Article published online: 2024-09-18

Upfront Combined Hydroxyurea and Imatinib versus Imatinib Monotherapy in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia: A Randomized Controlled Trial

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South Asian J Cancer

Abstract

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Background Tyrosine kinase inhibitors like imatinib have become the cornerstone of therapy in chronic phase-chronic myeloid leukemia (CML-CP). However, the role of hydroxyurea (HU), a deoxyribonucleic acid synthesis inhibitor, has been less explored in the disease. Hence, the present study was conducted to compare the efficacy of structured dose of HU based on baseline total leukocyte count (TLC) with imatinib in CML patients.

Method An open-label randomized controlled trial was conducted in 90 newly diagnosed CML-CP patients, aged $\geq$ 18 years. Patients were randomized to receive either baseline leucocyte count-based structured dose of HU with imatinib or imatinib monotherapy for 3 months. Quantitative real-time polymerase chain reaction for *BCR-ABL1* to assess early molecular response (EMR) and safety evaluation according to the Common Terminology Criteria for Adverse Events version 5 was done.

Results Median age of patients was 36.5 years (36 [interquartile range [IQR]: 30–45] in I-HU, 38 [IQR: 31–47] in imatinib monotherapy) with male predominance. Fatigue

Keywords

- chronic phase chronic myeloid leukemia
- early molecular response

DOI https://doi.org/10.1055/s-0044-1789579 ISSN 2278-330X

How to cite this article: Chetia R, Palepu S, Dutta V, et al. Upfront Combined Hydroxyurea and Imatinib versus Imatinib Monotherapy in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia: A Randomized Controlled Trial. South Asian J Cancer 2024;00 (00):00–00.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

was the most common symptom at diagnosis. Splenomegaly was seen in 89% (median spleen size: 10 [IQR: 6–15] cm). At 3 months, complete hematological response was seen in 74 patients (36 in I-HU, 38 in imatinib monotherapy). Overall, 68 patients achieved EMR (34 in I-HU, 34 in imatinib monotherapy, $p = 0.53$). The most common hematological toxicity, anemia, was seen in 80 patients (41 in I-HU, 39 in imatinib monotherapy). In 37 patients, nonhematological toxicities seen were nausea and vomiting (20 in I-HU, 17 in imatinib monotherapy). No dose limiting toxicities were reported.

Conclusion Addition of upfront TLC-based dosing of HU to imatinib was not found to significantly improve the hematological response and EMR at 3 months. However, long-term studies with a larger sample size with structured dose of HU can be undertaken as it forms a preferred adjunctive therapy for initial, rapid cytoreduction in hyperviscosity or leukostasis-related symptoms in patients of CML.

- imatinib
- randomized controlled trial
- RCT
- structured dose hydroxyurea

Introduction

Chronic myeloid leukemia (CML) is a well-defined myeloproliferative disease where the clonal cells originate from pluripotent hematopoietic progenitor cell (stem cell) that exhibits growth advantage over normal hematopoietic progenitors.[1] The clinical hallmark of CML is uncontrolled production of mature and maturing granulocytes, predominantly neutrophils, basophils, and eosinophils. Tyrosine kinase inhibitors (TKIs) like imatinib have become the standard therapy for CML-chronic phase (CP).[2,3] Though adverse reactions are reported with it, no significant interactions have been found from available literature.[4] Imatinib has a high interindividual variability in the pharmacokinetic parameters. This interindividual variability is due to factors such as genetic polymorphisms in transporters and metabolizing enzymes, body age, gender, white blood cell count, and hemoglobin (Hb) value.[5,6] Several biosimilars of imatinib have shown promising results.[7]

Hydroxyurea (HU), a nonalkylating antineoplastic drug is often used for initial cytoreduction in suspected CML patients.[4] The role of upfront structured total leukocyte count (TLC)-based dosing of HU with imatinib in diagnosed CML has not been explored till date.[8] Hence, this randomized controlled trial was designed to compare the efficacy and safety of HU and imatinib combination versus imatinib monotherapy (IM) for upfront treatment of newly diagnosed CML-CP patients in terms of achievement of early molecular response (EMR).

