CML in Elderly: Does Age Matter?

Kadabur Nagendrappa Lokesh¹ · Jitendra Kumar Pehalajani¹ · Dassappa Loknatha¹ ·
Linu Abraham Jacob¹ · M. C. Suresh Babu¹ · A. H. Rudresha¹ · Lakkavalli Krishnappa Rajeev¹ ·
S. C. Smitha¹ · Khandare Pravin Ashok¹ · D. S. Madhumathi²

Received: 6 April 2019 / Accepted: 30 May 2019 / Published online: 6 June 2019
© Indian Society of Hematology and Blood Transfusion 2019

Abstract The median age of diagnosis for chronic myeloid leukemia (CML) in India is 35 years on the contrary to western literature which is 47 years. The outcome of the elderly patient in CML TKI era is not reported from the Indian population. However, Western literature suggests that use of TKI alleviate the adverse impact of age in outcomes of CML. This study was carried out to analyze the clinical profile and outcome of elderly, in comparison with younger patients with CML. We retrospectively analyzed CML patients treated at our department from January 2008 to December 2017. The data cutoff date was December 2018. The cohorts of 712 patients were divided into two groups. Patients belonging to the age group of ≥ 60 years were classified as the study group and those who were 18–60 years were used as controls. Patient's clinical history, examination and milestones in terms of achieving hematological, molecular responses and toxicity profile were also recorded. The total of 712 patients, 52 patients in the study group and 660 patients in the control group were treated during the study period. The study group was having more co-morbidities than the control group (15.3% vs. 4.5%). Patients having high-risk EUTOS score were similar in both groups (38.4% vs. 37.6%). The patients presented in blast phase were higher in the study group as compared to control group (9.6% vs. 6.36%) but the differences were not statistically significant. Rates of achieving a hematological

response at 3 months (85.1% vs. 86.89%) and the major molecular response at 18 months (54.3% vs. 60.16%) were almost similar in both groups. However, hematological toxicity, muscle cramps and gastritis were reported more in elderly patients. The outcome of CML patients in TKI era do not differ in elderly patients. However, toxicity profile was not significantly inferior in elderly patients.

Keywords Chronic myeloid leukemia · Major molecular response · Tyrosine kinase inhibitors

Introduction

The median age of diagnosis for chronic myeloid leukemia (CML) in India is 35 years on the contrary to western literature which is 47 years [1]. Previous studies depicted age as a poor prognostic factor for survival. Thus, age was incorporated in many risk stratification models [2, 3]. However, it was not clear whether this age effect was due to poorer disease biology, or other age-related factors such as competitive causes of death, increased risk of treatment-related complications or contraindications to curative bone marrow transplant [4]. The introduction of tyrosine kinase inhibitors (TKI) has changed the treatment paradigm of CML. TKI is better tolerated than previous treatments and prolongs the survival of majority of patients indefinitely [5]. This paradigm allowed a fresh look at the interactions of advanced age and CML. This issue is relevant now considering the aging of the Indian population [6]. One expects that the median age of CML and the prevalence of the disease in older individuals will progressively increase in India. Aging is associated with a progressive reduction in functional reserve and increased co morbidity. Individualized

✉ Jitendra Kumar Pehalajani
jitnanhe@gmail.com

¹ Department of Medical Oncology, Kidwai Cancer Institute, Marigowda Road, Bangalore 560029, India

² Department of Pathology, Kidwai Cancer Institute, Marigowda Road, Bangalore 560029, India

treatment of cancer in the older aged person implies an estimate of life expectancy and risk of treatment-related complications [7]. Thus, we analyzed our CML cohort to assess the effect of age on various aspects including presentation, adverse effects and treatment outcomes in TKI era.

