Original Article

Correlation of Bone Marrow Morphological Changes with Cytogenetic and Molecular Response in Imatinib (TKI) Treated Chronic Myeloid Leukaemia Patients : A Prospective Study from Tertiary Care Center of Eastern India

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Background : Imatinib is an effective first-line Tyrosine Kinase Inhibitor (TKI) in Chronic Myeloid Leukaemia (CML). This drug induces haematological, cytogenetic and molecular responses in most patients.

Aims and Objectives : This prospective observational single arm study was done to evaluate the morphological changes in bone marrow of CML patients treated with Imatinib and to correlate these changes with the Cytogenetic and Molecular (BCR-ABL1) response.

Materials and Methods : 51 patients of CML on treatment with Imatinib at doses of 400 mg per day were evaluated for cytogenetic, BCR-ABL1 (RT-PCR) and Bone Marrow Morphological Changes at 6 months of therapy.

Results : Morphological changes observed in the bone marrow at the end of six months of therapy were reduction in cellularity, reduction in the M:E ratio, normalization of megakaryocytic morphology, variable decrease in angiogenesis and Bone Marrow reticulin fibrosis. In our study, 96% (49 out of 51) patients showed complete haematological response at 3 months and 58.8% showed major cytogenetic response at the end of six months of treatment. BCR-ABL1 response was optimal in 49%, warning in 11.8% and failure in 39.2% cases. None of the morphological changes had any significant correlation and association with the patients' Cytogenetics and BCR-ABL1 response. Significant ($p<0.001$) strong positive correlation and association was observed between Cytogenetics and BCR-ABL1 response.

Conclusion : Apparently everything like morphology, cytogenetics and BCR-ABL decreases or responds with TKI but significant positive correlation and association was observed only between cytogenetics and BCR-ABL1 response; these have no clear correlation and association with morphological changes.

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Key words : TKI, Bone Marrow Morphological Changes, Cytogenetic Response, BCR-ABL1, CML.

Chronic Myeloid Leukaemia (CML) is a myeloproliferative neoplasm and clonal stem cell disorder which is associated with the BCR-ABL1 fusion gene located on the Philadelphia chromosome t(9;22)[1]. Breakpoint Cluster Region-Abelson (BCR-ABL) fusion protein leads to constitutive activation of receptor tyrosine kinase and acts as an oncogene in the hematopoietic stem cells. Imatinib mesylate binds and inhibits the ATP binding site of the BCR-ABL kinases[2]. Imatinib mesylate, a first generation Tyrosine Kinase Inhibitor (TKI), has been widely used and it induces high frequency of hematologic, cytogenetic and molecular remission[3]. At diagnosis, Bone Marrow in CML is markedly hypercellular with marked myeloid hyperplasia. Erythropoiesis usually is decreased and megakaryocytes are normal or increased in number. Dysplasia is also seen[1]. Variable reticulin fibrosis is seen in trephine biopsy. The Bone Marrows of CML patients have more angiogenesis and have a higher micro-vessel density compared to healthy controls[4]. Our aims and objectives were to evaluate the morphological changes in the peripheral

Editor's Comment :

- Apparently everything like morphology, cytogenetics and BCR-ABL decreases or responds with Tyrosine Kinase Inhibitor (TKI) but significant positive correlation and association was observed only between cytogenetics and BCR-ABL1 response.
- Chromosomal analysis and BCR-ABL1 parameter have no clear correlation and association with morphological changes. But bone marrow study helps us to understand the disease tempo and phases, additional chromosomal abnormality with adverse outcome, effects of drug toxicity like cytopenia in patients on TKI therapy.

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blood and Bone Marrow (including angiogenesis) of patients of CML treated with Imatinib Mesylate and to correlate these changes with the Cytogenetic Response and Molecular Response.

