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Original Research Article

Response of dasatinib in different phase of chronic myeloid leukaemia patients

Moshammat Naznin Begum[1]*, M. A. Khan[2], Tasneem Ara[1], Akhil Ranjon Biswas[2], Mafruha Akter[1], M. Manirul Islam[2], Humayra Nazneen[2], Muhammad Nurul Farhad[1]

[1]Department of Haematology, Dhaka Medical College, Dhaka, Bangladesh
[2]Department of Haematology & BMT Unit, Dhaka Medical College, Dhaka, Bangladesh

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***Correspondence:**
Dr. Moshammat Naznin Begum,
E-mail: mstnaznin7@gmail.com

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ABSTRACT

Background: Chronic myeloid leukemia (CML) is a stem cell disorder caused by a chromosomal abnormality that results in the formation of the Philadelphia chromosome. This abnormality leads to the production of the Bcr-Abl tyrosine kinase, which drives the uncontrolled proliferation of cells. Imatinib, a tyrosine kinase inhibitor (TKI), revolutionized the treatment of CML, but resistance and intolerance in some patients have necessitated alternative therapies such as Dasatinib, a potent multitargeted inhibitor of Bcr-Abl and Src-family kinases. This study was aims to assess the efficacy and safety of Dasatinib in CML patients who were either newly diagnosed or resistant/intolerant to Imatinib.
Methods: A prospective observational study was conducted at Dhaka Medical College & Hospital from July 2016 to June 2017. A total 31 patients with different phases of CML were included in this study. All patients were treated with Dasatinib 100 mg daily and monitored over 12 months. Molecular responses were assessed through quantitative PCR and hematologic responses were evaluated via complete blood counts.
Results: Among the 31 patients, two died and two discontinued treatment. Of the remaining 27, 23 (85%) achieved complete hematologic response (CHR), 12 (44%) achieved major molecular response (MMR) and 3 (11%) attained complete molecular response (CMR). All four chronic-phase CML (CML-CP) patients who received Dasatinib as frontline therapy achieved molecular response within one month of starting therapy. Responses were lower in more advanced disease stages, with two blast-phase patients dying.
Conclusions: Dasatinib demonstrated significant efficacy and safety in treating CML, particularly in chronic-phase patients and those resistant to Imatinib.

Keywords: Chronic myeloid leukemia, Dasatinib, Philadelphia chromosome, Imatinib resistance, Molecular response

INTRODUCTION

Chronic myeloid leukaemia is a clonal disease that results from an acquired genetic change in a pluripotential haemopoietic stem cell. This altered stem cell proliferates and generates a population of differentiated cells that gradually displaces normal haemopoiesis and leads to a greatly expanded total myeloid mass.[1] This abnormality was discovered by Nowel in 1960 and is a consequence of fusion between the Abelson, (Abl) tyrosine kinase gene at chromosome 9 and the break point cluster (Bcr) gene at chromosome 22, resulting in a chimeric oncogene (Bcr-Abl) and a constitutively active Bcr-Abl tyrosine kinase that has been implicated in the pathogenesis of CML.[2] The product of this translocation is a tyrosine kinase that activates many signal transduction pathways, leading to uncontrolled cell proliferation and reduced apoptosis. The Philadelphia chromosome is found in about 95% patients diagnosed with CML.[3]

The course of CML is bi- or triphasic, the initial, chronic phase (CP) is asymptomatic in approximately 40% of cases, but can be followed by an advanced accelerated phase (AP) and/or a blast crisis phase, which may prove fatal.

Imatinib was the first drug developed and marketed in the United States that targets the BCR-ABL tyrosine kinase, produced higher percentages of complete hematologic responses, as well as major and complete cytogenetic responses. Before Imatinib, no drugs were available to alter the natural progression of CML. Although Imatinib changed the landscape dramatically, resistance has created a new set of challenges. Around 50% of patients with accelerated phase CML (CML-AP) were estimated to have developed Imatinib resistance after 2 years of treatment; that percentage increased to 75% after 4 years of treatment. In addition to the problem of Imatinib resistance, intolerance may be a concern among a small subset of patients.

