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Leukemia – Lymphoma and Myeloma

A Retrospective Cohort Study of Upfront Nilotinib in Chronic Myeloid Leukemia: A Single-Center Experience

Reema Singh[1] Jyotsna Kapoor[1,] Rayaz Ahmed[1] Pallavi Mehta[1] Vishvdeep Khushoo[1] Pragya Agrawal[1] Dinesh Bhurani[1] Narendra Agrawal[1,]

[1]Department of Hemato-Oncology and Bone Marrow Transplantation Unit, Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India

Address for correspondence Narendra Agrawal, DM, Department of Hemato-Oncology, Rajiv Gandhi Cancer Institute and Research Centre, Sector 5, Rohini, Delhi 110085, India (e-mail: Narendra_ag1@rediffmail.com).

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Abstract

Narendra Agrawal

Context Nilotinib is a second-generation BCR-ABL1 tyrosine kinase inhibitor used in the treatment of chronic myeloid leukemia (CML).

Aims We aim to evaluate the responses and safety of upfront Nilotinib therapy in Indian CML patients.

Setting and Design We retrospectively reviewed the medical records of CML patients who received Nilotinib as an upfront treatment at our center between January 1, 2011 and October 15, 2019.The follow-up was taken till March 31, 2020.

Results Forty One patients (n = 36 chronic phase and five accelerated-phase CML) received frontline Nilotinib. Median age was 39 years (21–63) with male-to-female ratio of 1.1: 1. At 3 months, 96.9% patients achieved BCR-ABL of ≤10% at international scale. By the end of 12 months, 71.5% patients achieved major molecular response (BCR-ABL ≤0.1%) and 91.4% patients achieved complete cytogenetic response assessed by BCR-ABL polymerase chain reaction of ≤1%. Common toxicities observed were weight gain, thrombocytopenia, corrected QT prolongation, and elevated serum amylase in 14 (34.1%), 7(17.07%), 4(9.7%), and 4(9.7%) patients, respectively. Overall, five patients had loss of response with further progression and death in three patients. At a median of 43.7 months, 38 patients survived with estimated 3 year event-free survival and overall survival of 65 ± 9 and 93 ± 5%.

Conclusion This study showed remarkable good response with upfront Nilotinib in Indian patients with CML.

Keywords

- Upfront Nilotinib
- Early molecular response
- Major molecular response
- Chronic myeloid leukemia
- Toxicity

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Introduction

BCR-ABL tyrosine kinase inhibitors (TKIs) have become cornerstone in the management of patients with chronic myeloid leukemia (CML).[1] The primary goal of therapy in CML patients should be to prevent progression of the disease as the median survival following progression is poor (≈10.5 months).[2] With wide availability of TKIs, most of CML patients are now able to avoid progression to the blast phase and to lead a near-normal life.[3]

Early molecular response (EMR) defined as BCR-ABL transcript of <10% at 3 months or <1% at 6 months of Imatinib therapy has emerged as a powerful tool to predict long-term survival outcome.[4,5]

Phase 3 ENESTnd trial of Nilotinib versus Imatinib in patients with newly diagnosed CML in chronic phase (CP) showed faster and higher rates of molecular response and significant reduction of risk of progression to accelerated phase (AP)/blast crisis with Nilotinib with EMR a strong predictor of reduced risk of progression.[2,6]

We aim to evaluate the responses and safety of upfront Nilotinib therapy in Indian CML patients.

Subjects and Methods

Study Design and Patient Selection

We retrospectively studied patients with newly diagnosed CML in CP or AP diagnosed based on standard diagnostic criteria, started on upfront Nilotinib therapy from January 1, 2011 to October 15, 2019 and followed them for outcome till March 31, 2020. The patients were identified through the common patient record system at our institute. Patients were stratified by Sokal and ELTS (EUTOS long-term survival) scores at baseline. Patients who received Nilotinib for less than 3 months were excluded from the study. The study was reviewed and approved by the institutional review board of the institute.