Materials and Methods

This prospective Observational Study was done on 51 patients of CML at the department of Haematology. The patients of CML in chronic or accelerated phase (either pre-treated with hydroxyurea or newly diagnosed) received 6 months of Imatinib and were analysed for Cytogenetic response. Standard criteria were used to determine the phase of the disease[1]. Patients already receiving imatinib or other TKIs for more than 6 months or patients with treatment failure/ suboptimal response were excluded from the study. To maximise sample size of the study, all patients of CML, who were registered at the hospital and fulfilled the inclusion criteria of the study were recruited. Written informed consent was obtained from all patients for participation in the study and for the use of patient data for research and educational purposes. All study protocols and procedures were as per the guidelines laid down in the Declaration of Helsinki, 1975, further revised in 2013.

The parameters studied were peripheral blood changes, morphological changes in the Bone Marrow and Cytogenetics at 6 months. Complete Blood Counts were monitored fortnightly till patient achieved Complete Haematological Remission (CHR) and then monthly. CHR was defined as Total Leucocyte Count <10,000/cumm, platelet count <4,50,000/cumm, no immature cells in peripheral blood and absence of splenomegaly[5]. Partial Haematological Response (PHR) was defined as >50% reduction in Total Leucocyte Count from pre-therapy levels, presence of circulating immature granulocytes and/or persistence of splenomegaly[5]. Bone Marrow aspiration and biopsy was done at diagnosis and at 6 months of therapy for morphological as well as cytogenetic evaluation. Response to Imatinib as assessed by bone marrow morphological changes at 6 months was scored using the criteria given by Lugli, *et al*[6]. The parameters included: increased cellularity, M:E ratio >4, fibrosis > grade 2, more than 10% abnormal megakaryocytes, blasts > 5% and basophils > 1%. Each of the 6 criteria were given 1 point and the total score was calculated. A score of 0 meant complete morphological response while higher scores implied poor response to therapy. Immuno-histochemistry with Cluster of Differentiation (CD) 34 (applied as the endothelial antigen of choice) was done on the Bone Marrow biopsies for evaluation of micro vessel density. The morphological changes were noted and then correlated with the Cytogenetic and Molecular Response according to ELN guidelines [complete cytogenetic response: no Philadelphia (Ph)+ metaphases; partial cytogenetic response: 1-35% Ph+ve; minor cytogenetic response: 36-65% Ph+ve; minimal cytogenetic response: 66-95% Ph+ve and nil cytogenetic response: >95% Ph+ve. Optimal BCR-ABL1 at 6 th month <1%, warning 1-10% & failure >10%] to assess response to therapy[5].

Statistical Analysis :

The data was analysed using IBM SPSS statistics software, version 19. The continuous and quantitative variables were expressed as mean ± Standard Deviation and categorical variables were expressed in terms of frequency and percentages. Associations between two categorical variables were assessed by Chi-square (χ^2) test, and correlations were judged by Spearman's rank order correlation (ρ) coefficients. Paired 't' tests were used to compare the continuous variables before and after therapy. P value of 0.05 or less was considered for statistical significance.

Results

Patient Characteristics and Response to TKI Therapy :

The mean age of the total cohort of 51 patients was 32 years with an age range of 11-74 years and a Male: Female ratio of 1.31 [29 males (56.8%) & 22 females (43.1%)]. Forty-five patients were in chronic phase and 6 were in accelerated phase at the time of diagnosis. None of the patients had blast crisis. A total of 49 (96%) patients showed CHR at a median period of 3 months (range 1 to 4 months) with imatinib treatment. Bone marrow examination done at end of study period (after Imatinib therapy for 6 months) showed morphologic score 0 in all patients with CHR and a score of 3 in the 2 patients with PHR (Table 1). At six months of treatment, complete, partial, minor, minimal and no cytogenetic response was seen in 23 (45.2%), 7 (13.7%), 8 (15.7%), 4 (7.8%) and 9 (17.6%) patients respectively (Table 1). Six out of the 51 patients (11.7%) developed additional cytogenetic abnormalities which included multiple breaks, trisomy 8, tetraploidy along with trisomy 8, deletion Y, +mar, hyperdiploidy, additional Ph (Fig 4) and 9qh+. Out of these six patients, four had Complete Cytogenetic Response (Ph+ 0%), one patient had no response (Ph+ 100%) and one patient showed minimal response (Ph+ 70%). BCR-ABL1 response was optimal in 49%, warning in 11.8% and failure in 39.2% cases (Table 1).