Materials and Methods

This study was conducted to analyze the clinical profile and outcome of elderly, in comparison with younger patients with CML treated from January 2008 to December 2017 at our department. Written informed consent was taken from all patients prior to the clinical examination, any procedure and before starting treatment. The data cutoff date was December 2018. Reverse transcription polymerase chain reaction (RT-PCR) for BCR–ABL was documented at baseline. Cytogenetic analysis was performed by karyotyping at baseline as per institution policy in accordance to guidelines. The cohorts of patients were divided into two groups. Patients belonging to the age group of ≥ 60 years were classified as the study group and those who were 18–60 years were classified as controls. The data regarding clinical profile, treatment milestones in terms of hematological, molecular responses and toxicity profiles were tabulated and analyzed with SPSS 21.

Results

The cohort of 712 CML patients was divided into 52 patients in study group and 660 in control group. The mean age of patients was 67 years in the study group and 34 years in the control group ($p = 0.31$). The percentages of male patients were similar in study group 59% and control group 61.9% ($p = 0.54$). Patients having co-morbidities were significantly higher in the study group than control group 15.3% and 4.5% ($p = 0.04$). The number of patient with hypertension in study group were 11.53% and 4.2% in control group, diabetes mellitus in study group 7.6% and 1.2% in control group and Coronary Heart Disease in study group 3.84% and none in control group. The following drugs were avoided or used with cautions due to possible interactions: proton pump inhibitors, amlodipine, aspirin and atorvastatin.

The mean spleen size (cm) was 8.8 in the study group and 9.1 in the control group ($p = 0.61$). The median hemoglobin level (g/dL) was 10.4 in study group and 10.6 in control group ($p = 0.28$). The median platelet count ($10^9/L$) was 5.40 in study group and 4.16 in control group ($p = 0.48$). The median basophil and eosinophil count was 4% and 2% in the study group and 6% and 3% in the

Fig. 1 Event free survival curves EFS curve

control group. Patients in advanced stages were 9.6% in study group and 6.36% in control group ($p = 0.33$). The patients with high risk EUTOS scores were similar in 38.4% study group and 37.6% control group ($p = 0.28$) (Table 1).

The median follow up for the study group was 66 months (13–130) and 71 months (12–132) for the control group. The doses of TKI used were as prescribed in standard guidelines. The patients treated with first generation TKI were 94.5% in study and 98.4% in control group ($p = 0.62$). Second generation TKI was prescribed as per patient profile. Patients with chronic phase (CP) achieving complete hematological response (CHR) at 3 months were 85.1% in the study group and 86.89% in the control group ($p = 0.18$). Patients achieving major molecular remission (MMR) at 18 months were observed in 54.3% in the study group and 60.16% in the control group ($p = 0.07$) (Table 2).

Patients progressed to an advanced stage during this period were 8.5% in the study group and 5.01% in the study group ($p = 0.62$). Patients changed to second-line therapy were 12.76% in the study group and 7.25% in the control group ($p = 0.46$). At the time of data interpretation, 76% patients in the study group and 81% patients in the control group were on first generation TKI ($p = 0.52$) (Fig. 1).

The toxicities reported as higher in study group in comparison with the control group were hematological toxicity 25.5% versus 16.8% ($p = 0.06$), muscle cramps 34.04% versus 29.12% ($p = 0.7$), fatigue 38.3% versus 34.62% ($p = 0.4$) and edema 25.5% versus 22.97% ($p = 0.5$). The toxicities reported as higher in control group in comparison with the study group were skin changes 25.5% versus 33.8% ($p = 0.6$) and gastrointestinal disturbances 21.27% versus 24.11% ($p = 0.9$). The frequency of drug interruption was 34.04% in the study group and 29.15% in the control group ($p = 0.65$) (Table 3).

