Online Journal of Health and Allied Sciences
Peer Reviewed, Open Access, Free Online Journal
Published Quarterly : Mangalore, South India : ISSN 0972-5997
Volume 11, Issue 4; Oct-Dec 2012

Original Article:

Chronic Myeloid Leukemia with Variant Chromosomal Translocations: Results of Treatment with Imatinib Mesylate.

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Citation
Bhise R, Purohit S, Lokanatha D, Jacob L, Suresh TM, Govind Babu K, Babu S, Lakshmaiah KC. Chronic Myeloid Leukemia with Variant Chromosomal Translocations: Results of Treatment with Imatinib Mesylate. *Online J Health Allied Scs.* 2012;11(4):5. Available at URL:http://www.ojhas.org/issue44/2012-4-5.html

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Submitted: Nov 2, 2012; Accepted: Jan 4, 2013; Published: Jan 25, 2013

Abstract: Objective: To evaluate the efficacy of imatinib in chronic myeloid leukemia patients with variant translocations. **Methods:** Forty eight chronic myeloid leukemia patients carrying variant translocations and treated with imatinib at our institute were considered for the study. Survival and response rates were evaluated. **Results:** The median follow up was 48 months(m). Forty three (89.58%) patients achieved complete hematologic response. Thirty one (64.58%) patients achieved complete cytogenetic response and 19(39.58%) achieved major molecular response anytime during their follow up period. Only 18.75% of the patients achieved complete cytogenetic response and major molecular response within the stipulated time frames. The estimated overall survival at 48 m median follow up was 81.2%.The progression free survival was also 81.2% and the event free survival was 79.1%.There was no significant survival difference between low vs intermediate and high risk sokal group. **Conclusion:** We report suboptimal responses to imatinib in chronic myeloid leukemia with variant translocations. Further studies with imatinib and the newer more active drugs dasatinib and nilotinib are justified.
Key Words: Chronic myeloid leukemia; Imatinib; Variant translocation

Introduction:
Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by the presence of the Philadelphia (Ph) chromosome resulting from the reciprocal translocation t(9; 22) (q34; q11).[1,2] The molecular consequence of this translocation is the generation of the BCR-ABL fusion gene, which encodes a constitutively active protein tyrosine kinase. Although the vast majority of patients with CML show the classical t (9; 22) (q34; q11) translocation, variant Ph translocations are present in 5%-10% of CML cases. In these cases, one or more additional chromosomes are added to 9 and 22 and these are involved in the translocation.[3-5] In almost all the cases with variant Ph chromosome, the BCR-ABL rearrangement can be detected by molecular methods or by fluorescence in situ hybridization (FISH). Evaluation of the prognostic significance of these translocations has been analyzed in case reports or small series giving controversial results.

We report our experience with 48 CML patients carrying variant translocations treated with imatinib as a first-line therapy. To our knowledge this is the first study from India and the single largest report from Asia on CML patients carrying variant cytogenetics and treated with imatinib.

Patients and methods

Patients: Between January 1998 and September 2011, 735 patients were diagnosed with CML at our institution.Amongst these patients we identified 75(10.20%) patients with variant cytogenetics. Twenty seven patients were treated with hydroxyurea alone and excluded from the study. Forty eight patients were hence considered for the study. Written informed consent was obtained before treatment initiation from every patient and the study was approved by the institutional review board.

Treatment Monitoring and Definition of Response: Blood count and serum chemistry were performed at enrolment. They were then followed up with monthly blood counts. A complete hematologic response (CHR) was defined as a white blood cell count of less than $10x10^9$/L, a platelet count of less than $450x10^9$/L, no immature cells (blasts, promyelocytes, or myelocytes) in the peripheral blood, and the disappearance of all signs and symptoms related to leukaemia (including palpable splenomegaly).