Treatment options for patients with CML-AP who have Imatinib-intolerant or -resistant disease are extremely limited. Allogeneic stem cell transplantation is an alternative, but it is associated with significant early morbidity and mortality and is restricted by the availability of suitable donors. Therefore, alternative therapies are needed for this patient group.[4,5]

Dasatinib is a new novelmultitargeted tyrosine kinase inhibitor that, has demonstrated ability to overcome Imatinib resistance and produce clinical responses.

Dasatinib was rationally designed to comprehensively target the underlying causes of Imatinib resistance that have been identified to date. Dasatinib has demonstrated durable responses in patients with CML showing equivalent efficacy and significantly fewer key side effects compared with alternative dosing schedules.[6-9]

In the randomized phase-2 trial, 150 patients were randomly assigned in either Dasatinib (70 mg twice daily) or high-dose Imatinib (800 mg/day). With a median follow-up of 15 months, 93% of Dasatinibpatients had achieved a complete hematologic response compared with 82% of patients treated with high-dose Imatinib. Major cytogenetic responses were obtained in 52% of patients treated with Dasatinib compared with 33% of patients treated with high-dose Imatinib. Time to treatment failure and progression-free survival were longer with Dasatinib.

Since increased inhibition of BCR-ABL kinase correlates with a better clinical response. Administration of Dasatinib as the initial therapy may improve responses in patients with newly diagnosed chronic-phase CML. Because Dasatinib is less vulnerable to resistance- conferring mutations in the BCR-ABL kinase domain than Imatinib, the incidence of disease progression may be reduced among patients treated with Dasatinib.[10,11] Dasatinib as initial therapy to patients in clinical trials shown remarkable rates of early responses, with nearly 90% of patients achieving a CCyR by 3 months of therapy and excellent EFS, TFS and survival, It is hypothesized that initial therapy with more potent tyrosine kinase inhibitors that may improve the rate of complete cytogenetic response early after diagnosis could improve the long-term outcome in patients with CML.[12-15] Dasatinib is a new drug has been approved for treatment of CML. New research, innovations in treatment and clinical trials, people are not only living longer with CML, but can often live with this type of leukemia as a manageable chronic condition. The aim of the study is clinical and patient-reported outcomes as well as safety of therapy by Dasatinib in CML patients.

The objective of this study was to evaluate the response of Dasatinib chronic myeloid leukemia patients.

METHODS

This prospective observational study was conducted at Dhaka Medical College & Hospital, Dhaka from July 2016 to June 2017. A total 31 patients with CML were included in this study. Among them 4 with CML-CP, 23 with CML-AP and 4 with CML-BT. All patients were treated with Dasatinib 100 mg daily and monitored over 12 months. Molecular responses were assessed through quantitative PCR and hematologic responses were evaluated via complete blood counts.

Inclusion criteria

Age: Patients, aged 18-65 years were eligible for inclusion if they had Ph positive or BCR-ABLpositive CML either new cases or previously treated cases.

Eastern cooperative oncology group performance status of 0 or 3 for chronic phase patients

Patient able to take Dasatinib daily.

Exclusion criteria

Patient having hypersensitivity to Dasatinib. Ph chromosome/BCR-ABL negative CML. Patients with an Eastern cooperative oncology group performance status score of more than 3. Patients with cardiac, hepatic and renal involvement when Dasatinib is contraindicated

Data collection

Blood for CBC and PBF analysis was collected under aseptic conditions into EDTA tubes and processed under aseptic conditions. Bone marrow aspiration was performed aseptically, with samples divided into three tubes: For morphology, EDTA, for PCR, sodium heparin; for FISH. Sysmex XE-5000 was used to analyze CBC and were examined under Leishman stained PBF microscopically. Other test like liver and kidney function, electrolytes, uic acid, LDH, ECG and chest x ray. Treatment response was assessed by BCR ABL transcript molecular monitoring,

which was repeated every 3 months using quantitative PCR.

