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Research Article

Prognostic Significance of Early Molecular Response in Patients Diagnosed with Chronic Myeloid Leukemia in Chronic Phase Treated with Nilotinib: A First-Line Therapy

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ABSTRACT

Background: Chronic Myeloid Leukemia (CML) is one of malignant hematologic disorders arises from hematopoietic stem cells. BCR-ABL transcript levels on the international scale at 3 and 6 months are defined as indicators of the early efficacy of first line TKI treatment.

Aim To investigate the impact of Early Molecular Response (EMR; BCR-ABL ≤ 10% on the International scale at 3 or 6 months) on outcome of the newly diagnosed CML in chronic phase treated with Nilotinib.

Patients and Methods: The study was enrolled from 2018 to 2020 at Nasser Institute for Research and Treatment. This is a prospective cohort study done on 94 newly diagnosed CML cases in Chronic Phase.

Results: A statistically significant difference was detected between patients not achieved EMR with peripheral blasts ≥ 5%, when compared to others achieved EMR with peripheral blasts <5% (P<0.001). 75% of patients not achieved EMR were ≥ 55 years age at diagnosis; and 90% of patients achieved EMR were<55 years of age at diagnosis with (P<0.001). 25% of cases not achieved EMR were compliant, while other cases achieved EMR were compliant with (P<0.001).Overall survival remained higher in patients who achieved EMR (N=90) compared to patients who did not achieve EMR (N=4) (P=0.0001).

Conclusion: EMR is an important prognostic significance for CML patients received treatment with Nilotinib. Patients suffered with who achieved EMR had significantly better outcome. Achieving MR3.0 should be the aim in patents with CML-CP who have a 3-month BCR-ABL ≤ 10% and 6-month BCR-ABL ≤ 10%.

Keywords: Chronic myeloid leukemia; Nilotinib; Treatment; Patients

Abbreviations: CML: Chronic Myeloid Leukemia; EMR: Early Molecular Response.

INTRODUCTION

Chronic Myeloid Leukemia (CML) is the paradigm of bench-to-bedside translational research [1]. One of the first cancers to be definitively linked to a genetic mutation, the Philadelphia Chromosome, which produces the chimeric BCR-ABL protein, was CML. Numerous investigations using cellular and murine models all agreed that the oncogenic gene BCR-ABL can generate a strong leukaemogenic signal [2,3].

Tyrosine Kinase Inhibitors (TKIs) that target BCR-ABL have been the main treatment for CML since their appearance in 2001. While Allogeneic Hematopoietic Stem Cell Transplant (Allo-HSCT) is a recognized curative treatment for CML, TKIs dramatically reduce the disease burden and overall survival of CML patients by delaying the onset of advanced phase in the majority of patients [4,5].

BCR-ABL transcript measurements every three months were advised during TKI treatment monitoring to assess whether or not patients achieve molecular remission [6]. Real-time quantitative polymerase chain reaction, the current standard method, was suggested for use in this diagnostic test. Although the use of peripheral blood cells as a sample source for BCR-ABL quantitation was recently allowed. The diagnostic procedure using bone marrow cells continues to be the gold standard [6]. In addition to the BCR-ABL transcripts, the return of normal hematopoiesis and a few associated immune cells,

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including neutrophils, blast cells, and basophils, were used to assess the response for CML.

Aim of the work

To investigate the impact of Early Molecular Response (EMR; BCR-ABL ≤ 10% on the International scale [BCR-ABLIS] at 3 or 6 months) on outcome of the newly diagnosed patients with chronic myeloid leukemia in chronic phase treated with Nilotinib.

PATIENTS AND METHODS

The present study was enrolled from 2018 to 2020 at Nasser Institute for Research and Treatment and the National Cancer Institute. This is a prospective cohort study done on 94 newly diagnosed patients of CML in Chronic Phase.

Exclusion criteria

1. Patients presented in Accelerated phase and Blast crisis.

2. Patients received another TKI as first line therapy other than Nilotinib.

Methods

All participants underwent full history taking and thorough physical examination, complete blood picture, blood chemistry [including liver and kidney function tests, serum electrolytes, and Lactate DeHydrogenase (LDH)], Bone marrow aspirate stained by Giemsa stain with assessment of blast percentage to determine the stage of CML either chronic phase <5%blasts, accelerated phase >5% and <20% blasts and blast phase ≥ 20% blasts and basophil percentage. PCR for BCR-ABL was done at diagnosis by quantitative reverse transcriptase polymerase chain reaction. Spleen size was assessed by abdominal US.

Statistical analysis: Data were collected, revised, coded, and entered to the Statistical Package for Social Science (IBM SPSS), version 20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Qualitative data were described in the form of numbers and percentages. Quantitative data were described in the form of means (SD), and ranges. χ^2 test and Fisher exact test was used to compare between two independent groups regarding qualitative data. While the comparison between two independent groups regarding quantitative data with parametric distribution was done by using independent t-test.

