Morphologic Changes in the Bone Marrow in Patients of Chronic Myeloid Leukemia (CML) Treated with Imatinib Mesylate

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Abstract Imatinib mesylate (Gleevec) is an effective treatment for chronic myeloid leukemia (CML). Though cytogenetic and molecular analyses are essential disease monitoring parameters in CML bone marrow morphological response is not well defined. We examined marrow samples from 40 patients with CML which have at least 2 or more follow-up marrow. A significant positive correlation with complete cytogenetic response shown for normalization of cellularity ($P = 0.0097$), absence of dry tap ($P = 0.0368$) and abnormal megakaryocytes ($P = 0.005$), reduction of blasts ($P = 0.019$), basophils ($P = 0.031$), M:E index ($P = 0.018$) and fibrosis ($P = 0.018$). Morphological criteria for complete cytogenetic response in CML patients treated with Imatinib can be defined. Morphologic response is also of potential clinical value in addition to cytogenetic and molecular response in patients of CML treated with Imatinib.

Keywords Morphology · Bone marrow · Chronic myeloid leukemia · Imatinib mesylate

Introduction

Chronic myeloid leukemia (CML) is a clonal stem cell disorder of hemopoietic stem cells, characterized by a

reciprocal translocation between chromosomes 9 and 22, $t(9;22)$ resulting in a fusion gene product BCR-ABL on chromosome 22 [1]. This gene encodes for an activated tyrosine kinase that has been associated with expansion of the pluripotent stem cells, defective adhesion and decreased apoptosis of the hematopoietic cells [2].

Imatinib mesylate (Gleevec) is a signal transduction inhibitor that specifically targets a set of protein tyrosine kinases and their oncogenic form BCR-ABL. It was demonstrated that Imatinib is superior to the standard interferon- α in combination with cytarabine in terms of cytogenetic response rates and abrogation of disease progression [3].

Disease monitoring of patients with CML during treatment with Imatinib is usually based on peripheral blood counts, cytogenetics, and molecular analysis. There is a paucity of information about changes in bone marrow morphology during such treatment. Bone marrow morphologic response lags behind peripheral blood response [4]. Though a study based on morphological response was introduced by Lugli et al. [5], it has not been in regular use.

In the present study the bone marrow cytology and histomorphology at regular intervals in patients of CML on Imatinib mesylate was reviewed. We tried to use this scoring system based on bone marrow morphologic response in correlation with cytogenetic response [5].

Materials and Methods

Patients

A total of 40 patients diagnosed as of CML were included in this study. The definition of chronic, accelerated and blast crisis was that of model proposed by WHO:

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The Inclusion Criteria

Patients diagnosed as CML (Ph+ve) in chronic, accelerated or blast crisis with 2 or more follow-up bone marrow aspirate/biopsy (2 or more) and follow-up cytogenetics were included in this study.

Exclusion Criteria

Patients previously treated with any other drugs (Busulfan/ Interferon/Hydrea.)

Characteristics of Patients

At diagnosis all the clinical, hematological and karyotyping details were noted. The laboratory parameters included complete blood picture—hemoglobin, total leucocyte and platelet count which were evaluated by the automated cell counters, standardized and regularly checked with control values. For the purpose of differentials, a manual differential count for 200 cells was done. Karyotyping was done by the conventional G-banding technique and the percentage of metaphases positive for Philadelphia chromosome was recorded.

The follow-up details were retrieved from the records of department of Pathology and Medical Oncology and included any CML related symptoms, spleen size, complete blood counts, differential counts and karyotyping results. All details were registered at the time of diagnosis, and at every follow up bone marrow evaluation.

Definitions/Response Criteria

Hematological Response [6, 7].

Complete Hematological Response (CHR)

was defined as white blood cell count $\leq 10 \times 10^9/l$, a normalized platelet count $\leq 450 \times 10^9/l$, no splenomegaly, blasts + promyelocytes + myelocytes = 0% and no CML related symptoms.

Partial Hematological Response (PHR)

was defined as at least 50% reduction of WBC (only if the WBC lower than $20 \times 10^9/l$), but with immature granulocytes in peripheral blood or splenomegaly.

A response worse than partial was classified as Nil hematological response (NHR) [8].

Cytogenetic Response

Cytogenetic response was classified according to MDACC criteria as follows [9].