Conventional cytogenetics on bone marrow was done at baseline, after 6 and 12 months of treatment, and every yearly thereafter or in case of failure or disease progression. Cytogenetic response, based on the results of conventional banding analysis, was identified as complete (CCyR) when no Ph positive metaphases were identified after analysis of atleast 20 metaphases.[6,7] Real-time quantitative PCR(q-PCR) was performed on peripheral blood at baseline and every 6 months thereafter. The molecular response was defined as major (MMR) if the BCR-ABL/ABL ratio was 0.10% or less on the International Scale.[8-10]

Definition of Progression and Events: Progression was defined as progression to accelerated/blast phase or death during follow up.Progression to the accelerated phase was defined using WHO criteria as one or more of the following : blasts 10%-19% of peripheral blood white cells or bone marrow cells, or peripheral blood basophils of at least 20% or persistent thrombocytopenia ($100\ x10^9$/L) unrelated to therapy or persistent thrombocytosis ($1000\ x10^9$/L) unresponsive to therapy or increasing spleen size and increasing WBC count unresponsive to therapy or cytogenetic evidence of clonal evolution or megakaryocytic proliferation in sizable sheets and clusters, associated with marked reticulin or collagen fibrosis, and/or severe granulocytic dysplasia. Blast phase was identified by a blood or bone marrow myeloblast percentage of $\geq$ 20%, or by any extramedullary blast involvement or large foci or clusters of blasts in bone marrow biopsy.[11] Events included progression, death and loss of CHR, loss of MMR or CCyR.

Statistical Analysis: Overall survival (OS) was defined as the time since the treatment began to the last follow up. OS, progression free survival (PFS) and event free survival (EFS) curves were plotted according to the methods of Kaplan and Meier. Sokal score was analysed for an association with survival, using the log-rank test. Stata (version 11.2) software was used for statistical analysis.

Results

Patient Characteristics: Characteristics of the patients are described in Table 1. Forty six (95.84%) patients presented in chronic phase, 1(2.08%) patients in accelerated phase and 1 (2.08%) in blast phase. The median follow up period was 48m with a range of 4-102m.

Table 1: Baseline clinical features of the patients

Total number	48
Age(years)	
Median	40
Range	12-67
Sex	
Male	32(66.66%)
Female	16 (33.33%)
Spleen size(cm)	
Median	12
Range	0- 20
Blasts(%)	
Median	3
Range	1-60
Sokal score	
Median	0.62
Range	0.45-2.57
Sokal score	
High	2(4.16%)
Intermediate	6(12.5%)
Low	40(83.33%)

Efficacy Results: Response rates are described in Table 2. Forty three (89.58%) patients achieved CHR. Five (10.42%) patients did not achieve CHR. The median time to achieve CHR was 1m.Of the five patients who did not achieve CHR two died at 4m, one at 7m and one at 15 m follow up. The last patient is still alive at 25 m follow up. Out of the 43 patients who had achieved CHR 4 patients lost CHR during their follow up. Out of them only 1 patient had achieved CCyR, 1 patient was on irregular treatment and 1 patient progressed to blast crisis.

Table 2: Response rates

Milestone	Status	Number(%)	Median time to achieve the milestone(m)
CHR	Achieved	43(89.58)	1
	Not achieved	5(10.48)	
CCyR	Achieved	31(64.58)	15
	Not achieved	17(35.42)	
MMR	Achieved	19(39.38)	
	Not achieved	29(60.62)	19

Of the 48 patients 31(64.58%) patients achieved CCyR anytime during their follow up period. Seventeen(35.42%) patients did not achieve CCyR. The median time to achieve CCyR was15m. The range was 4- 27 m. Only 9 (18.75%) patients achieved CCyR within 12 m. Of the 17 patients who did not achieve CCyR, 3 patients had multiple interruptions during their treatment (2 patients due to imatinib toxicity,1 patient due to lack of compliance), 3 patients died before 1 year of treatment. Only 2 patients who achieved CCyR died during follow up.

The median time to achieve MMR was 19m. Nineteen(39.58%) patients achieved MMR anytime during their follow up. Nine (18.75%) patients achieved MMR within 18 m. Twelve patients who had achieved CCyR did not attain MMR.

Eleven (22.9%) patients progressed during their follow up. Nine (18.75%) patients died and 2 patients progressed to

blast crisis(one at 79m and the second at 84 m). Out of the 9 patients who died 3 died within a year of treatment. Imatinib resistance mutation analysis was done in 5 patients. All of the tests were negative for mutations.