P-value greater than 0.05 was considered as insignificant, P less than 0.05 was considered significant. P less than 0.01 were considered highly significant.

RESULTS

A statistically significant difference was detected between cases not achieved EMR with peripheral blasts ≥ 5%, when compared to cases achieved EMR (90%) with peripheral blasts <5%, and P<0.001 (Table 1).

Table 1: Comparison between studied cases achieved EMR and studied cases not achieved EMR regarding baseline peripheral blasts.

Baseline peripheral blasts	EMR not achieved (N=4)	EMR achieved (N=90)	Total (N=94)	P-value
<5%	0 (0.0%)	81 (90.0%)	81 (86.2%)	<0.001
≥ 5%	4 (100.0%)	9 (10.0%)	13 (13.8%)	

A statistically significant difference was detected between the two groups regarding splenomegaly. Splenomegaly was found in (50%) of cases not achieved EMR and in (98.9%) of cases who achieved EMR with P-value <0.001 (Table 2).

Table 2: Comparison between studied cases achieved EMR and studied cases not achieved EMR regarding splenomegaly.

Splenomegaly	EMR not achieved (N=4)	EMR achieved (N=90)	Total (N=94)	P-value
Present	2 (50.0%)	89 (98.9%)	91 (96.8%)	<0.001
Absent	2 (50.0%)	1 (1.1%)	3 (3.2%)	

A statistically significant difference was also detected between the two groups regarding age at diagnosis. Where 75% of cases not achieved EMR were ≥ 55 years age at diagnosis; and 90% of cases achieved EMR were <55 years age at diagnosis with P-value <0.001 (Table 3).

Table 3: Comparison between studied cases achieved EMR and studied cases not achieved EMR regarding age at diagnosis.

Age at diagnosis	EMR not achieved (N=4)	EMR achieved (N=90)	Total (N=94)	P-value
<55 years	1 (25.0%)	81 (90.0%)	82 (87.2%)	<0.001
≥ 55 years	3 (75.0%)	9 (10.0%)	12 (12.8%)	

A statistically significant difference was detected between the two groups regarding compliance. 25% of cases not achieved EMR were compliant, while other cases achieved EMR were compliant with P-value <0.001 (Table 4).

Table 4: Comparison between studied cases achieved EMR and studied cases not achieved EMR regarding compliance.

Compliant	EMR not achieved (N=4)	EMR achieved (N=90)	Total (N=94)	P-value
Non-compliant	3 (75.0%)	0 (0.0%)	3 (3.2%)	<0.001
Compliant	1 (25.0%)	90 (100.0%)	91 (96.8%)	

After a minimum follow up of 1 year after achieving EMR, and by using Log Rank test, Overall survival remained significantly higher in patients who achieved EMR (N=90) compared to patients who did not achieve EMR (N=4) with p-value=0.0001 (Table 5 and Figure 1).

Table 5: Overall survival by using Chi-Square.

	Chi-Square	Sig.
Log rank (Mantel-Cox)	75.286	0.0001

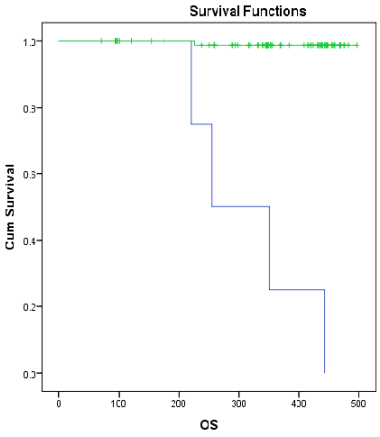

Figure 1: Overall survival functions of patients with chronic myeloid leukemia. **Note:** (—|) No, (—|) Yes, (—|) No-censored, (—|) Yes-censored.

DISCUSSION

Historically, Chronic Myeloid Leukemia (CML) was thought to be a deadly condition. It was the first known cancer with a reliable chromosomal marker. The BCR-ABL1 oncoprotein is produced by the Philadelphia Chromosome, which involves a reciprocal translocation between chromosomes 9 and 22. This oncoprotein's tyrosine kinase activity results in a considerable leucocytosis and a huge clonal proliferation of multipotent stem cells. Tyrosine kinase Inhibitors (TKIs) has changed the course of CML from a deadly sickness to a more common chronic condition [7,8].

Molecular response is the most sensitive measure currently used to monitor the disease. It is determined by quantifying the BCR/ABL1 transcript level *via* quantitative real-time reverse-transcriptase polymerase chain reaction of a sample from either the peripheral blood or the bone marrow [9]. Early Molecular Response (EMR; BCR-ABL 10% on the International Scale at 3 months) is now considered as a reliable indicator of how well frontline TKI therapy is working for CML-CP patients. According to the recommendations of the European Leukemia Net and the National Comprehensive Cancer Network, failing to achieve EMR is seen as a warning response and an insufficient first response, respectively [10].