Table 1 — *Patient characteristics and response to TKI*

Parameter		Patients (n=51)
Sex :	Male	29
	Female	22
	Male: Female	1.31
Phase of disease at enrolment :		
	Chronic phase	45
	Accelerated phase	6
	Blast crisis phase	0
Haematological Response to TKI :		
	CHR (morphological score[#])	49*
	PHR(morphological score[#])	2
Cytogenetic response at 6 months :		
	Complete response	23 (45%)
	Partial response	7 (13.7%)
	Minor response	8 (15.7%)
	Minimal response	4(7.8%)
	No response	9(17.6%)
BCR-ABL transcript at 6 months (% IS) :		
	Failure	20 (39.2%)
	Optimal	25(49%)
	Warning	6(11.8%)

* = Median time to attain response = 3 months, range= 1-4 months
[#] = Morphological score – as per criteria proposed by Lugli *et al*[6]
% = Percentage in parentheses: Mean BCR-ABL transcript (IS ratio) of the patients assessed

Bone Marrow Morphological Changes :

(1) Bone Marrow Cellularity :

Prior to treatment, all patients had Panmyelosis. Normalisation of bone marrow cellularity occurred in 27 patients (52.9%). Twenty-two patients (43.1%) developed Bone Marrow Hypoplasia (Table 4) during therapy out of which 3 patients also developed pancytopenia, necessitating therapy interruption for 2 to 4 weeks. Platelet and neutrophil counts recovered and were maintained after resumption of therapy in 2 patients, while they remained low in the third patient. In another 7 cases, either Leucopenia or Thrombocytopenia (<40,000/cmm) occurred, necessitating cessation of imatinib therapy for 1-2 weeks during the study period. No patient developed severe hypoplasia (<5%cellularity). Two patients (3.9%), however, had increased cellularity even after 6 months of therapy, but remained in CHR (Figs 1A-1C).

(2) Myeloid/Erythroid (M:E) Ratio :

The pre-treatment bone marrow M:E ratio more than 5:1 in 50/51 patients. During imatinib therapy, the marrow exhibited a relative decrease in myeloid and an increase in erythroid elements respectively. The M:E ratio decreased to less than 5:1 in 44 patients (86.27%) after 6 months of therapy (at 6 months of therapy, mean M:E ratio = 2.7:1). These changes were seen in patients treated in all phases of CML. Relative erythroid hyperplasia (myeloid/erythroid ratio $\leq$1) developed in 12 patients (23.5%)(Table 2).

(3) Bone Marrow Reticulin Fibrosis :

Out of 51 patients, 36 showed Myelofibrosis in the pre-treatment biopsies. Resolution of Reticulin Fibrosis occurred in 25 (69.4%) patients (Table 2). Two patients had a reduction of at least 2 reticulin grades from an initial grade-3 myelofibrosis after 6 months of therapy (Figs 2A-2C). On the contrary, development of myelofibrosis during therapy was uncommon and was a relatively late event, occurring in 5 patients in 6 months of therapy.

(4) Megakaryocyte Changes :

Thirty-nine patients (76.47%) had abnormal megakaryocyte morphology (>50% Megakaryocytes with monolobated nuclei) on the pre-treatment biopsies. Out of these, morphology in 38 (97%) patients normalized (<25% monolobated forms) after 6 months of therapy (Table 2). These morphologic changes did not always coincide with a decrease in megakaryocyte number. Out of the 51 patients, 45 had increased megakaryocyte numbers ($\geq$3/low

Table 2 — *Correlation and association analyses of morphological changes with cytogenetic response and BCR-ABL1 response*