Objectives

The primary objective of this study was to evaluate the EMR at 3 months defined as BCR-ABL at international scale (IS) <10% and to correlate it with outcome like major molecular response (MMR) and survival.

Other objective was to assess toxicities of therapy according to the Common Terminology Criteria for Adverse Events version 5.0.[7]

Survival Outcomes

Overall survival (OS) was defined as the time from start of Nilotinib till death from any reason or last follow-up, and event-free survival (EFS) was defined as the time from start of Nilotinib till the date of event (death, loss of response, progression, no response or withdrawal from study because of toxicity, or financial constraints).

Statistical Analysis

Descriptive statistics (mean, median, range) was used to describe the central tendency and dispersion of baseline characteristics. Time to event analysis included OS, EFS was done using the Kaplan–Meier method and single factor association between time to event endpoints and baseline or outcome variables was done by using the log-rank method. Independent *t*-test was used to assess the association of continuous variables with molecular response. Chi-square test was used to determine the association of categorical variable with molecular response. All the statistical analysis was performed using Statistical Package for Social Science software (SPSS 21, IBM SPSS Statistics for Windows, version 21.0; IBM Corp., Armonk, New York, United States).

Table 1 Demographic characteristics of the patients and baseline disease characteristics

Characteristics	*N* (%)	Median (range)
Median age (range), y	–	39 y (21–63 y)
Sex		–
Male	22 (53.7)	
Female	19 (46.3)	
Disease phase		–
Chronic phase	36 (87.8)	
Accelerated phase	05 (12.2)	
Duration of symptoms (in days)	–	52.5 (2–365)
Spleen (bcm), median (range)	–	8 (1–25)
Hb gm/dL, median (range)	–	10.3 (5.9–14.6)
White blood cells (× 10^9/L), median (range)	–	176.29 (16.8–407.5)
Platelet count (× 10^9/L), median (range)	–	307 (73–758)
Peripheral blood blasts (%), median (range)	–	2 (1–14)
Bone marrow blasts, (%) median (range)	–	2 (0–15)
Basophils (%), median (range)	–	3 (0–28)
Comorbidities	4 (9.75)	–
Risk stratification	Evaluable: 39	
Sokal risk, no. (%)		
Low	15 (38.5)	–
Intermediate	15 (38.5)	–
High	09 (23)	–
ELTS risk, no. (%)		
Low	19 (48.8)	–
Intermediate	9 (23)	–
High	11 (28.2)	–
Compliance		
Good	33 (80.5)	–
Fair	1 (2.5)	–
Poor	7 (17)	–

Abbreviations: ELTS, EUTOS long-term survival; Hb, hemoglobin.

Results

Forty-one patients (CP: n = 36, AP: n = 5) with median age of 39 years (21–63 years) were included in this study as per the inclusion criteria. Twenty-two were males and 19 were females with male-to-female ratio of 1:1.15. Comorbid conditions were present in four patients at the time of presentation. Median duration of therapy, i.e., frontline Nilotinib, is 49.2 months (5.8– 103.6 months). Seven (17%) patients had poor compliance to therapy as per medical records (►Table 1).

Thirty-nine patients were eligible for the risk stratification as per the Sokal and ELTS scoring. Fifteen (38.5%), 15 (38.5%), and 9 (23%) patients were classified low-, intermediate-, and high-risk Sokal scores, respectively, while19 (48.8%), 9 (23%), and 11 (28.2%) patients were low, intermediate, and high risk as per the ELTS score (►Table 1).