In the current study, baseline peripheral blasts were <5% in 86.2% of the studied cases

On the contrary of our results Jonte et al. found that the mean number of blast cells in the bone marrow was 1.72%. While, in Furtado et al. 9.35% of patients had peripheral blood blasts 10-29% [11,12]. Kumar et al. reported that 100% of chronic phase CML had <10% blast in their peripheral blood [13].

In our study, splenomegaly was detected in 96.8% of the studied cases

In agreement with our results, Jonte et al. found that splenomegaly was present in 73.8% of patients [11]. Malhotra et al. found that splenomegaly was present in 89% of patients in chronic phase [14]. Pandey et al. reported that 70.96% of patients had splenomegaly. While Furtado et al. found that 27.34% of patients had splenomegaly [15]. Also, we found that splenomegaly was detected in 50% of cases not achieved EMR and in 98.9% of cases achieved EMR. There was statistically significant difference between the two groups as regard splenomegaly. This is in contrast to what reported by Cai et al. that spleen size make no difference in EMR [16].

In the current study, treatment compliance was found in 96.8% of the studied cases

This goes with what stated by Sacha et al. that low compliance patients represented (1.7% of the total) [17]. Also, 25% of our cases not achieved EMR were compliant, while all cases achieved EMR were complaint with a statistically significant difference between the two groups as regard compliance. Haznedaroglu reported that when predicting the prognosis of a patient with CML, the depth of the response acquired with TKI and the time it took to reach this response are crucial factors [18,19]. They also have a direct bearing on the patient's adherence to therapy.

In the current study, Early Molecular Response (EMR) was not achieved in 4 cases out of 94 studied subjects and achieved in 90 studied cases. National Comprehensive Cancer Network, 2014 reported that achieving EMR is associated with improved long-term outcomes, involving a greater chance of achieving future deep molecular responses (e.g. MR4.5) and a decreased risk of progression to AP/BC, and improved Progression Free Survival (PFS) and overall survival (OS). Kuo et al. reported that at three months, 27 patients were still eligible for EMR analysis [20]. 20 of these patients (BCR-ABL1IS-10%) obtained EMR. 25 of the 35 patients who were eligible for a 6-month EMR analysis did so [20].

The present study results showed that 75% of cases not achieved EMR were ≥ 55 year's age at diagnosis, while 90% of cases achieved EMR were <55 years age at diagnosis. There was statistically significant difference between the two groups as regard age at diagnosis. Cai et al. showed that the age at diagnosis make no difference in EMR. Meanwhile, Smith et al. highlighted a greater benefit for younger patient [16,21].

Results of the current study showed that the mean OS in cases not achieved EMR3 was (95%CI: 219.210-415.290); the mean OS in cases achieved EMR3 was (95%CI: 485.666-499.321) and the mean OS in cases achieved EMR3 was (95%CI: 469.447-494.077). In patients who achieved EMR, median survival was not reached. Overall survival remained significantly higher in patients who achieved EMR (N=90) compared to patients who did not achieve EMR.

Claudiani et al. reported that 5 and 10 year OS were 98.8% (95%CI: 98.7-98.9) and 96.8% (95%CI: 94.2-97.3), while CML-OS were 100% and 99.4% (95%CI: 98-99.8). Zaidi et al. noticed that the estimated OS for patients received Nilotinib 600 mg/day was 92.3%. Kantarjian et al. stated that the overall survival at 24 months was 87%. Hughes et al. stated that compared to EMR accomplishment, EMR failure was linked to lower rates of molecular response, a higher risk of progression, and shorter overall survival [22-26].

CONCLUSION

Early Molecular Response (EMR) is an important prognostic significance for Chronic Myeloid Leukemia (CML) patients treated with Nilotinib. Patients suffering with Chronic Myeloid Leukemia who achieved Early Molecular Response (first line therapy) had significantly better outcomes in Chronic Phase by using Nilotinib. Achieving MR3.0 should be a priority in Chronic Myeloid Leukemia-Chronic Phase (CML-CP) patients who have a 3-month

BCR-ABL ≤ 10% and 6-month BCR-ABL ≤ 10%.

ETHICAL APPROVAL

Approval was obtained from Ain Shams University Academic and Ethical Committee. Also an informed consent to participate and publish was obtained.

COMPETING INTERESTS

No interests of a financial or personal nature.

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AUTHOR CONTRIBUTION

Authors contribute equally in the study.

AVAILABILITY OF DATA AND MATERIALS

Data can be accessed after publishing the paper.