		Complete cytogenetic response	Partial cytogenetic response	BCR-ABL1 Optimal response
Morphological features	Number of Cases (percentage)	23 (45.1)	7 (13.7)	25 (49.0)
Normalization of cellularity	27 (52.9)	ρ: P value = 0.517 χ^2: P value =0.507	ρ: P value = 0.815 χ^2: P value = 0.811	ρ: P value = 0.218 χ^2: P value =0.210
Marrow hypoplasia	22 (43.1)	ρ: P value = 0.549 χ^2: P value =0.540	ρ: P value = 0.987 χ^2: P value =0.987	ρ: P value = 0.218 χ^2: P value =0.210
Relative erythroid hyperplasia	12 (23.5)	ρ: P value = 0.302 χ^2: P value =0.292	ρ: P value = 0.544 χ^2: P value =0.535	ρ: P value = 0.168 χ^2: P value =0.162
Resolution of reticulin fibrosis	25 (49.0)	ρ: P value = 0.880 χ^2: P value =0.877	ρ: P value = 0.253 χ^2: P value =0.244	ρ: P value = 0.214 χ^2: P value =0.206
Reduction in megakaryocyte number	40 (78.4)	ρ: P value = 0.044 χ^2: P value =0.043	ρ: P value = 0.146 χ^2: P value =0.140	ρ: P value = 0.353 χ^2: P value =0.343
Normalization of megakaryocyte morphology	38 (74.5)	ρ: P value = 0.473 χ^2: P value =0.463	ρ: P value = 0.099 χ^2: P value =0.096	ρ: P value = 0.694 χ^2: P value =0.687

Spearman rank correlation coefficient (ρ); Pearson Chi-square (χ^2)

power field) on the pre-treatment biopsy specimens (Table 2). Of these, 40 (88.9%) showed a decrease in megakaryocyte numbers to <3/low power field and absence of clustering after 6 months of imatinib therapy.

(5) Lymphopoiesis :

Increase in the lymphocytes was evident in only 3 cases (5.88%) and two of them showed major cytogenetic response (one complete response and another partial response). One patient showed no response.

(6) Micro Vessel Density (MVD) :

Angiogenesis was studied in the form of Micro Vessel Density by CD34 immunostaining. Micro vessel density was measured as CD34 stained vessels/mm^2 area of Bone Marrow Biopsy section observed in high power (magnification x 400)[7]. Mean MVD was decreased from 20.28 to 5.52 after 6 months of imatinib therapy which was statistically significant (Table 3, Figs 3A-3D).

By doing paired 't' test we found significant (P<0.001) differences in Bone Marrow Morphological parameters, cytogenetics and BCR-ABL1 (continuous variables) before and after therapy (Table 3).

Correlation of Morphologic Changes with Cytogenetic Response & Molecular Response :

None of the above-mentioned morphologic changes had any significant correlation and association with cytogenetic and BCR-ABL1response (Table 2).

Correlation of Cytogenetic Changes with Molecular Response :

Significant (ρ=0.901, P<0.001) strong positive correlation and association was observed between cytogenetics and BCR-ABL1 response (Table 4).

Table 4 — *Statistical relation between post therapy BCR-ABL1 response and cytogenetic response*

Cytogenetic response	BCR-ABL1 Response			
	Optimal	Warning	Failure	Total
Complete	22 (88.0)	1 (16.7)	0 (0.0)	23 (45.1)
Partial	3 (12.0)	3 (50.0)	1 (5.0)	7 (13.7)
Minor	0 (0.0)	1 (16.7)	7 (35.0)	8 (15.7)
Minimal	0 (0.0)	1 (16.7)	3 (15.0)	4 (7.8)
No response	0 (0.0)	0 (0.0)	9 (45.0)	9 (17.6)
Total	25 (100.0)	6 (100.0)	20 (100.0)	51 (100.0)

Spearman rank correlation coefficient (ρ)=0.901 and P<0.001;
Pearson Chi-square (χ^2)= 53.708 and P <0.001;
Column percentage in the parentheses.