Materials and Methods

An open-label randomized controlled trial was conducted at a tertiary care center in northern India. Study duration was 18 months (January 2019 to June 2020). Newly diagnosed patients of CML-CP, age $\geq$ 18 years, were included. Exclusion criteria included de novo accelerated phase or blast phase CML, who had already started either HU or any TKI treatment prior to randomization, pregnancy, and active secondary malignancy. Written informed consent was taken from all patients before enrolment.

Detailed history and physical examination were performed. The baseline investigations and determination of disease staging were done. Sokal,[9] Hasford,[10] and European Treatment and Outcome Study (EUTOS)[11] risk scores were calculated for prognostication. Eligible patients were randomized equally in 1:1 ratio to either of the two treatment groups:

Group A: Imatinib + HU (I-HU)
Group B: Imatinib Monotherapy (IM)

Dose of imatinib was 400 mg orally once daily in both groups.

Initial dose of HU in the I-HU group was based on TLC at baseline: $< 100 \times 10^9$/L: 1000 mg, 100–199 $\times 10^9$/L: 2000 mg, 200–399 $\times 10^9$/L: 3000 mg, $\geq 400 \times 10^9$/L: 4000 mg per day. HU daily dose was rounded off to nearest 500 mg multiples and was administered as divided doses. The maximum daily dose of HU did not exceed 35 mg/kg body weight. HU dose was subsequently adjusted on each follow-up visit according to TLC, absolute neutrophil count, and platelet count. HU was discontinued when TLC was less than 10×10^9/L, or if patient developed grade ≥ 3 hematological or nonhematological toxicity as per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.[12]

Patients were followed up every 2 weeks in the outpatient department for clinical evaluation and monitoring complete blood count (CBC). After completion of 3 months, 5 mL of ethylenediaminetetraacetic acid-anticoagulated blood sample was collected from each patient, and samples were sent for CBC and examination of peripheral blood smear for hematological response. Quantitative real-time polymerase chain reaction (PCR) for *BCR-ABL1* (international scale; I.S.) was performed for assessment of EMR at 3 months of therapy in both groups. EMR was considered as *BCR ABL1* (I.S.) levels $\leq$ 10%.

Sample size was determined to be 90 (45 patients in each group). Statistical analysis was performed using STATA version-12 (StataCorp, United States). Descriptive statistics was

used to summarize baseline characteristics of patients. Normality was assessed using the Shapiro–Wilk test. Median and interquartile ranges (IQRs) were calculated. Wilcoxon rank sum test was used to compare quantitative variables and chi-square test and Fisher's exact test were used to compare categorical variables in the two treatment groups. A p-value of < 0.05 was considered as statistically significant.

Ethical issues: Ethical clearance was obtained from the Institutional Ethics Committee prior to the commencement of the study. Written informed consent was obtained from patients and their confidentiality was maintained. The trial was prospectively registered in Clinical Trial Registry India (CTRI) database (CTRI/2019/08/020879).

Results

Newly diagnosed CML-CP patients ($n = 123$) were consecutively assessed for eligibility. Among them, 33 patients were excluded (13 were in pediatric age group, 9 had already started TKI treatment prior to first visit, 7 had accelerated phase/blast phase disease, 2 were pregnant, and 2 did not follow-up after the first visit). Hence, 90 patients were randomized into two treatment groups: I-HU and IM, with each group consisting of 45 patients (►Fig. 1).