Complete (CGR) no Ph+ve metaphases, Partial (PGR) 1–34% Ph+ve, Minimal (MGR) 35–95% Ph+ve, Nil (NGR) > 95% Ph+ve metaphases were present.

Major cytogenetic response was defined as the presence of CGR or PGR. [10].

Proposed Morphologic Response Score [5]

Morphologic response score was assessed based on the following parameters:

Cellularity (age-adjusted), M:E ratio >4:1, Fibrosis > grade II [11], abnormal megakaryocytes >10% of all megakaryocytes and cytologic parameters of blasts >5%, basophil count $\geq 1\%$ and presence or absence of dry tap.

Morphologic scoring system defined the morphologic response during treatment with Imatinib.

Each feature was given 1 point in case of failure of its normalization. A score of 0 point is the best value indicating morphologically complete remission. A high score indicates no morphologic response. This morphologic bone marrow response was then correlated with the cytogenetic response.

Transformation

For the purpose of study, disease transformation or progression from chronic phase to accelerated phase or blast crisis were also included.

Statistics

Morphologic features and morphologic scores among patients with complete versus other cytogenetic responses were compared by a 2-sided Fisher Exact test. A *P* value of 0.05 or less was considered statistically significant. Statistical analysis was performed by GraphPad statistical software.

Results

A total of 40 patients were included for which the follow-up data was also available. The pretreatment patient characteristics are depicted in Table 1. Age ranged from 13 to 64 years with a median age of 31 years, only 10% patients belonged to ≥ 50 years group. Male Female ratio was 2:1.

Almost all the patients presented with splenomegaly which disappeared after Imatinib therapy. Spleen size ranged between 4 and 20 cm. The hemoglobin of the patients varied from 9.8 and 15.6 g/dl. Total leukocyte count between 22,800/cumm and 2,56,000/cumm with a median of 1,29,500/cumm.

Table 1 Pre-treatment patient characteristics ($n = 40$)

Number of patients	40 (chronic phase-37; accelerated phase-3)
Age range (in years); median	13–64; 31
Male (%)	68%
Pre-treatment hematologic parameters	
Hemoglobin (g/dl), median	9.8–15.6; 11.5
Total leucocyte count (c/cumm), median	22,500–2,56,000; 1,29,000
Platelet count (c/cumm), median	1.0–5.0; 3.0
Spleen size, cm below L costal margin, median	4–20; 8.4

Treatment Response

At diagnosis, of the 40 patients, 37 were in chronic phase, and the remaining 3 in accelerated phase. All were evaluated after first and second follow up. Only 24 patients had third follow up bone marrow evaluation. The average median time was 8 months for first follow up and 16 months for second follow up. Due to financial constraints of individual patients, there was no fixed time period at which the patient had their follow-up bone marrow evaluation. After first follow up 15/37 (40.5%) achieved complete hematological response (CHR) and 22/37 (59.5%) partial hematological response (PHR). After the second follow up 28/37 (75.7%) achieved CHR and 8/37 (21.6%) PHR while 1 (2.7%) patient remained in chronic phase (NHR). Three of the patients in accelerated phase, 1 (33.3%) achieved CHR and the remaining 2 (66.7%) PHR after 1st follow up and all 3 achieved CHR after 2nd follow up (Table 2). A summary of the cytogenetic results is shown in Table 3.

Morphologic Bone Marrow Response

Bone marrow morphological response is illustrated in Table 4. From the table it is obvious that cellularity, M:E

Table 2 Hematologic Response (HR) following Imatinib therapy

At diagnosis	1st follow-up ($n = 40$)	2nd follow-up ($n = 40$)	3rd follow-up ($n = 24$)
Chronic phase (37)	CHR—15 (40.5%)	CHR—28 (75.7%)	CHR—16 (76.1%)
	PHR—22 (59.5%)	PHR—8 (21.6%)	PHR—3 (14.2%)
		CP (NHR)—1 (2.7%)	CP—1 (4.7%)
			AP—1 (4.7%)
Accelerated phase (3)	CHR—1 (33.3%)	CHR—3 (100%)	CHR—3 (100%)
	PHR—2 (66.7%)		

ratio, blasts and basophils decreased from the time of 1st diagnosis in the subsequent biopsies (Fig. 1b). Pathologically increased abnormal megakaryocytes disappeared completely in 72.5% patients at first follow up and 78.2% patients after second follow up. A fibrosis of greater than >2 was initially seen in 17.5% of patients this was reduced to 7.5% of patients after first follow up, 5.1% after second follow up, increased to 8.33% at 3rd follow up as there was one patient presenting in accelerated phase with massive fibrosis.