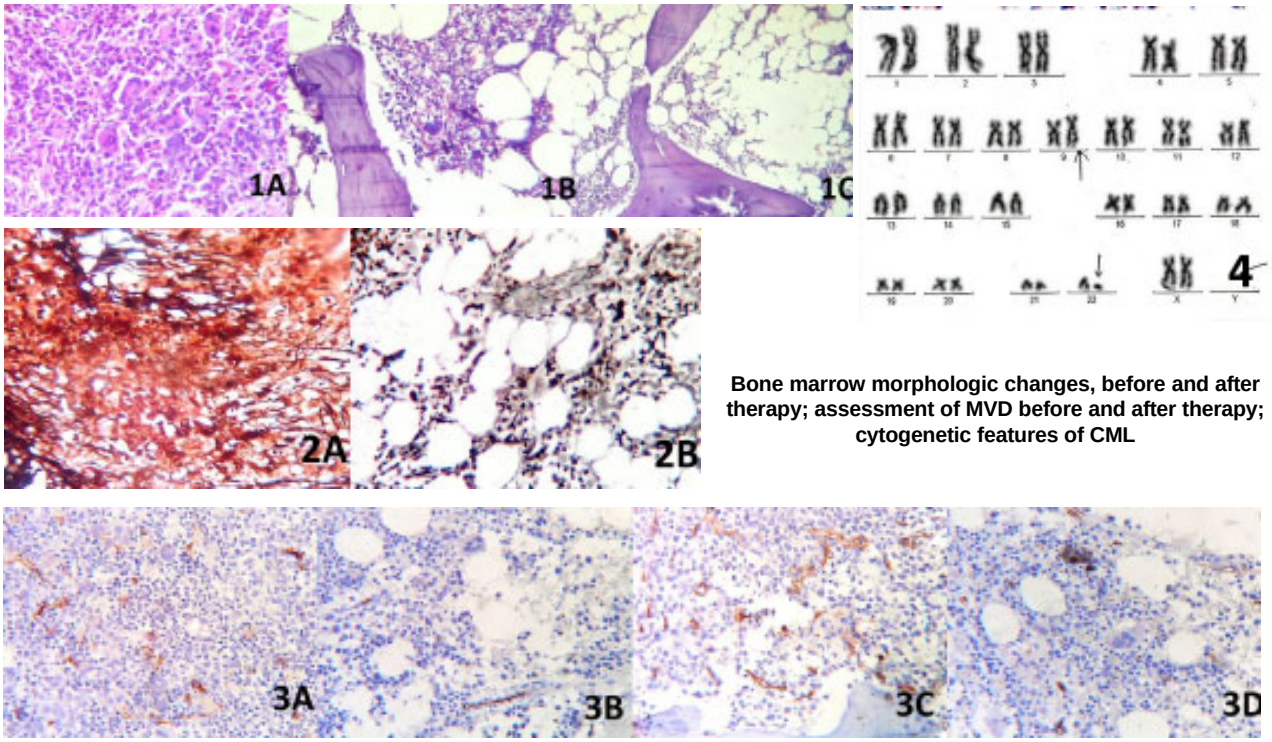
Discussion

Imatinib is a landmark target specific drug in CML which has been designed specifically against a selective domain (BCR-ABL Tyrosine Kinase). Additional to this specific activity, other Tyrosine Kinases namely Platelet Derived Growth Factor (PDGF) receptor and c-kit are also affected which might reflect the effects of this drug on the non-neoplastic marrow elements[8]. On the contrary, hydroxyurea and interferon-alpha treated CML patients show normalization of counts in peripheral blood and marrow but rest of the abnormalities persist[2].

There are previous reports on Bone Marrow Morphological changes in imatinib treated CML patients and their correlation with the Cytogenetic response, with variable results. Pandey N et al studied with inexhaustive morphological changes with genetic markers for response assessment[9]. But our study is the first of its kind in Eastern India with robust data in detail. Previously, Lugli, *et al* developed a prognostic scoring system for morphological changes and found good correlation with cytogenetic response[6]. It was validated by other authors. Srinivas, *et al* examined 40 marrow samples of CML patients and found a significant positive correlation of morphologic changes such as normalization of cellularity, basophils, megakaryocytes and M:E ratio, reduction of blasts, absence of dry tap and reduction in fibrosis with Cytogenetic Response[10]. Hasserjihan, et al showed similar reduction in the overall marrow cellularity, M:E ratio, marrow fibrosis and megakaryocyte number in their study and in addition showed that patients whose marrow cellularity decreased to 50% or less were found more likely to have a cytogenetic response (p= 0.04)[3]. However, we found no such correlation. Similar to our study, Joshi, *et al* also failed to show any significant correlation of morphological changes with Cytogenetic Response[11]. Braziel, *et al*, McNamara, *et al* and Frater, *et al*, have all reported insignificant changes in the Bone Marrow of Imatinib treated patients beyond the first five months of therapy[2,12-14]. In

