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Original Research Article

CHRONIC MYELOID LEUKEMIA– A CLINICOHAEMATOLOGICAL STUDY

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Abstract

Background: Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by translocation involving chromosome number 9 and 22 resulting in Philadelphia (Ph) Chromosome. This study was carried out to fill the void in the data on clinico-haemotological correlation in CML in Western Maharashtra. **Objective:** To evaluate the clinical and hematological parameters in all 3 phases of CML patients. **Methodology:** An observational retrospective study was conducted over a period of 3 years at a tertiary care center. The samples of 63 patients of CML were evaluated for haematological parameters and correlated with clinical presentation. **Results:** Age of the study group varied from 16-66 yrs. The most common age group affected was 31- 40 yrs. Male preponderance was noted (M:F - 1.42:1). Out of 63 cases diagnosed as CML, 47 (74.6%) were in chronic phase, 2 (3.18%) in accelerated phase, and 14 (22.2%) in blast crisis. The most common symptoms in all the three phases were weakness, easy fatiguability and fever. Splenomegaly was the most common clinical sign in all phases of CML Anemia, leukocytosis, and thrombocytosis were found in all chronic phase cases while thrombocytopenia was observed in the cases in blast crisis phase. **Conclusion:** In the study conducted, CML tends to occur at a younger age which is comparable with other Indian studies.

INTRODUCTION

Leukemias are characterized by abnormal proliferation of haemopoietic cells causing progressively increasing infiltration of the bone marrow and other organs including lymphatic tissues. Chronic myeloid leukemia (CML) is a clonal stem cell disorder characterized by increased proliferation of myeloid elements at all stages of differentiation.[1]

CML belongs to the category of myeloproliferative neoplasms (MPN) that also includes Polycythemia Vera, Essential Thrombocytosis, Primary Myelofibrosis, Chronic Neutrophilic Leukemia, Chronic Eosinophilic leukemia and MPN, classification.[2]

The common feature in all MPNs is effective clonal myeloproliferation (peripheral blood leucocytosis, erythrocytosis or thrombocytosis) with no evidence of dysplasia or monocytosis. The presence of any one of the latter three features mandates disease assignment to either Myelodysplastic Syndrome (MDS) or MDS/MPN.[3]

MPNs often have an insidious clinical onset & all of them have the potential to undergo clonal evolution & stepwise progression that terminates in bone marrow failure due to myelofibrosis or ineffective hematopoiesis or transformation to an acute blast phase.[2]

The complicating feature of MPN is the frequent overlap of clinical, laboratory & morphologic findings among the diseases.[2] The cardinal feature of CML is the presence of Philadelphia (Ph) chromosome. It was originally described by Nowell and Hungerford as a small chromosome 22 and Rowley later demonstrated that it typically results from a specific balanced (reciprocal) translocation t(9;22)(q34.1 ;q 11 .21).[4-5]

The worldwide incidence of CML is 1-2 cases per 1 lac population per year and accounts for 15-25% of all hematological malignancies.[2] In Indian population, it accounts for 30-60% of all adult leukemias.[6]

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CML runs a biphasic or triphasic course, an initial chronic phase (CP) that ends in a blast crisis (BC), often preceded by an accelerated phase (AP). In the past few years, the course of CML has changed due to early diagnosis and availability of Tyrosine kinase inhibitors.[7]

Hence, the purpose of the study was to analyze the clinical presentation of these cases and correlate them with hematological findings.

MATERIALS AND METHODS

The retrospective study was carried out over a period of two years at a Tertiary Care Centre. The study sample comprised of Sixty-three patients diagnosed with CML on the basis of clinical and hematological parameters and who were positive for Philadelphia chromosome. Patients with similar clinical and hematological parameters who were Ph chromosome negative were excluded. Blood samples from these cases were processed on 3part differential automated blood cell counter to obtain hemoglobin (Hb), total leucocyte count (TLC) and platelet count. Smears were prepared, stained with Romanowsky's stains and a detailed study regarding the morphology of various cells seen in CML was carried out.and the results were analyzed. Detailed examination of bone marrow aspirates was carried out in 44 patients and biopsy was carried out in 12 patients. Bone marrow aspirate slides were stained with Giemsa stain. Bone marrow biopsies were decalcified using formic acid after formalin fixation. Routine processing was carried out using absolute alcohol and xylene. The slides were stained with H & E stain. Special stains such as reticulin stain were used wherever indicated.