Marrow Morphologic Response (MMR) Scores

Patients who achieved complete hematologic response (CHR) on peripheral blood smear showed a marrow morphologic score of predominantly 0 or 1 (95.4%), very few patients (4.5%) showed ≥ 2 marrow morphologic score. Patients who achieved partial hematologic response (PHR) on peripheral blood study showed marrow morphologic score predominantly ≥ 2 (82.8%), few patients (17.1%) showed 0, 1 marrow morphologic score. One patient who continued to be in chronic phase and another who progressed to accelerated phase at the end showed marrow morphologic scores 4 and 5, respectively (Table 5).

Correlation Between Cytogenetic and Morphologic Bone Marrow Response

A significant correlation between complete cytogenetic response (CGR) and morphologic bone marrow responses was seen for all evaluated morphologic parameters. Normalization of cellularity ($P = 0.0097$), M: E index ($P = 0.018$), reduction of the abnormal megakaryocytes ($P = 0.0053$) and fibrosis ($P = 0.018$) showed a significant positive correlation with a complete cytogenetic response compared with other types of cytogenetic responses. Significant positive correlation between blasts ($P = 0.019$), basophils ($P = 0.036$) and dry tap ($P = 0.0368$) was also observed. A very significant positive correlation ($P = 0.0001$) between peripheral smear morphology and complete cytogenetic response was observed (Table 6).

Correlation of Cytogenetic Response and Morphologic Response Score

The morphologic score was evaluated in all (40) patients at first follow up for a correlation with the cytogenetic response. After first follow up 16 patients were in CHR with a median morphologic score of 1 and median cytogenetic response of grade 2. The remaining 24 patients were in PHR with a median morphologic score of 2 and median cytogenetic response of grade 3. In the second follow up, the number of CHR patients increased from 16 to 31 with a median morphologic score of 0 and median

Table 3 Cytogenetic responses at first, second & third follow up

Cytogenetic response	Score	1st follow up (<i>n</i> = 40)	2nd follow up (<i>n</i> = 40)	3rd followup (<i>n</i> = 24)
Complete cytogenetic response (0%)	1	2 (5%) All CHR	12 (40%) All CHR	14 (58.33%) 13—CHR: 1—PHR
Partial cytogenetic response (1–34%)	2	13 (32.5%) All CHR	16 (40%) 15—CHR; 1—PHR	7 (29.1%) 5—CHR: 2—PHR
Minimal cytogenetic response (35–90%)	3	25 (62.5%) 1—CHR 24—PHR	11 (27.5%) 3—CHR 8—PHR	1 (4.1%) 1 CHR
Nil cytogenetic response (>90%)	4	—	1 (2.5%) CP	2 (8.33%). 1 CP: 1-AP

Table 4 Bone marrow morphology and cytogenetics during treatment with Imatinib; Comparison between present study (*n* = 40) and study by Lugli et al 2005

Morphologic parameters	Present study				Lugli et al.			
	At diagnosis	1st FU	2nd FU	3rd FU	At diagnosis CP (<i>n</i> = 21) Adv (<i>n</i> = 18)	Week 13 CP (<i>n</i> = 14) Adv (<i>n</i> = 15)	Week 25 CP (<i>n</i> = 19) Adv (<i>n</i> = 14)	Week 49 CP (<i>n</i> = 21) Adv (<i>n</i> = 10)
Increased cellularity (age-related)	100	20.4	15.7	12.3	86 89	14.3 53.3	5.6 18.1	6.3 22.2
M:E ratio > 4:1	100	35.1	25.6	16.8	95 83	64.3 46.7	11.1 16.7	12.5 66.7
Dry tap	42.9	35.1	20.5	12.5	9.5 39	14.3 33.3	15.8 42.9	23.8 40.0
Blast count > 5%	17	10.6	7.1	4.1	10.5 72.7	8.3 30.0	6.3 37.5	12.5 16.7
Basophil count ≥ 1%	61	25.5	17.5	9.3	57.9 72.7	25.5 45.5	25.0 50.0	18.8 33.3
Abnormal megakaryocytes	100	27.5	21.8	20.8	100 100	71.4 63.6	47.1 66.7	20.0 37.5
Fibrosis > Grade 2	17.5	7.5	5.1	8.3	15.0 58.9	7.1 13.3	0 18.1	6.3 12.5
Cytogenetic response								
Complete	0	5.0	40.0	58.3	0 0	25.0 14.3	42.9 12.5	33.0 11.8