Median patient age was 36.5 (IQR: 30–46) years (I-HU: 36 [IQR: 30–45] years and IM: 38 [IQR: 31–47] years, $p = 0.58$). Fifty-nine percent ($n = 53$) of the study population were

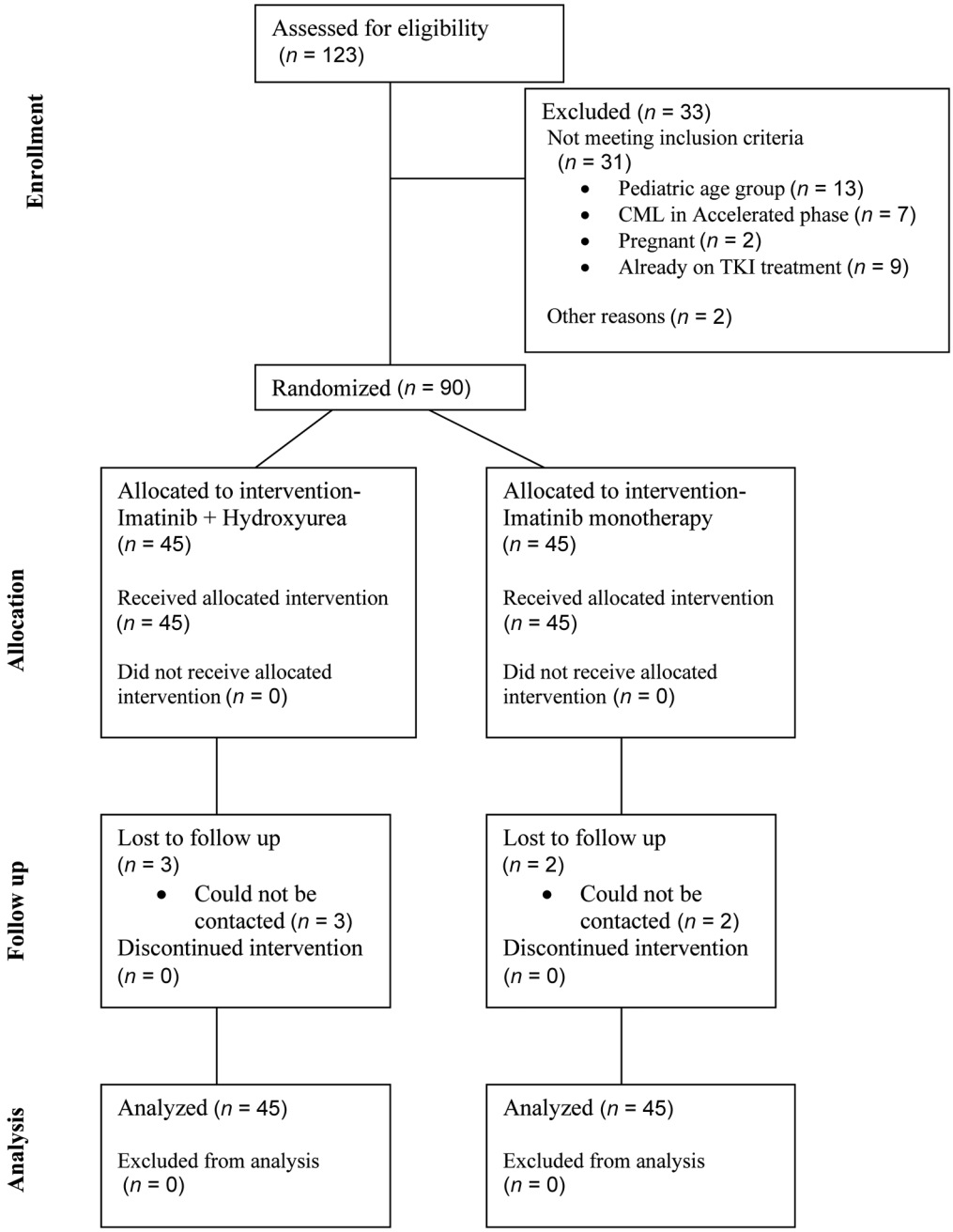

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) diagram of the trial.

males. There was no statistically significant difference in the gender composition of the two groups ($p = 0.83$).