Ethical approval

The research protocol is approved by the Institutional Ethics committee. The aims and objective of the study along with its procedure, alternative diagnostic methods, risk and benefits will be explained to the patients in easily understandable local language and then informed consent will be taken from each patient.

It will be assured that all records would be kept confidential and the procedure will be helpful for both the physician and patients in making rational approach regarding management of the case.

Statistical analysis

The data was analysed using SPSS statistical software. Continuous variables were described with descriptive statistics including means, standard deviations, medians and interquartile ranges, categorical variables with frequencies and percentages. Independent t test, chi-square test or Fisher's exact test was used to perform comparative analyses between groups. Significantly statistically significant was considered when p value was<0.05.

RESULTS

In this study, thirty one patients in different phases of CML received Dasatinib 100 mg OD. Follow up from starting up to 12 months. Among the study population 4 patients in CML –CP, 23 patients in CML-AP, 3 patients in CML-BT.

Four CML CP patients received Dasatinib as 1st line therapy and remaining 24 patients received Dasatinib as 2nd line therapy. Three patients of CML-BT died within 1 month of starting Dasatinib and 1 patient discontinued treatment due to pregnancy. Table 1 shows age of the study population, it was observed that majority (58.0%) patients belonged to age 40-60 years. The mean age was found 48.1±13.7 years with ranged from 17 to 70 years.

Table 2 shows sex of the study population, it was observed that twenty three (74.2%) patients were male and 8 (25.8%) were female.

Out of 27 patients, all 4 (100%) patients who took Dasatinib as 1st line therapy were achieved CHR within 6 months, 19 (82.6%) most of the patients achieved CHR within 9 months who took Dasatinib as 2nd line and 4 (17.4%) were failed to achieved CHR within 12 months of study period. The difference was statistically not significant (p>0.05) between two groups.

Out of 27 patients, all patients 4 (100%) who took Dasatinib as 1st line were achieved MMR, 11 (47.8%) patients achieved MMR who took Dasatinib as 2nd line and 12 (52.2%) were failed to achiev MMR within 12 months of study period. The difference was statistically significant (p<0.05) between two groups.

Out of 27 patients, 2 (50%) patients who took Dasatinib OD as 1st line therapy were achieved CMR and 2 (50%) were failed to achieve. To the 1 (4.3%) patients achieved CMR who took Dasatinib as 2nd line therapy and 22 (95.72%) were failed. The difference was statistically significant (p<0.05) between two groups.

Out of 27 patients, all 4 (100%) CML-CP phase who receive Dasatinib as 1st line therapy achieve CHR and MMR, 2 (50%) were in CMR, about 19 (82.6%) were took Dasatinib as 2nd line therapy CML-AP phases in CHR, 11 (47.8%) were in MMR, 1 (4.3%) were in CMR.

All 3 patients of CML-BT died within 1 month of starting Dasatinib and 1 patient discontinued treatment due to pregnancy, who achieve MMR within 6 months of starting therapy. The difference was statistically not significant (p>0.05) among three groups.

Table 1: Distribution of the study population by age (n=31).

Age(years)	Number of patients	%
>20	2	6.6
20-40	6	19.4
40-60	18	58
<60	5	16
Mean±SD	48.1±13.7	
Range (min-max)	17-70	

Table 2: Distribution of study population by age (n=31).

Sex	Number of patients	%
Male	23	74.2
Female	8	25.8

Table 3: Distribution of the study population by CHR among the patients receiving Dasatinib 100 mg OD for 12 months (n=27).