The estimated OS at 48 m median follow up was 81.2% (Figure 1). There was no significant survival difference between patients with low versus intermediate and high risk sokal group (p=.608). The estimated PFS(Figure 2) was also 81.2%. Again there was no significant PFS difference between low versus high and intermediate risk sokal group (p= .813). The estimated event free survival was 79.1%(Figure 3). There was no significant event free survival difference between low vs intermediate and high risk sokal group (p=.551).

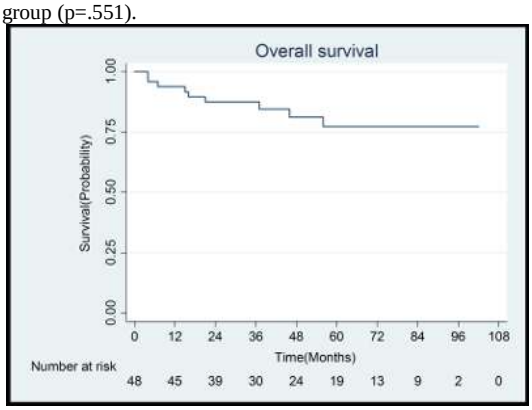

Figure 1: Overall Survival

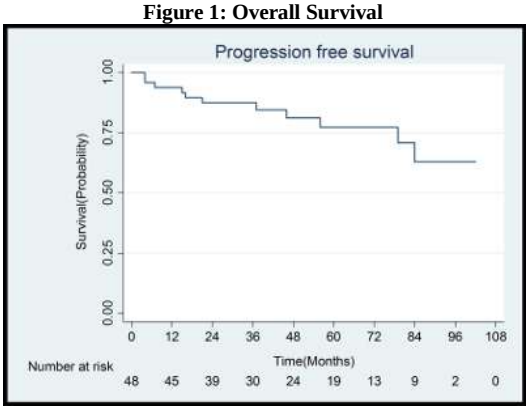

Figure 2: Progression Free Survival

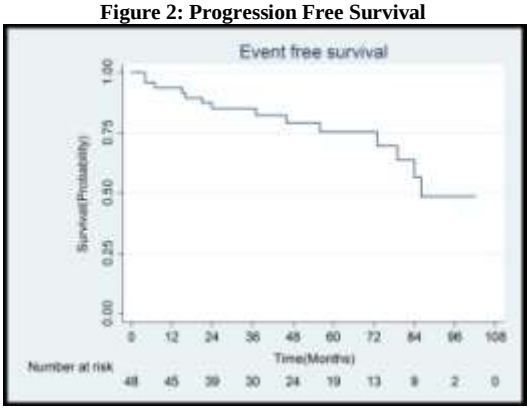

Figure 3: Event Free Survival

One patient had blast crisis (60% blasts) at presentation. He did not achieve CHR anytime during follow up and died at 21 m. Another patient who presented with accelerated phase (10% blasts) achieved CHR within a month, CCyR at 4 m and MMR at 9m and continued to be in CCyR and MMR at his last follow up(32m).

Discussion

Variant translocations are found in 5-10% of CML patients at diagnosis. Many studies have been published on their prognostic significance but there is limited data on their response to imatinib. A previous analysis reported 44 cases with variant translocations in a series of 721 patients (4%) who had failed prior interferon therapy and were either in chronic phase or the accelerated phase. No differences in outcome were evident in that study. Multivariate analysis showed that the variant translocations had no impact in response rate, OS, or duration of response when the patients were treated with imatinib.[11]

Another report described 10 CML patients carrying variant translocations among 153 newly diagnosed CP cases (6.5%). Only 2 patients achieved an optimal response to tyrosine kinase inhibitor (imatinib and nilotinib) treatment according to European Leukemia Net (ELN) recommendations in that study.[13] The investigators assumed that the involvement of additional chromosomes in the BCR/ABL rearrangement could adversely affect outcome when a selective tyrosine kinase inhibitor such as imatinib was used, because these genetic changes might be markers of genomic instability and can be considered as clonal evolution. The results of our study also suggest high rates of suboptimal response as only 18.75% of our patients achieved CCyR and MMR within the stipulated time frames.