Note: Values given as percentages represent patients with the finding

The present study included 40 patients (37 in chronic phase; 3 in accelerated phase. The study by Lugli et al included 21 in chronic phase & 18 in advanced phase; values of both are included

In the present study, time intervals are not fixed; whereas in Lugli's study, investigations are done at 13, 25 & 49 weeks

cytogenetic response of grade 1. The remaining 9 patients were in PHR with morphological and cytogenetic scores similar to first follow up PHR. In the third follow up 19 patients were in CHR with the median morphologic score increasing from 0 to 1 and median cytogenetic response 1. The remaining patients showed median morphologic score 2 with median cytogenetic response decreasing from 3 to 2. (Graph.1).

Several histopathological findings have been examined during treatment with Imatinib in CML patients. The predominant changes included sea blue histiocytes in 18%

(Fig. 2a) followed by lymphoid aggregates in 16% (Fig. 2b), erythroid hyperplasia in 9.5% (Fig. 2c), marrow hypoplasia in 5.6% (Fig. 3a), gelatinous change in 0.9% (Fig. 3b) and granuloma in 0.9% (Fig. 3c).

Discussion

Very few studies have been reported in the literature for CML patients correlating post treatment (Imatinib)

Fig. 1 a CML-Chronic phase. Bone marrow biopsy at the time of diagnosis showing packed marrow (H & E $\times$ 100). **b** Bone marrow biopsy after Imatinib therapy showing normal marrow (H & E $\times$ 200)

Table 5 Hematologic response and marrow morphological scores

Hematologic response in total follow up marrows ($n = 104$)	MMR score	
CHR ($n = 66$)	0–1	63 (95.4%)
	≥ 2	3 (4.5%)
PHR ($n = 35$)	0–1	6 (17.1%)
	≥ 2	29 (82.8%)
NHR ($n = 3$)	≥ 4	3 (100%)

hematological and cytogenetic responses with the morphologic response [2, 4, 5] (Fig. 4).

Though the morphological scoring system was introduced by Lugli et al. in 2005, it has not been frequently used. This study systematically analyzed morphologic parameters of all bone marrow aspiration smears and biopsies for which a corresponding cytogenetic analysis was available.

In comparison with earlier Indian studies [12, 13], patients in the present study presented at a much younger age in contrast with patients from the west. The median age of presentation was 31 years as compared to 50 years in the west [14].

On every follow up there was rapid normalization of cellularity, M:E index and decrease in blasts and basophil counts were detected in most of the patients (Fig 1b). Imatinib was found to be effective in reducing—cellularity, M:E ratio, blasts, abnormal megakaryocytes and fibrosis in contrast to interferon alfa which induced an increase in megakaryocyte number and causes fibrosis [15]. Hematological remissions (normalization of peripheral blood counts with absence of circulating immature forms) are nearly universal in patients treated in the chronic phase as well as in patients treated in other than chronic phase [16, 17].

Specific bone marrow morphologic responses in patients treated with Imatinib, have been described in recent studies with small number of patients [18, 19]. Where investigators reported normalization of most morphologic parameters, but no unequivocal correlation with cytogenetic response.

Early response to Imatinib may be a predictor of further response to therapy as patients with CHR at 1st follow-up continued to be in CHR at 2nd follow-up. In contrast, of the 22 patients with PHR at 1st follow-up 70.8% were in CHR, 25% were in PHR and 1(4.1%) in chronic phase after second follow up.

In this study we applied a morphologic score comprising seven parameters for response evaluation. To test the utility of this score, the morphological score of each parameter was compared with cytogenetic responses at follow up bone marrows (Table 5). In this regard P value < 0.05 for cellularity, M:E ratio, fibrosis grade > 2 , abnormal megakaryocytes, blasts, basophils, presence of dry tap as similar to a study by Frater et al. [20]. Patients with minimal cytogenetic response had partial hematological response and higher morphological response scores in comparison with complete cytogenetic response.

