommendations for the management of CML. Ann Hematol 2015;(94 Suppl 2):S141-147.
[3] Goldman JM, Melo JV. Chronic myeloid leukemia — advances in biology and new approaches to treatment. N Engl J Med 2003;349(15):1451-1464.
[4] O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348(11):994-1004.
[5] Manley PW, Cowan-Jacob SW, Mestan J. Advances in the structural biology, design and clinical development of Bcr-Abl kinase inhibitors for the treatment of chronic myeloid leukaemia. Biochim Biophys Acta 2005;1754(1-2):3-13.
[6] Weisberg E, Manley PW, Breitenstein W, et al. Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl. Cancer Cell 2005;7(2):129-141.
[7] Kantarjian HM, Hochhaus A, Saglio G, et al. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-months minimum follow-up of the phase 3 randomised ENESTnd trial. Lancet Oncol 2011;12(9):841-851.
[8] Jain P, Kantarjian H, Sasaki K, et al. Analysis of 2013 European LeukaemiaNet (ELN) responses in chronic phase CML across four frontline TKI modalities and impact on clinical outcomes. Br J Haematol 2016;173(1):114-126.
[9] Mishra P, Seth T, Mahapatra M, et al. Report of chronic myeloid leukemia in chronic phase from All India Institute of Medical Sciences, 1990-2010. J Indian Soc Med Paediatr Oncol 2013;34(3):159-163.
[10] Cortes JE, Jones D, O'Brien S, et al. Nilotinib as front-line treatment for patients with chronic myeloid leukemia in early chronic phase. J Clin Oncol 2010;28(3):392-397.
[11] Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 2010;362(24):2251-2259.
[12] Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 2006;355(23):2408-2417.