HIGH BCR-ABL1 GENE PERCENTAGE AT TIME OF PRESENTATION: A TOOL TO PREDICT FAILURE IN ACHIEVING EARLY MOLECULAR RESPONSE IN CHRONIC MYELOID LEUKEMIA (CML): A TERTIARY CARE CENTER EXPERIENCE

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ABSTRACT

Objective: To determine the relationship of baseline quantitative BCR ABL1 gene percentage and therapeutic response i.e. Early Molecular Response (EMR) at 3 months with first generation Tyrosine kinase inhibitors (Imatinib) in patients with Chronic Myeloid Leukemia (CML) in chronic phase (CP)

Study Design: Prospective observational study.

Place and Duration of Study: Combined Military Hospital, Rawalpindi, Pakistan, and Armed Forces Institute of Pathology Rawalpindi, Pakistan from Oct 2017 to Oct 2019.

Methodology: One hundred and seventy patients, 18 years of age or older with newly diagnosed Chronic Myeloid Leukemia (CML) in chronic phase (CP) with quantitative baseline BCR-ABL (IS) transcript were included in the study. All enrolled patients were placed on Imatinib therapy (400 mg/day) and Reverse transcription polymerase chain reaction (RT-PCR) for BCR ABL transcript was repeated at 3 months to document EMR (BCR-ABL (IS) <10%). Patients who were in accelerated/blast phase, or already taking any Tyrosine Kinase Inhibitors (TKI) or chemotherapy were excluded from the study

Results: In our study 101 (59.4%) patients achieved early molecular response. Out of these 80 (70.8%) patients with BCR-ABL<50% at baseline value showed early molecular response. However, only 21 (36.8%) with BCR-ABL >50% at baseline achieved early molecular response (*p*-value <0.001).

Conclusion: A significant number of patients achieved early molecular response with Imatinib therapy that had BCR ABL below 50%, however those with baseline BCR ABL >50%, the rate of EMR was comparatively lower.

Keywords: Chronic Myeloid Leukemia, Early molecular response, Imatinib.

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that has translocation between chromosome 22 and chromosome 9[1]. CML accounts for about 15-20% of adult leukaemias with a slight male predominance. About 85% of patients present in chronic phase and if left untreated the disease usually progresses to accelerated or blast phase in three to five years, which is associated with unfavourable prognosis and poor clinical outcomes[2].

CML usually presents with constitutional symptoms (i.e. lowgrade fever, weight loss and night sweats), splenomegaly and a high WBC count. Characteristic pathogenesis of the disease is t (9;22) which results in production of Philadelphia chromosome which is detected by RT-PCR and is present in approximately 90-95% of CML patients. Approximately 5% patients have atypical transcript of BCR ABL which is detected by FISH (fluorescence in situ hybridization)[3].

Sensitive residues of tyrosine are carried close to adjacent kinase domains of ABL1, which contribute to autophosphorylation and activation. These changes result in constitutive activation of ABL1 resulting in loss of growth inhibition, decreased apoptosis and decreased adherence to stromal cells in the bone marrow[4]. In CML-CP, Imatinib is given as first line treatment in most

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patients however, in Advance Phase (AP) second generation TKI like Nilotinib or Dasatinib are preferred[5]. Response to treatment is assessed at 3 months as per ELN 2013 guideline and NCCN guidelines[6,7].

The treatment target has recently been switched to early molecular reaction (EMR), i.e. BCR-ABL1 transcript ≤10% at 3 months as a deeper response and clinical improvement forecast[8]. After 3 months of imatinib therapy EMR was stated by a study as a 77.6% (n=410/528)[8]. Usually EUTOS Score is calculated to determine probability of achieving Complete cytogenetic response at 18 months[9]. We planned this study to determine the response of TKI therapy in association with baseline BCL ABL percentage with EMR in our study population.

METHODOLOGY

This was a prospective observational study done at the department of medical Oncology, Combined Military Hospital and Armed Forces Institute of Pathology, Rawalpindi from October 2017 to October 2019. Consecutively patients of CML in the chronic phase were recruited after the informed consent through universal sampling method. Newly diagnosed cases of CML with age ≥18 years, in CP with quantitative BCR-ABL were included in study. Patients in accelerated, blast phase, with atypical BCR-ABL transcript and base line BCR-ABL <10% were excluded from the study. A total of 170 patients were included in the study, which was carried out after taking approval from institutional ethics review board (IERB No. 53/2017/CMH). All chosen patients had a detailed history and physical exam. For the entire baseline blood picture, blood samples were drawn with chemistry profile and quantitative RT-PCR for BCR-ABL1 transcript. The sample was analyzed on sysmex Kx21 and BCR-ABL was done by gene expert. The international baseline BCR-ABL value was reported through by RT-PCR.