REFERENCES

1. Freireich J, Wiernik P. Steensma PThe leukemias: A half-century of discovery. J Clin Oncol. 2014;32:3463–3469.
2. Sontakke P, Jaques J, Vellenga E. Modeling of chronic myeloid leukemia: An overview of in vivo murine and human xenograft models. Stem Cells Int. 2016;1625015.
3. Melo J, Barnes J. Chronic myeloid leukaemia as a model of disease evolution in human cancer. Nat Rev Cancer. 2007; 7(6):441–453.
4. Barrett J, Ito S. The role of stem cell transplantation for chronic myelogenous leukemia in the 21st century. Blood. 2015; 125(21):3230–3235.
5. Baccarani M, Deininger M, Rosti G. European Leukemia Net recommendations for the management of chronic myeloid leukemia. Blood. 2013; 122(6):872–884.
6. Hochhaus A, Saussele S, Rosti G. Chronic myeloid leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(4):41–51.
7. Brück O, Blom S. Dufva O. Immune cell contexture in the bone marrow tumor microenvironment impacts therapy response in CML. Leukemia. 2018;32:1643–1656.
8. Yong A , Barrett J, Rodgers GP, Young N. Chronic myelogenous leukemia. The Bethesda handbook of clinical hematology. Philadelphia. LWW. 2013;170–171.
9. Talati C, Ontiveros P, Griffiths A. How we will treat chronic myeloid leukemia. Blood Rev. 2015;29(2):137–142.
10. Akard L, Bixby D. Considering baseline factors and early response rates to optimize therapy for chronic myeloid leukemia in chronic phase. Leuk Lymphoma. 2016; 57(5):1002-1014.
11. Jonte F, Barez A, Soto I. Features of chronic myeloid leukemia at diagnosis. Study of a series of 134 cases. Sangre. 1992; 37(5):345-50.
12. Furtado V, Santos G, de Carvalho S. Accelerated phase chronic myeloid leukemia: Evaluation of clinical criteria as predictors of survival, major cytogenetic response and progression to blast phase. Rev Bras Hematol Hemoter. 2015; 37(5):341–347.
13. Kumar S, Gupta V, Bharti A. A study to determine the clinical, hematological, cytogenetic, and molecular profile in CML patient in and around Eastern UP, India. J Family Med Prim Care. 2019;8(7):2450–2455.
14. Malhotra P, Varma N, Varma SA. short report on chronic myeloid leukemia from Post Graduate Institute of Medical Education and Research, Chandigarh. Indian J Med Paediatr Oncol. 2013;34(3):186–188.
15. Pandey N, Yadav G. Kushwaha R. Effect of imatinib on bone marrow morphology and angiogenesis in chronic myeloid leukemia. Adv Hematol. 2019;1-8.
16. Cai l, Liu C, Guo Y. Analysis of 48 cases pediatric chronic myeloid leukemia from china: Results from a single institute in China. Blood . 2019;134(1):5911.
17. Sacha T, Góra-Tybor J, Wlsak-Szulkowska E. Quality of life and adherence to therapy in patients with chronic myeloid leukemia treated with nilotinib as a second-line therapy: A multicenter prospective observational study. Clin Lymphoma Myeloma Leuk. 2017;17(5):283-295.
18. Haznedaroglu ICCurrent concerns of undertreatment and overtreatment in chronic myeloid leukemia based on European LeukemiaNet 2013 recommendations. Expert Opin Pharmacothery. 2013;14:2005–10.
19. National Comprehensive Cancer Network NCCN Clinical Practice Guidelines in Oncology: Chronic Myelogenous Leukemia. 2014; 3.
20. Kuo Y, Wang N. Hwang W. Safety and efficacy of nilotinib in routine clinical practice in patients with chronic myeloid leukemia in chronic or accelerated phase with resistance or intolerance to imatinib: Results from the NOVEL study. Ther Adv Hematol. 2018;9(3):65–78.
21. Smith G, Painter D, Howell A. Determinants of survival in patients with chronic myeloid leukaemia treated in the new era of oral therapy: Findings from a UK population-based patient cohort. BMJ Open. 2014;4(1):004266.
22. Claudiani S, Gatenby A. Szydlo RMR4 sustained for 12 months is associated with stable deep molecular responses in chronic myeloid leukemia. Haematologica. 2019;104(11):2206–2214.
23. Zaidi U, Kaleem B, Borhany M. Early and sustained deep molecular response achieved with nilotinib in high Sokal risk chronic myeloid leukemia patients. Cancer Manag Res. 2019;11:1493–1502.
24. Kantarjian M, Giles J, Bhalla N. Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. Blood. 2011;117(4):1141-1145.
25. Hughes T, Saglio G, Kantarjian H. 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.
26. Srinivas H, Paul R, Uppin G. Morphologic changes in the bone marrow in patients of Chronic Myeloid Leukemia (CML) treated with imatinibmesylate. Indian J Hematol Blood Transfus .2012;28(3):162–169.