Dasatinib as	N	Total no. of patients		P value
		Achieve CHR (%)	Failed to achieve CHR (%)	
1st line therapy	4	4 (100)	0	
2nd line therapy	23	19 (82.6)	4 (17.4)	0.505ns
Total	27	23 (85.2)	4 (14.8)	

ns=not significant, P value reached from fisher's exact test

Table 4: Distribution of study population by Major Molecular Response (MMR) (<0.1 BCR-ABL transcript gene) (n=27).

Dasatinib	N	Follow up (up to 12 months)				Total no. of patients		P value
		3	6	9	12	Achieve MMR (%)	Failed MMR (%)	
1st line therapy	4	1	2	1	0	4 (100)	0	
2nd line therapy	23	0	3	2	6	11 (47.8)	12 (52.2)	0.042ns
Total	27					15 (55.56)	12 (44.44)	

ns=not significant, P value reached from fisher's exact test

Table 5: Distribution of study population by complete molecular response (CMR) (BCR-ABL transcript gene not detected) by QT PCR.

Dasatinib OD 100 mg as	N	Total no. of patients		P value
		Achieve CMR (%)	Failed CMR (%)	
1st line therapy	4	2 (50)	2 (50)	
2nd line therapy	23	1 (4.3)	22 (95.7)	0.048ns
Total	27	3 (11.1)	24 (88.9)	

ns=not significant, P value reached from fisher's exact test

Table 6: Distribution of the study population by different phases of CML (n=27).

Different phases of CML	N	CHR		MMR		CMR		P value
		N	%	N	%	N	%	
CML-CP	4	4	100.0	4	100.0	2	50.0	
CML-AP	23	19	82.6	11	47.8	1	4.3	0.168ns
CML-BT	3 (died)	0	0.0	0	0.0	0	0.0	

ns=not significant, P value reached from fisher's exact test

DISCUSSION

Dysregulated protein tyrosine kinase (PTK) activity is the hallmark of multiple neoplasms.[16] Over the past decade, a broad array of drugs designed to selectively inhibit PTKs have emerged as novel therapies for patients with cancer.[16] Perhaps the most well-known PTK target to date is theBCR-ABLI oncoprotein, which is critical to the pathogenesis of chronic myeloid leukemia. The successful treatment of patients with CML with TKI Imatinib has definitively validated this therapeutic strategy and established CML as a model disease for targeted cancer treatment.[16]

Imatinib, a tyrosine kinase inhibitor (TKI), is highly effective in the treatment of CML However, some patients treated with Imatinib will fail to respond, will respond suboptimally or will relapse because of resistance or intolerance. Cytogenetic and molecular techniques are currently used to monitor CML therapy for both response and relapse. With multiple and more potent therapeutic options now available. This approach should benefit patients by increasing the potential for better long-term outcomes.[17-19]

Dasatinib induced a 98% complete cytogenetic response rate in patients treated for at least 3 months, with nearly 90% of patients achieving complete cytogenetic response by 3 months of therapy, Furthermore, randomized phase III trials have demonstrated improved response rates and decreased rates of transformation in patients treated with Dasatinib compared to the rates in patients treated with Imatinib.[16,18-22] In addition, these tyrosine kinase inhibitors are more potent as inhibitors of the kinase activity of BCR-ABL1 and overcome the resistance imposed by most BCR-ABLI mutants identified in patients with CML in whom Imatinib therapy fails. When Dasatinib is used after failure of Imatinib therapy, these agents induce complete

cytogenetic responses in approximately 50% of patients.[23-25] Dasatinib is a highly potent BCR-ABL inhibitor that has shown durable efficacy in patients with chronic phase (CP) chronic myeloid leukemia (CML) after resistance, suboptimal response or intolerance to prior Imatinib. In patients with CML, BCR-ABL transcript measurement is the most sensitive method for assessing minimal residual disease. Here, molecular responses were analyzed in 1067 patients with CML-CP treated with Dasatinib during phase II/III trials. After 3, 6, 12 and 24 months of follow-up, a major molecular response (MMR) was achieved by 12, 22, 35 and 40% of patients, respectively.