The patients presented with symptoms ranging from 1 to 3 months in duration, the median duration being 1.5 months. About 37% patients ($n = 33$) presented with at least two symptoms. The most common symptom (60%) among the study population was fatigue followed by fever, abdominal heaviness, and weight loss ($p = 0.34$). Most common presenting sign was splenomegaly (89%) followed by pallor (34%) and hepatomegaly (27%). The median spleen size at presentation was 10 cm (6–15 cm) below left costal margin (I-HU: 11 cm [8–16 cm], IM: 10 cm [6–15 cm], $p = 0.15$).

Median TLC was 192.5×10^9/L (IQR 116–278 $\times 10^9$/L) (I-HU: 224 [136–355] vs. IM: 173 [164.1–225], $p = 0.01$). Thirty percent patients had TLC in the range of 100 to 199 $\times 10^9$/L. Median Hb level was 9.7 g/dL (IQR 8.4–11.2 g/dL), and median platelet count was 338 $\times 10^9$/L (IQR 199–460 $\times 10^9$/L). The median reticulocyte count was 2.8% (1.99–3.5%). Median peripheral blood blast%, basophil%, and eosinophil% were 3 (2–5), 5 (3–7), and 3 (2–5), respectively. Median bone marrow blast% was 2 (2–4) (2 [2–3] % in I-HU, 3 [2–5] % in IM, $p = 0.14$). The World Health Organization grade 2 myelofibrosis on baseline bone marrow biopsy was seen in 48% patients (23 [51%] in I-HU, 20 [44%] in IM). Risk score assessment is reported in ►Table 1.

Baseline cytogenetics of 57 (63%) patients showed the presence of characteristic *t*(9; 22) (q34; q11) translocation, 5 (6%) had variant Philadelphia chromosome, and 1 (1%) had additional cytogenetic abnormalities. Cytogenetic reports were not available in 27 (30%) who were either not willing for bone marrow study, had a dry tap, or had undetectable metaphases. Treatment for these patients was started after confirmation of CML diagnosis by BCR-ABL PCR.

At the end of 3 months, complete hematological response (CHR) and EMR were assessed. CHR was seen in 74 (82.2) patients and EMR (*BCR-ABL1* ≤ 10%, I.S.) was seen in 68 (76%). Data was not available in 5 patients who were lost to follow-up (3 patients in the I-HU group and 2 patients in the imatinib group). There was no significant statistical difference between the two treatment groups (►Table 2).

The most common hematological adverse drug reaction was anemia in both groups. The most common nonhematological toxicity was nausea and vomiting. Treatment discontinuation due to adverse drug reactions was not observed in either of the groups. There was no statistically significant difference in adverse events in the two groups (►Table 3).

Discussion

In this study, 90 patients were recruited. Age of CML presentation was similar to a study by Bansal et al[13] and Mishra et al.[14] This younger age of Indian CML patients has been the most consistent fact confirming that patients present at least a decade younger when compared to the Europeans (median age: 55 years)[15] and Americans (median age: 66 years).[16] It might be due to nutritional deficiencies, exposure to herbicides/pesticides, heavy metals mining, and carcinogens because of geographical variations and occupational reasons. These may have implications related to fertility and childbearing in female patients and keeping "treatment-free remission" as one of the goals of treatment in the newly diagnosed patients.[17] Asians' studies have reported younger onset as compared to west but these have smaller sample sizes and focused mainly on the treatment issues rather than risk factors associated with the disease.[18,19] Male-to-female ratio was 1.43:1, similar to a study by Mishra et al (1.6:1)[14] and Goni et al (1.2:1).[20]

Most common presenting symptom was fatigue (62%), followed by fever (48%) and abdominal heaviness (48%). Only 6% of them were asymptomatic and incidentally diagnosed to have CML during workup for asymptomatic leukocytosis similar to Mishra et al.[14] Splenomegaly was detected in 89% patients which was similar to findings by Mishra et al.[14] On the contrary, in the western population, Hoffman et al[15] reported that more than half of the patients did not have palpable splenomegaly. Pallor was seen in 34%, similar to a meta-analysis by Singh et al.[21] In comparison to western data[22] where approximately 40% were asymptomatic and diagnosed on the basis of abnormal blood counts, majority of Indian patients were symptomatic and mostly presented with dull aching abdominal pain secondary to splenomegaly.