Table 1 Baseline characteristics

	Study population (≥ 60 years) (n = 52)	Control population (18–60 years) (n = 660)	<i>p</i>
Age (years)	67 (60–80)	34 (18–59)	0.31
Male	31 (59%)	409 (61.9%)	0.54
Comorbidities %	15.3%	4.5%	0.043
Mean spleen size (cm) below costal margin	8.8 (0–17)	9.1 (0–20)	0.61
Median HB (gm/dL)	10.4 (7–14.8)	10.6 (8–16.8)	0.28
Median basophil %	4 (1–19)	6 (1–23)	0.19
Median eosinophil %	2 (0–5)	3 (0–10)	0.61
Median platelet $10^9/L$ median (range)	5.40 (0.78–7.48)	4.16 (0.85–12.32)	0.48
CP/AP + BP %	90.4/9.6	93.64/6.36	0.33
EUTOS high risk	20 (38.4%)	248 (37.6%)	0.28
First generation TKI	94.2%	98.4%	0.62

Table 2 Treatment outcomes

	Study population (≥ 60 years) (n = 47) (%)	Control population (18–60 years) (n = 618) (%)	<i>p</i>
CHR at 3 month %	85.1	86.89	0.18
MMR at 18 month %	54.3	60.16	0.07

Table 3 Toxicity profile

	Study population (≥ 60 years) (n = 47) (%)	Control population (18–60 years) (n = 618) (%)	<i>p</i>
Hematological toxicity	12 (25.5)	104 (16.8)	0.07
Fatigue	18 (38.3)	214 (34.62)	0.32
Muscle cramps	16 (34.04)	180 (29.12)	0.62
Periorbital puffiness and edema	12 (25.5)	142 (22.97)	0.61
Skin changes	12 (25.5)	209 (33.8)	0.56
Gastrointestinal disturbance	10 (21.27)	149 (24.11)	0.85

Discussion

Although a number of early studies demonstrated that advanced age is an independent prognostic factor for poor survival in patients with CML [2, 3], certain studies never demonstrated a more advanced disease stage at presentation or a higher prevalence of multiple cytogenetic abnormalities in older individuals [8]. Similarly, more recent studies failed to demonstrate an association of age with BCR/ABL mutations purporting resistance to TKI [9]. However, it is still possible that age-related changes in

hematopoietic stroma or age-associated immune dysfunctions may lead to more aggressive disease [10].

Two large population studies have examined the changes in CML survival among patients of all ages, since the advent of imatinib [11, 12]. The Surveillance, Epidemiology, and End Results (SEER) study reported that the survival of patients in all age groups had improved to the same extent. A Swedish study encompassing all patients treated in the country since 1958 until 2008 showed that the survival of all patients had improved with the exception of those aged 79 + . The causes of this age-related divergence could not be analyzed based on the registry data. It is not implausible to assume that competitive causes of death and inadequate treatment due to elder age might have played a major role. The Italian study involving 31 medical centers showed that patients aged 75 + seemed to gain from TKI treatment to the same extent as younger people. [13] The present literature evidence doesn't suggest that biology of CML changes with age. Also, there is a significant body of evidence which reported that older patients benefit from TKI to the same extent as the young. Thus, one may conclude that age-related biological differences do not seem to impact the prognosis of CML in the elderly. Western literature suggests that use of TKI mitigate the adverse impact of age in outcomes of CML [14]. However, the outcomes of an elderly patient with CML aren't reported from the Indian population.

This analysis focused on the prognostic significance of older age in the era of imatinib therapy. We hypothesized that if the poor prognosis for older patients with CML was not related to intrinsic age-associated biologic features, then the prognostic effect of older age would be reduced significantly with an oral, well tolerated, highly effective therapy.

Various studies in India reported the median age at diagnosis of CML is 38–40 years. [1] Our study showed

similar trends reported in literature for first generation TKI. Majority of the patients were aged less than 60 years as reported in various Indian literatures. The outcomes and toxicity profile of our study was similar to other reported literature. The current study suggests that there is no statistically significant difference in various clinical parameters of a patient with CML in the elderly population [15, 16]. This study depicts that the patient with age of more than 60 years is having equivalent CHR and MMR rates in comparison to the younger population. The differences were seen in the toxicity profile of the two subgroups but the toxicity profile was manageable. These finding suggests that the previously described prognostic effects of age may not have been related to biologic differences in CML among older patients versus younger patients.