In our early molecular response research, BCR-ABL rates <10 percent on the IS were described three months after imatinib therapy begun. Imatinib treatment (400 mg/day) was performed on all the patients enrolled, and after three months, quantitative BCR-ABL transcript RT-PCR was replicated according to NCCN guidelines.

All the data were analyzed using SPSS-22. Quantitative variables were measured as mean ± SD while frequencies and percentages were calculated for qualitative variables. Paired sample t-test was applied between pretreatment and post treatment BCR-ABL levels with *p*-value <0.05 taken as significant. Chi-square test was applied for gender, Age groups and EMR between the two groups with BCR-ABL transcript of more than 50% and those less than 50% with *p*-value <0.05 taken as significant.

RESULTS

In our targeted population, there were 45 (26.5%) females while 125 (73.5%) males. The mean age of presentation was 53.3 ± 8.0 years (ranging from 18 to 86 years) and 116 (68.3%) were from rural background or currently living in villages.

Out of 170 patients included in our study 113 (66.5%) of patients had BCR-ABL below 50% at time of presentation while 57 (33.5%) had BCR-ABL percentage above 50%. Fig-1 showed

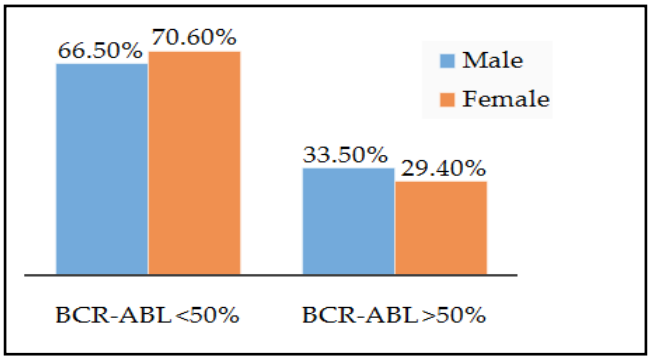

Figure-1: BCR ABL1 gene percentage at presentation.

the comparison of pretreatment BCR-ABL levels of 41 ± 21 IS with post treatment BCR-ABL levels of 18 ± 19 IS showed significant reduction after 3 months of imatinib therapy (*p*<0.001). Overall 101 (59.4%) patients achieved EMR while 69 (40.6%) cases did not achieve this milestone (fig-2).

In our study population 80 (70.8%) patients with BCR-ABL <50% baseline value achieved

EMR, however only 21 (36.8%) with BCR-ABL >50% at baseline showed EMR at 3 months. In total 69 (40.6%) cases did not show EMR status,

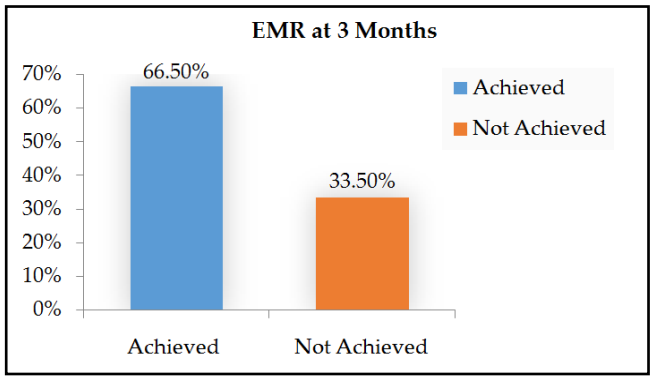

Figure-2: Early molecular response achievement at 3 months (n=170).

out of which 33 (29.2%) had baseline BCR-ABL <50% while a significant proportion of 36 (63.2%) having BCR-ABL >50% at baseline did not achieve EMR (table).

Table: Comparison between the two groups with BCR-ABL transcript of <50% and those >50% (n=170).

Parameter	BCR-ABL <50% (n=113), n (%)	BCR-ABL >50 % (n=57) n (%)	*p*-value
Gender			
Male	84 (74.3)	41 (71.9)	0.738
Females	29 (25.7)	16 (28.1)	
Age Groups			
<30 years	8 (7.1)	4 (7)	0.886
30 – 50 years	37 (32.7)	18 (31.6)	
>50 years	68 (60.2)	35 (61.4)	
Early Molecular Response			
Not Achieved	33 (29.2)	36 (63.2)	<0.001
Achieved	80 (70.8)	21 (36.8)	