Table 1 CML risk scores of patients in study

CML risk scores	Imatinib + HU ($n = 45$)	Imatinib ($n = 45$)	*p*-Value
Sokal score			
Low-risk (< 0.8) Intermediate-risk (0.8–1.2) High-risk (> 1.2)	13 (29%) 18 (40%) 14 (31%)	15 (33%) 20 (45%) 10 (22%)	0.39
Hasford (EURO) score			
Low-risk (< 780) Intermediate-risk (780–1480) High-risk (> 1480)	21 (46%) 16 (36%) 8 (18%)	26 (57%) 16 (36%) 3 (7%)	0.09
EUTOS score			
Low (< 87) High (> 87)	27 (60%) 18 (40%)	30 (67%) 15 (33%)	0.51

Abbreviations: CML, chronic myeloid leukemia; EUTOS, European Treatment and Outcome Study; HU, hydroxyurea.

Table 2 Complete hematological response (CHR) and early molecular response (EMR) in the study population

Variable		Imatinib + HU ($n = 45$)	Imatinib ($n = 45$)	*p*-Value
Hematological response at 3 months	CHR	36 (80%)	38 (84%)	0.71
	No CHR	6 (13%)	5 (11%)	
BCR-ABL (I.S.) at 3 months	$\leq$ 10%	34 (76%)	34 (76%)	0.53
	> 10%	8 (18%)	9 (20%)	0.28
	Median (IQR)	5.2% (1.24–9.06)	6.5% (1.66–9.54)	0.96

Abbreviations: HU, hydroxyurea; IQR, interquartile range; I.S., international scale.

Table 3 Adverse effects of treatment in study population

Adverse effects	Imatinib + HU *n* (%)	Grade $\geq$ 3 *n* (%)	Imatinib *n* (%)	Grade $\geq$ 3 *n* (%)	*p*-Value
Hematological toxicity					
Anemia	41 (91)	2 (4)	39 (87)	2 (4)	0.5
Leukopenia	24 (53)	1 (2)	22 (49)	1 (2)	0.67
Neutropenia	14 (31)	1 (2)	10 (22)	0	0.34
Thrombocytopenia	29 (64)	2 (4)	22 (49)	1 (2)	0.14
Febrile neutropenia	2 (4)	2 (4)	1 (2)	1 (2)	0.55
Nonhematological toxicity					
Edema	6 (13)	1 (2)	4 (9)	1 (2)	0.50
Hyperpigmentation	5 (11)	0	4 (9)	0	0.72
Hypopigmentation	7 (16)	0	6 (13)	0	0.76
Stomatitis/Mouth ulcer	3 (7)	1 (2)	2 (4)	0	0.64
Diarrhea	4 (9)	1 (2)	2 (4)	0	0.39
Nausea/Vomiting	20 (44)	1 (2)	17 (38)	1 (2)	0.52
Muscle cramps	15 (33)	2 (4)	13 (29)	0	0.64
Grade $\geq$ 3 treatment-related AE (*n*)					0.08

Abbreviations: AE, adverse effect; HU, hydroxyurea.

In our study, baseline TLC was higher as compared to Lange et al[8] (median: 59.5×10^9/L), suggestive of a higher need for cytoreduction. Hb level at CML-CP diagnosis was 9.7 g/dL, similar to the study by Bansal et al[13] (9–11 g/dL) and varied from a study by Lange et al[8] (12.7 g/dL). This difference was due to early presentation in western patients.