Conclusion

The biology of CML is not affected by a patient's age and that older individuals may benefit from TKI treatment to the same extent as the younger ones in the Indian population also.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed Consent Written informed consent was taken from all patients prior to the clinical examination, any procedure and before starting treatment.

References

- Mishra P, Seth T, Mahapatra M et al (2013) Report of chronic myeloid leukemia in chronic phase from All India Institute of Medical Sciences, 1990–2010. *Indian J Med Paediatr Oncol* 34:159–163
- Sokal JE, Cox EB, Baccarani M, Tura S, Gomez GA, Robertson JE et al (1984) Prognostic discrimination in “good-risk” chronic granulocytic leukemia. *Blood* 63:789–799
- Hasford J, Pfirrmann M, Hehlmann R, Allan NC, Baccarani M, Kluin-Nelemans JC et al (1998) A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. *J Natl Cancer Inst* 90:850–858
- Berger U, Engelich G, Maywald O et al (2003) Chronic myeloid leukemia in the elderly: long-term results from randomized trials with interferon alpha. *Leukemia* 17(9):1820–1826
- Woessner DW, Lim CS, Deininger MW et al (2011) Development of an effective therapy for chronic myelogenous leukemia. *Cancer J (Sudbury, MA.)* 17(6):477–486
- Bali AM (2017) Population ageing in India. *Can Stud Popul* 43:299. <https://doi.org/10.25336/P61G7S>
- Balducci L, Dolan D (2014) Chronic myelogenous leukemia (CML) in the elderly. *Mediterr J Hematol Infect Dis* 6(1):e2014037
- Costes J, Talpaz M, O'Brien S et al (2003) Effects of age on prognosis with imatinib mesylate therapy in patients with Philadelphia chromosome positive chronic myelogenous leukemia. *Cancer* 98:1105–1113
- Hochhaus A (2011) Educational session: managing chronic myeloid leukemia as a chronic disease. *Hematol Am Soc Hematol Educ Program* 2011:128–135. <https://doi.org/10.1182/asheducation-2011.1.128>
- Rosti G, Iacobucci I, Bassi S et al (2007) Impact of age on the outcome of patients with chronic myeloid leukemia in late chronic phase: results of a phase II study of the GIMEMA CML Working Party. *Haematologica* 92:101–105
- Brunner AM, Campigotto F, Sadrzadeh H et al (2013) Trends in all cause mortality among patients with chronic myeloid leukemia: a Surveillance Epidemiology and End Results Data base analysis. *Cancer* 119:2620–2629
- Bjorkholm M, Ohm L, Eloranta S et al (2011) Success story of targeted therapy in Chronic Myeloid leukemia: a population based study of patients diagnosed in Sweden from 1973 to 2008. *J Clin Oncol* 29:2514–2520
- Latagliata R, Ferrero D, Iurlo A et al (2013) Imatinib in very elderly patients with chronic myeloid leukemia in chronic stage: a retrospective study. *Drugs Aging* 30:629–637
- Sheehy OM, Irvine AE, Cuthbert RJ, Humphreys MW, McMullin MF (2008) Use of imatinib mesylate in elderly patients in Northern Ireland: evidence of comparable haematological and molecular responses to younger patients. *Hematology* 13(3):133–136
- Kantarjian H, Smith TL, McCredie K et al (1985) Chronic myelogenous leukemia: a multivariate analysis of the associations of patients' characteristics and therapy with survival. *Blood* 66(6):1366–1375
- Breccia M, Tiribelli M, Alimena G et al (2012) Tyrosine kinase inhibitors for elderly chronic myeloid leukemia patients: a systematic review of efficacy and safety data. *Crit Rev Oncol Hematol* 84(1):93–100

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.