The results of this study are compared to that of Lugli et al. and depicted in Table 4. The score is of significant potential clinical value. Almost 93.6% of CHR patients showed 0, 1 morphologic scores, only 6.4% of the patients showed ≥ 2 morphologic scores. In other words, a high score ≥ 2 predicts a poor prognosis in terms of cytogenetic response. Majority (81.2%) of the patients with PHR in the peripheral blood achieved ≥ 2 marrow morphologic score with only 18.8% of the patients showing low scores of 0 or 1. Only one patient had NHR on peripheral blood and marrow morphologic score of 4 at the end of the second follow up. Hence, morphological changes in the bone marrow of Imatinib treated patients of CML are predictors of cytogenetic response [4]. These findings reflect that patients who do not achieve early morphologic response to Imatinib should be followed by cytogenetic techniques, and patients who do not achieve a cytogenetic response may become candidates for alternative therapy [21].

The basis for the clinical response to ST157I is presumed to be inhibition of growth and selective killing and/or apoptosis of CML cells bearing the bcr-abl tyrosine kinase, this should allow eventual repopulation of the marrow by normal hematopoietic cells lacking bcr-abl [22].

Table 6 Morphologic parameters in correlation with cytogenetic response

		Complete cytogenetic response	Other cytogenetic response	<i>P</i> value	No. of smears/ marrows/ biopsies
Cellularity	Normal	28	61	0.0097	104
	Increased	0	15		
Dry tap	No	27	60	0.0368	104
	Dry tap	01	16		
M.E. ratio	≤ 4	28	63	0.018	104
	> 4	0	13		
Blasts	$< 5\%$	28	62	0.019	104
	$\geq 5\%$	0	14		
Basophils	$< 1\%$	28	65	0.036	104
	$\geq 1\%$	0	11		
Abnormal Megakaryocytes	$< 10\%$	28	60	0.0053	104
Fibrosis	$\geq 10\%$	0	16	0.018	62
	≤ 2	24	30		
Peripheral blood smear	> 2	0	8	0.0001	104
	CHR	28	48		
	PHR	0	28

Fig. 2 **a** Bone marrow aspiration after Imatinib therapy showing prominence of *sea blue* histiocytes (Giemsa $\times 400$). **b** Bone marrow biopsy showing reactive lymphoid nodule (H&E $\times 200$). **c** Erythroid hyperplasia following therapy (H&E $\times 200$) **Fig. 3** **a** Bone marrow biopsy after Imatinib therapy showing severe marrow hypoplasia (H&E $\times 200$). **b** Bone marrow biopsy after Imatinib therapy showing gelatinous transformation (H&E $\times 400$).**c** Bone marrow biopsy after Imatinib therapy showing epithelioid cell granuloma (H&E $\times 200$)

Fig. 4 Comparison between hematological, marrow morphologic (M) and cytogenetic (C) response at first 3 follow ups post Imatinib. The X axis depicts visits of the patients. The blue color bars represent patients in complete hematologic response (CHR) and red color represents patients in Partial hematologic response (PHR). The Y axis depicts the median of cytogenetic and morphologic response scores. (Color figure online)

Sea blue histiocytes are prominent in many of the patients receiving imatinib, containing phagocytosed cellular debris related to rapid cell turnover and associated with prolonged survival [23]. Increase in marrow lymphocytes is definitely related to the therapy and did not correlate with Ph status [11]. Bone marrow hypoplasia has also been reported in a study in five cases [24]. Granuloma formation may be attributed one of the rare complication of Imatinib or the patient may have developed a granulomatous condition like tuberculosis [25]. Gelatinous marrow transformation is an unusual pathological manifestation reported recently in 2 cases of CML treated with Imatinib. It is unknown whether the effect of disease or drug [26].

In conclusion morphologic criteria based on cellularity, M:E ratio, dry tap, percentage of blasts, basophils, presence or absence of abnormal megakaryocytes, degree of fibrosis for complete cytogenetic response in patients with CML treated with Imatinib can be defined. Hematological response was rapid and complete compared to cytogenetic response (slow & partial). Hematological response along with morphologic scores is also of potential clinical value in addition to cytogenetic and molecular response. As Imatinib is a commonly used drug in all phases of CML, it is essential for all hematologists to be aware of morphological changes produced by this drug.

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