Table 3 — *Paired 't' test*
Comparison of parameters (continuous variables) before and after therapy

Parameters	Before therapy Mean, SD	After therapy Mean, SD	't' value of paired t test	P value of paired t test
Cellularity	95.29; 7.31	45.78; 19.06	17.967	P <0.001
M:E ratio	33.94; 24.43	2.72; 1.96	9.297	P <0.001
Megakaryocyte number (per mm^2)	58.33; 36.91	21.43; 5.99	7.351	P <0.001
BCR-ABL1 level	95.36; 9.78	8.59; 9.69	44.002	P <0.001
Cytogenetics	99.12; 5.6	33.78; 39.45	11.331	P <0.001
Microvessel density	20.28; 5.44	5.52; 3.79	22.545	P <0.001



Bone marrow morphologic changes, before and after therapy; assessment of MVD before and after therapy; cytogenetic features of CML

Fig1 — BM biopsy **A.** pre-treatment BM - increased cellularity & dyspoietic megakaryocytes (H&E, x400). **B.** BM post-therapy - normal cellularity & megakaryocytes (H&E, x 400). **C.** BM with hypoplasia. (H&E, x 100)
Fig 2 — BM biopsy showing fibrosis (reticulin stain x400). **A**. Pre-treatment - Myelofibrosis grade 3 **B**. Myelofibrosis grade 1 post therapy.
Fig 3 — CD34 IHC showing micro vessels (x 400). **A & C**. Increased MVD pre-therapy **B & D**. Reduced MVD post-therapy.
Fig 4 — G-banding: 46, XX, t(9;22) (q34;q11)

our study CHR at six months of therapy were seen in all six patients with accelerated phase of CML. Bone Marrow changes in these patients, after 6 months, were to some extent similar to that seen in chronic-phase CML prior to start of therapy.

Varying degrees of myelosuppression were seen in 43% of our patients. This however, was not found to have any adverse effect on the Cytogenetic Response. In contrast, Sneed, *et al* described myelosuppression as an independent poor prognostic factor[15]. With regard to relative increase in lymphocytes, Joshi, *et al* reported that all patients in their study had increase in peripheral blood as well as marrow lymphocytes. However, there was no significant correlation (p=0.543) with Cytogenetic Response[11]. But we noted similar finding in only three cases (5.88%) and two of them showed Major Cytogenetic Response in our study.

Micro vessel density was decreased (Mean from 20.28 to 5.52; P<0.001) significantly in our study. Kvasnicka, *et al* reported the effect of Imatinib therapy on angiogenesis and myelofibrosis and showed that it induced a significant reduction of microvessel density and reticulin fibres after eight months of therapy. The authors also reported that most of patients with decreased Bone Marrow vascularity showed a positive association with a Complete Cytogenetic Response[7].

Pandey N, *et al*[9] showed correlation of few morphological changes with cytogenetic as well as molecular markers. On the contrary, in our study none of the above-mentioned morphologic changes had any significant correlation and association with cytogenetic and BCR-ABL1response but significant (ρ=0.901, P<0.001) strong positive correlation and association was observed between cytogenetics and BCR-ABL1 response.

Conclusion

Study of Bone Marrow morphology is essential at diagnosis and at various time points in the treatment of CML for specific indications. It helps us understand the disease tempo (including reversal of angiogenesis, reduction in micro vessel density and reversal of marrow fibrosis), additional chromosomal abnormality with adverse outcome, effects of drug toxicity and is especially of use in situations of prolonged peripheral blood cytopenia in patients on

TKI therapy. This study elucidates the fact that apparently everything like morphology, cytogenetics and BCR-ABL decreases or responds with TKI but significant positive correlation and association was observed only between cytogenetics and BCR-ABL1 response; these have no clear correlation and association with morphological changes.

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