Disease risk scoring showed majority had Sokal intermediate-risk scores, Hasford low-risk scores, and EUTOS low-risk scores at baseline. This is similar to Bansal et al[13] and Malhotra et al[23] where majority had Sokal intermediate-risk score of 27 to 47% and 38.17%, respectively. However, a study by Mishra et al,[14] 40% patients had Sokal high-risk scores at baseline. In the study by Lange et al,[8] 56% had Hasford intermediate-risk score and 91% had EUTOS high-risk scores. This could be ascribed to the older age of presentation in the Western population. CHR rates in the two treatment groups were comparable (80% in the I-HU group vs. 84% in the imatinib group, $p = 0.71$). In the study by Lange et al,[8] 86% patients attained CHR at the end of 3 months (89.6% patients in the imatinib group and 82.6% patients in the I-HU group).

A recent East German Study Group (OSHO) study by Lange et al explored the efficacy of in vitro and in vivo study of potential additive effect of HU with imatinib. CHR at 3 months was seen in 82% in I-HU and 89% in the imatinib arm with nonsignificant difference. Our study used a TLC-based structured HU regimen from the initiation of therapy as compared to OSHO study where HU was gradually increased over time based on patient response. Moreover, our patients were young age group, hence genetic and regional variation in the response to therapy can also be considered.[24] EMR was achieved in 76% patients. Lange et al[8] reported that there was no statistically significant difference between the two groups in terms of major molecular response (MMR) rates at 18 months whereas the OSHO study reported that major cytogenetic and molecular response at 6 months was higher in the IM group. MMR at 12 months were 58.9 versus 41.9% in combination. These studies did not

mention 3 months EMR which is a preliminary predictor of EMR at 6 months and MMR.[24] Side effect profile of drugs was similar to Bansal et al.[13] Overall higher treatment-related adverse effects were seen among the patients in the I-HU group. Similar findings were reported by OSHO study where grade 1 to 4 adverse events did not differ in each group.[24]

Conclusion

Addition of HU to imatinib in the present study was not found to significantly improve the hematological response or EMR at 3 months in our cohort of newly diagnosed CML-CP patients. However, HU is still a useful adjunctive therapy for initial, rapid cytoreduction in patients who present with very high leukocyte counts in combination with first-line imatinib therapy. Further studies can be considered to evaluate long-term molecular response with structured dosing of HU.

Trial Registration

Clinical Trial Registry India, CTRI/ 2019/08/020879, Registered August 26, 2019, http://ctri.nic.in/Clinicaltrials/showallp.php?mid1=33760&EncHid=&userName=CTRI/2019/08/020879

Ethical Approval and Consent to Participate

All participants were informed about the purpose of the trial, consented, and the trial was conducted in accordance with the Declaration of Helsinki. Authors confirm that necessary IRB and/or ethics committee approvals have been obtained. The study was approved by the Institute Ethics Committee (AIIMS/IEC/18/571). Trail has been registered under Clinical Trail Registry India (CTRI/ 2019/08/020879).

Consent for Publication

A written informed consent was obtained from the patients for publication.

Availability of Data and Materials

The raw data and materials are available upon request.

Competing Interests

The authors have declared no competing interest.

Authors' Contributions

R.C., U.K.N., P.D., N.S., and M.N.: Protocol design, methodology, and statistical considerations; R.C., U.K.N., A.B., D.C., S.V., A.R., A.Bak., and A.M.: Acquisition of data and patient management; A.B., S.P., R.C., V.D., and U.K.N.: Analysis and interpretation of data; A.B., S.P., R.C., V.D., and U.K.N.: Took part in drafting the article or revising it critically for important intellectual content; All authors agreed to submit to the current journal; All authors gave final approval of the version to be published; All authors agree to be accountable for all aspects of the work.

Conflict of Interest

None declared.

Acknowledgment

The authors acknowledge the contribution of Minakshi Chauhan, nursing officer, for her contribution in the conduct of study.

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