DISCUSSION

Chronic myeloid leukemia is a disorder characterized by dysregulated production and uncontrolled proliferation of mature granulocytes. The deregulated tyrosine kinase activity in this disease has become a primary target for the treatment of this disorder and has changed the perspective of the disease entirely over the past several years since the introduction of targeted therapy (tyrosine kinase inhibitors with first generation Imatinib in 2003)[10]. After landmark success of imatinib, second generation Nilotinib, Bosutinib, Dasatinib and third generation drugs such as Ponatinib were developed. These agents are able to achieve long-term control of the disease in the majority of patients and have tremendously improved survival[11]. Despite the encouraging outcomes, In some chronic CML patients the optimal response is not achieved, as described in the current guidelines. Imatinib (IM) is generally used as first line treatment in our set up for most patients with CML in chronic phase. A part from poor compliance, drug-drug interaction, emergence of drug resistance, certain disease related factors contribute to suboptimal response[12]. Disease related factors like WBC, plateletts, basophils count, splenic size and the assessment of the disease risk of Sokal and Hasford scores remained clinically relevant as the required cytogenetic and molecular responses were less likely to be obtained from patients identified as high risk[13,14]. Early determination of patients likely to achieve early molecular response is very important, as non-responders can be shifted to second generation TKI or alternative therapies like allogenic stem cell transplant. It is well established now that early molecular response (BCR-ABL1 transcript <10%) at 3 months not only translates into deeper molecular responses but also predicts overall survival and progression free survival (PFS)[15]. Marin *et al* recently underlined the most important factor in detection of patients with elevated risk of disease progression to determining 3 month BCR-ABL1 transcripts[16]. The patients who were not able to achieve early molecular response at three months were lesslikely to achieve molecular and cytogenetic targets at 6 and 12 months, leading to decreased overall survival and progression free survival[17].

In our analysis we assessed a molecular parameter easily detectable that identify CML patients less likely to achieve recommended molecular targets with Imatinib therapy. We describe the correlation between BCR–ABL1 transcript levels measured at diagnosis and the response to imatinib at three months.In our study, the higher BCR–ABL level has been related to unsatisfactory

drug responses, indicating lower probability of optimal answers to standard dose imatinib (400 mg/day). Out of 170 patients included in our study 66.5% of patients had BCR-ABL1 <50% at time of presentation while 33.5% had BCR-ABL percentage >50%. All patients were started on Imatinib 400 mg/day. The patients were reassessed at 3 months with quantitative BCR-ABL1 level for EMR. In our study 59.4% patients achieved EMR while 40.6% did not achieve this important milestone. Further analysis revealed that 70.8% patients with BCR-ABL <50% baseline value showed EMR, while only 36.8% with BCR-ABL1 >50% at baseline showed early molecular response. In our study population 40.6% did not show EMR, out of these 29.2% had baseline BCR-ABL <50% while a significant proportion of 63.2% had BCR-ABL >50%. Our findings are almost similar to a recently published Paolo *et al* study, which also found that patients with higher levels of BCR-ABL transcripts are less likely to benefit from standard IM18 dose[18]. In this landmark study, there was also no correlation of diagnostic and patient age transcripts of BCR-ABL, sex, hemoglobin level, social risk ratings, ph-positive metaphase and white blood cell counts. Interestingly, no link was observed between WBC diagnostic counts and BCR–ABL, which indicates the high BCR–ABL values are independent of the leukemia (i.e., the amount of Ph+ diagnostic cells).

Although there may be myriad other reasons for inferior therapeutic responses in our patient population including poor compliance, drug interactions, toxicities and genetic mutations causing TKI resistance[19]. Marin *et al* discussed various factors affecting adherence in chronic myeloid leukemia patients, including lower age group, adverse effects of TKI therapy, psychological differences among patients and perception about disease[20]. In our study comparison between the two groups with BCR-ABL transcript of more than 50% and those less than 50% showed no significant difference for gender and age groups but subset analysis revealed statistically significant difference for EMR showing better response for less than 50% BCR- ABL while poor response for BCR-ABL more than 50%. We report that CML patients who are less likely to benefit from IM can be determined by High BCR-ABL transcripts at diagnosis measured by RT-PCR. These patients may be considered for treatment with second generation TKIs or alternative forms of treatment at the outset as per recommended guidelines.

Our study was unique because it was carried out in Pakistani/South Asian population (which is known to have a different epidemiology with regard to CML[21,22]) and discussed association of BCR-ABL at time of presentation with EMR status. Our study was limited by the small sample size and predominantly male population. Another limitation was that we put all patients on imatinib irrespective of risk stratification due to limited availability and affordability issues in procurement of second generation TKI for all patients in upfront setting.

RECOMMENDATION

CML patients who are less likely to benefit from IM which can be determined by high BCR-ABL transcripts at diagnosis measured by RT-PCR. These patients may be considered for alternative forms of treatment including second or third generation TKI therapy or stem cell transplant. Extensive multi-center study with high number of study population with equal representation of female and males is required for further research on subject.

CONCLUSION

EMR was achieved in more than half of patients with CML in chronic phase, being treated with Imatinib at 3 months. Although majority of patients achieved EMR with Imatinib therapy that had BCR ABL below 50%, however those with baseline BCR ABL above 50%, the rate of EMR was significantly lower.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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