Another study was published by the GIMEMA working party on CML analysis.[14] The study included 30 patients with variant cytogenetics. The median follow up in that study was 61m.Overall 93% patients achieved CHR, 83% patients achieved CCyR and MMR anytime during the follow up. In the present study we report inferior results as compared to the above study. In our study though 89.58% patients achieved CHR, the rates of CCyR and MMR were far lower (64.58% and 39.58% respectively). The results can be considered inferior again because our study had more patients with low risk sokal score(83.33%) as compared to that in GIMEMA group(43%).

In conclusion, we report suboptimal responses to imatinib in CML with variant translocations. Contradictory results continue to be published in this setting. Further studies with imatinib and the newer more active drugs dasatinib and nilotinib are required to clarify the issue.

Table 3: Cytogenetic abnormalities in patients with variant translocations	
46,XY,t(9;11;14;22)(q34;p14;q21;q11)	46,XY,t(9;12;22)(q34;q12;q11)
46,XY, t(2;9;22)(p22;q34;q11)	46,XY,t(9;12;22)(q34;q13;q11)
46,XX,t(9;19;22)(q34;q13;q11)	46,XY,t(9;19;22)(q34;q1;q11)
46,XY,t(14;9;22)(p11;q34;q11)	46,XX,t(9;15;22)(q24;q22;q11)
46,XY,t(1;5;9;18;22)(p22;q28;q34;q11;q11)	46,XY,t(9;19;22)(q34;q13;q11)
46,XY,t(9;14;22)(q34;q32;q11)	46,XX,t(7;9;12;22)(q22;q34;q13;q11)
46,XY,t(9;15;22)(q34;q22;q11)	46,XX,t(9;16;22)(q34;q24;q1)
46,XX,(t7;9;22)(q22;q34;q11)	46,XY,t(4;9;22)(q21;q34;q11)
46,XX,t(9;18;22)(q34;q12;q11)	46,XY,t(9;11;22)(q34;q13;q11)
46,XX,t(4;9;22)(q11;q34;q11)	46,XY,t(1;9;22)(q32;q34;q11)
46,XX,t(9;?;22)(q34;?;q11)	46,XY,t(1;9;22)(p36;q34;q11)
46,XY,t(7;9;22)(p15;q34;q11)	46,XX,t(9;11;22)(q34;p11;q11)
46,XX,t(9;?;22)(q3;q?;q11)	46,XY,t(1;9;22)(p13;q34;q11)
46,XX,t(9;13;22)(q34;q14;q11)	46,XY,t(6;9;22)(q26;q34;q11)
46,XY,t(9;?;22)(q34;q?;q11)	46,XY,t(9;8;22)(q34;q24;q11)
46,XY,t(19;9;22)(p13;q34;q11)	46,XY,t(9;14;22)(q34;q24;q11)
46,XX,t(1;9;22)(q22;q34;q11)	46,XX,t(9;?;22)(q34;?;q11)
46,XY,t(1;14;9;22)(p13;q12;q34;q11)	46,XY,t(6;9;22)(q23;q34;q11)
46,XY, t(3;9;22)(q25;q34;q11)	46,XY,t(3;9;22)(p21;q34;q11)
46,Y,t(X;9;22)(p11;q34;q11)	46,XY,t(12;9;22)(q24;q34;q11)
46,XY, t(9;22;11)(34;q11;p13)	46,XY,t(3;9;22)(q22;q34;q11)
46,XY,t(9;15;22)(q34;q22;q11)	46,XX,t(9;13;19;22)(q22;q14;13;q11)
46,XX,t(9;11;22)(q34;q25;q11)	46,XY,t(3;9;22)(p11;q34;q11)
46,XY,t(9;19;22)(;q34;p13;q11)	46,XX,t(3;9;21;22)(q21;q34;q22;q11)

Acknowledgements

We are grateful to Max Foundation of India for providing free imatinib for patients in this study and Dr V.Shanmugam for his help with statistical analysis.

Disclosure

We declare no conflicts of interest.

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