The 24-month MMR rate was 34% in patients with resistance or suboptimal response to Imatinib (n%829) and 63% in Imatinib-intolerant patients (n%238). Among patients who had achieved a complete cytogenetic response (CCyR), 72% also achieved MMR. Responses with Dasatinib 100mg once daily were similar to other doses. In landmark analyses, 24-month progression free survival was higher in patients who had achieved MMR or CCyR at 12 months than in those without MMR or CCyR at 12 months. MMR at 12 months was associated with a longer duration of CCyR.[16,26]

Dasatinib was well tolerated: most nonhematologic adverse events (AEs) were mild to moderate; no Imatinib-intolerant patients discontinued Dasatinib because of AEs. Although common (76% of patients with severe neutropenia), cytopenias were manageable through dose modification. Further follow-up is warranted.[19,20]

In this study 31 patients of CML in different phases received Dasatinib 100mg OD. Among them 23 patients were CML AP and 3 patients of CML BT received 2nd line therapy and 4 patients newly diagnosed CMP-CP patients received Dasatinib as front line therapy. Among the 27 patients who received Dasatinib as 2nd line therapy, 23 (85.2%) patients have CHR, 11 (47.8%) patients have MMR and 1 (4.3%) patient have CMR.

All 4 (100%) CML CP patients have both CHR and MMR within 6 months of therapy and 2 (50%) have CMR. All 3 patients of CML BT died within 1 month of starting treatment. Two due to hepatic failure and 1 due to CVD. Probably they were previously heavily treated. So response of Dasatinib on CML BT patient is not properly observed in this study due to very few number of cases. 1 patient discontinued treatment due to pregnancy within 6 months of therapy who achieved CHR and MMR.

The total cumulative MMR rate was 40%, including 34% of patients with resistance or suboptimal response to Imatinib and 63% of patients with intolerance to Imatinib. MMRs were achieved rapidly, with a median time to MMR in responding patients of less than 6 months.[13,16]

Another study shown that among the 45 patients who started therapy not in CHR, 45 (100%) achieved CHR, with a median time to CHR of 4 weeks. 50 patients have been observed for≥3 months and are thus evaluable for cytogenetic and molecular response. An MMR was achieved in 41 (82%) of 50 evaluable patients and complete molecular response was achieved in five patients (10%). The higher number of MMR in this study is probably due to use of Dasatinib as initial therapy.

Dasatinib continued to demonstrate deep and fast responses. Several studies with BCR- ABLI tyrosine kinase inhibitors (TKIs) have reported that a deep, early response predicts improved outcomes of patients with CML-CP. The achievement of BCR-ABLI transcript levels of≤10% according to the International Scale (IS) at 3 months has been associated with significantly improved PES, event-free survival and OS and a reduced risk of transformation.[9]

Treatment options are limited for patients with Imatinib-resistant or intolerant accelerated phase chronic myeloid leukemia (CML-AP). Dasatinib is a novel, potent, oral, multitargeted kinase inhibitor of BCR-ABL and SRC-family kinases that showed marked efficacy in a phase I trial of patients with Imatinib-resistant CML.[20]

Overall these data indicates that Dasatinib has a similar potential for efficacy in the majority of patients with Imatinib resistance. Alternative treatment options should be considered for patients with baseline mutations that are clearly associated with resistance to Dasatinib or lower levels of response, that is, T3151.[16]

The duration of the study and study population is very small. So further study is required with large number of study population and with prolonged duration were the limitations of the study.

CONCLUSION

This analysis shows that Dasatinib induces rapid MMRs in a high proportion of patients with CML-CP after resistance, suboptimal response or intolerance to Imatinib. Progression-free survival is most favarable in patients who have achieved MMR or CCyR within 12 months. Overall, the results of this analysis demonstrate that Dasatinib is an effective treatment for the majority of patients with CML-CP who have developed an Imatinib-resistant BCR-ABL mutation and is associated with durable responses and favorable long-term outcomes.

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