Early Responses

Thirty-two patients were evaluable for molecular responses at 3 months, of which 96.9% of patients achieved EMR by BCR-ABL of <10% at the IS scale. By the end of 12 months, 71.5% of patients achieved MMR and 91.4% of patients achieved complete cytogenetic response (CCyR) assessed by BCR-ABL polymerase chain reaction (►Fig. 1). Median time to MMR was 12 months (interquartile range [IQR]: 5.9–15 months). A total of 45.7% of patients achieved MMR by the end of 6 months. At median follow-up of 43.7 months, 28 (68.3%) patients achieved MMR with majority (27 patients) achieving MMR by the end of 12 months.

Safety Profile

Most common adverse effect observed was weight gain in 14 (34.1%) patients. Other adverse effects were thrombocytopenia in 7 (17.07%), corrected QT (QTc) prolongation >475 m/s 4 (9.7%), elevated serum amylase in 4 (9.7%), and elevated alanine aminotransferase (ALT), hypopigmentation, body ache and fever each in 3 (7.3%) patients. Some uncommon adverse events were hyperglycemia in 2 (4.8%), papulopustular rash, weight loss, hypertension, deranged lipid profile and hyperpigmentation each in 1 (2.4%) patient. Elevated creatinine and IHD (ischemia heart disease) each was also observed in one patient. Grade 3 and 4 events were observed in 4 patients (9.7%) with thrombocytopenia in 2 and weight gain and elevated ALT in 1 patient each (►Table 2). Six patients had temporary cessation/dose reduction due to toxicities. One patient was discontinued to other TKI due to cardiac toxicity.

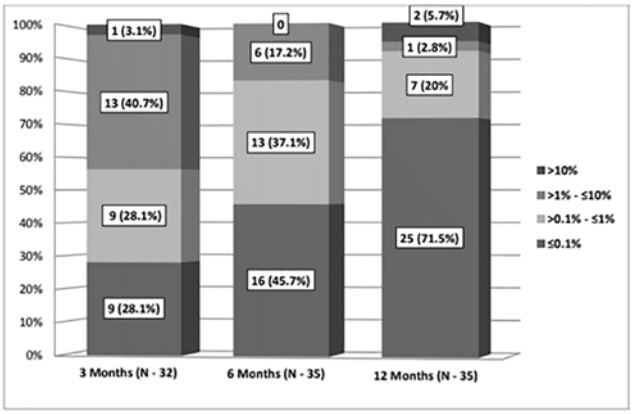

Fig. 1 BCR-ABL levels at 3, 6, and 12 months from start of treatment in evaluable patients.

Survival

Overall, five patients had loss of response with further progression and death in three patients. Rests of two patients are surviving, one each on Nilotinib and alternative TKI. Overall, eight patients were switched from Nilotinib to other TKI because of financial constraints (n = 4), toxicities (n = 1), and loss of response (n = 3).

At a median follow-up of 43.7 (IQR: 26–65) months, 38 patients survived with estimated 3-year EFS and OS of 65 ± 9 and 93 ± 5%.

OS was found to be adversely affected by AP (p = 0.001), higher spleen size (p = 0.016), low baseline hemoglobin, high

Table 2 Safety profile of Nilotinib observed during the study

Adverse events	Any grade, n (%)	Grade 3/4, n (%)
Biochemical abnormalities		
Elevated creatinine	1 (2.4)	–
Increased cholesterol	1 (2.4)	–
Increased TGA	1 (2.4)	–
TLC increased	1 (2.4)	–
Increased bilirubin	1 (2.4)	–
Hypokalemia	1 (2.4)	–
Elevated serum amylase	4 (9.7)	–
Elevated SGPT	3 (7.3)	1 (2.4)
Hyperglycemia	2 (4.8)	
Hematologic abnormalities		
Thrombocytopenia	7 (17.07)	2 (4.8)
Nonhematologic AEs reported		
Hypopigmentation	3 (7.3)	
Hyperpigmentation	1 (2.4)	
Edema limbs	1 (2.4)	
Papulopustular rash	1 (2.4)	
Bone pain	1 (2.4)	
Paresthesia	1 (2.4)	
Other AEs of interest		
Weight gain	14 (34.1)	1 (2.4)
QTc prolongation	4 (9.7)	
Fever	3 (7.3)	
Hypertension	1 (2.4)	
Weight loss	1 (2.4)	
Ischemic heart disease	1 (2.4)	

Abbreviations: AE, adverse event; QTc, corrected QT; TGA, triglyceride; TLC, total leukocyte count.

total leukocyte count, and lower platelet counts (p = 0.05, p = 0.05, and p = 0.004, respectively).

EFS was found to be adversely affected by male gender (p = 0.030), AP (p = 0.061), greater spleen size (p = 0.003), high ELTS ($p \leq 0.0001$), no MMR at 12 months (p = 0.038), and drug interruption >5 days overall ($p \leq 0.0001$). There was a trend of correlation of BCR-ABL of >1% at 3 months with poor EFS (p = 0.054).

Discussion

Nilotinib has shown good EMR at 3 months and its association with improved MMR rates and EFS when used in newly diagnosed patients as well as after Imatinib failure.[8-10]

Estimated rates of 3-year OS was found to be 93 ± 5%, which is similar to observation of Hughes et al who reported 3-year OS of 94.3%.[11]

Lee et al reported that the larger spleen size at baseline was an independent factor for failure to achieve MMR.[12] Similarly, the present study revealed that a larger spleen size at diagnosis is significantly associated with the EMR (p = 0.001) while a higher platelet count with failure to achieve MMR (p = 0.026).

ENEST1st data showed CCyR by 12 months in 82.5% of patients, whereas in our study CCyR was achieved in 91.4% of patients by 12 months.[9]

Molica et al reported that high ELTS is a risk factor for CML-related deaths ($p \leq 0.001$) either with Imatinib, Nilotinib, or Dasatinib.[13]

Yang et al reported 5-year OS probabilities of 98% (95% confidence interval [CI]: 96–100%), 89% (95% CI: 83–95%) and 79% (95% CI: 78–91%) in the low-, intermediate-, and high-risk ELTS groups (p = 0.001 and 0.009 for high versus low and high versus intermediate risk groups).[14]

Cortes et al reported two (3.2%) instances of QTc prolongation, whereas in our study group it is observed in four (9.7%) patients.[15] Saglio et al reported toxicity-related discontinuation rates of 5%.[4] Wei et al reported discontinuation of 2% of patients due to biochemical abnormalities.[16] Weight gain was seen in 34.1% (grade 3–4 in 2.4%) which is much higher for unknown reason than 4.6% reported by Zaidi et al.[17] Elevated SGPT (serum glutamic pyruvic transaminase) was seen in only 7.3% of our patients, which is much less than the reported data of 66% from the ENESTnd study.[4] Dose reductions and temporary cessation occurred in 59% of patients as reported by Saglio et al. While in our study group it occurred in 14.63% of patients.[4] This difference though unexplainable is possibly related to different ethnicity of patients and environmental factors.

Yu et al reported 25.1% of patients discontinued TKI due to financial toxicity whereas in our study 9.75% of patients discontinued Nilotinib. Discontinuation of TKI due to financial toxicity was found to be associated with lower TKI-therapy response rates.[18]

The low rates of progression and high rates of response in this study demonstrate the efficacy of frontline Nilotinib for the majority of patients.[18]

Study Limitations

It is a retrospective study in a small cohort with short follow-up.

Conclusion

With the use of frontline Nilotinib, 96.9% patients achieved EMR at 3 months. By the end of 12 months, 91.4% of patients achieved CCyR and 71.5% achieved MMR with good OS rates. This shows encouraging results of frontline Nilotinib in Indian CML patients. Long-term follow-up with a larger cohort is required for better identification of prognostic factor and role of EMR in predicting outcome in Indian patients with CML.

Author Contribution

Author's name	Credit author statement
Dr. Reema Singh	Conceptualization; data curation; formal analysis; methodology; roles/writing—original draft; writing—review and editing.
Dr. Narendra Agrawal	Conceptualization; data curation; formal analysis; methodology; roles/writing—original draft; writing—review and editing.
Ms. Jyotsna Kapoor	Statistical analysis, writing—review and editing, review and validation
Dr. Pallavi Mehta	Review and validation
Dr. Vishvdeep Khushoo	Review and validation
Dr. Pragya Agrawal	Review and validation
Dr. Rayaz Ahmed	Review and validation
Dr. Dinesh Bhurani	Review and validation

Conflict of interest

The authors declare that they have no conflict of interest.

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References

1 Bansal S. Is imatinib still the best choice as first-line oral TKI. South Asian J Cancer 2014;3(1):83–86
2 Larson RA, Hochhaus A, Hughes TP, 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):2197–2203
3 Jayakar V. Using 2(nd) generation tyrosine kinase inhibitors in frontline management of chronic phase chronic myeloid leukemia. South Asian J Cancer 2014;3(1):87–91
4 Hughes TP, Hochhaus A, Branford S, et al. IRIS investigators. Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS. Blood 2010;116(19):3758–3765

5 Hanfstein B, Müller MC, Hehlmann R, et al. SAKK; German CML Study Group. Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML. Leukemia 2012;26(9):2096–2102
6 Saglio G, Kim DW, Issaragrisil S, et al. ENESTnd Investigators. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 2010;362(24):2251–2259
7 National Cancer Institute. Common Terminology Criteria for Adverse Events v 5.0. November 27, 2017
8 Jain P, Kantarjian H, Nazha A, et al. Early responses predict better outcomes in patients with newly diagnosed chronic myeloid leukemia: results with four tyrosine kinase inhibitor modalities. Blood 2013;121(24):4867–4874
9 Hochhaus A, Rosti G, Cross NC, et al. Frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the European ENEST1st study. Leukemia 2016;30(1):57–64
10 Branford S, Kim DW, Soverini S, et al. Initial molecular response at 3 months may predict both response and event-free survival at 24 months in imatinib-resistant or -intolerant patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase treated with nilotinib. J Clin Oncol 2012;30(35):4323–4329
11 Hughes TP, Saglio G, Kantarjian HM, et al. Early molecular response predicts outcomes in patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib or imatinib. Blood 2014;123(9):1353–1360
12 Lee S-E, Choi S-Y, Kim S-H, et al. Baseline BCR-ABL1 transcript type of e13a2 and large spleen size are predictors of poor long-term outcomes in chronic phase chronic myeloid leukemia patients who failed to achieve an early molecular response after 3 months of imatinib therapy. Leuk Lymphoma 2018;59(1):105–113
13 Molica M, Canichella M, Alunni Fegatelli D, et al. The Eutos long-term survival score accurately predicts the risk of death in chronic myeloid leukaemia patients treated outside of clinical trials. Am J Hematol 2017;92(12):E661–E664
14 Yang X, Bai Y, Shi M, et al. Validation of the EUTOS long-term survival score in Chinese chronic myeloid leukemia patients treated with imatinib: a multicenter real-world study. Cancer Manag Res 2020;12:1293–1301
15 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
16 Wei G, Rafiyath S, Liu D. First-line treatment for chronic myeloid leukemia: dasatinib, nilotinib, or imatinib. J Hematol Oncol 2010;3:47
17 Zaidi U, Kaleem B, Borhany M, et al. Early and sustained deep molecular response achieved with nilotinib in high Sokal risk chronic myeloid leukemia patients. Cancer Manag Res 2019;11:1493–1502
18 Yu L, Qin YZ, Jiang Q. Analysis on tyrosine kinase inhibitor discontinuation in patients with chronic myeloid leukemia in the real world: experience from single center [in Chinese]. Zhonghua Xue Ye Xue Za Zhi 2017;38(9):754–760