Cytogenetic findings were recorded from the case records. Data pertaining to clinical presentation was retrieved from the case records and were analyzed and correlated with the hematological findings. Follow up data was analyzed in cases where it was available.

RESULTS

A total of 63 patients were included in the study. Mean age of the study group was 34.2 yrs with a male to female ratio of 1.42:1.

Table 1: Distribution of cases according to the phase of disease

Phase	No. of cases	% of cases
Chronic	47	74.60
Accelerated	02	3.18
Blast crisis	14	22.22
Total	63	100.00

Of the 63 cases studied, 47 cases (74.60%) were in chronic phase (Table 1).

Table 2: Age wise distribution of CML

Age in years	Chronic phase (n = 47)		Accelerated phase (n = 2)		Blast crisis (n = 14)		Total (n = 63)	
	No	%	No	%	No	%	No	%
11 – 20	05	10.64	-	-	03	21.43	08	12.70
21 – 30	11	23.40	-	-	03	21.43	14	22.22
31 – 40	14	29.79	-	-	04	28.57	18	28.57
41 – 50	07	14.89	-	-	01	07.14	08	12.70
51 – 60	05	10.64	02	100	03	21.43	10	15.87
61 – 70	05	10.64	-	-	-	-	05	07.94
Total	47		02		14		63	

Most of the patients 32(51%) were in the age group of 21 - 40 yrs followed by 18 (28.7%) in the age group of 41 – 60 yrs (Table 2).

Table 3: Frequency of symptoms among CML cases

Symptoms	Chronic phase (n = 47)		Accelerated phase(n = 2)		Blast crisis (n = 14)	
	No	%	No	%	No	%
Fever	28	59.57	01	50.00	10	71.43
Weakness/ Easy Fatiguability	34	72.34	01	50.00	11	78.57
Anorexia/ / Loss of apetite/ Nausea,Vomiting	22	46.81	01	50.00	07	50.00
Weight loss	11	23.40	-	-	01	07.14
Distension/ lump/	35	74.47	01	100	07	50.00

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Pain in abdomen						
Breathlessness	05	10.64	-	-	05	35.71
Bone pain	02	04.26	-	-	01	07.14
Bleeding symptoms	-	-	-	-	02	14.29

The most common symptoms in all the three phases were weakness, easy fatiguability, fever and anorexia, nausea vomiting, loss of appetite

Table 4: Frequency of various clinical signs among CML cases

Signs	Chronic phase (n= 47)		Accelerated phase (n = 02)		Blast crisis (n = 14)	
	No	%	No	%	No	%
Pallor	20	42.55	02	100	11	78.57
Splenomegaly	43*	95.56	02	100	13	92.85
Hepatomegaly	23	48.94	-	-	06	42.86
Lymphadenopathy	07	14.89	01	50	05	35.71
Sternal tenderness	03	06.38	-	-	01	07.14

*Two patients had already undergone splenectomy. In one case the reason being post-traumatic rupture and in other the details were not available.

Splenomegaly was the most common clinical sign in all phases of CML

Table 5: Distribution of Hemoglobin (Hb) concentration

Hb in gm%	Chronic phase (n = 47)		Accelerated (n = 2)		Blast crisis (n = 14)		Total (n = 63)	
	No	%	No	%	No	%	No	%
< 7	06	12.76	01	50	07	50.00	14	22.22
7 – 10	18	38.30	01	50	05	35.71	24	38.10
> 10	23	48.94	-	-	02	14.29	25	39.68
Total	47	100	02	100	14	100	63	100

In the chronic phase, 24/47 (51%) of the sample had Hb concentration less than 10 gms% whereas in blast crisis, 12/14 (86%) of the sample had Hb concentration less than 10 gms% (Table 3).

Table 6: Total leucocyte count (TLC)

TLC per cmm	Chronic phase (n = 47)		Accelerated phase (n = 2)		Blast crisis (n = 14)		Total (n = 63)	
	No	%	No	%	No	%	No	%
< 11,000	-	-	-	-	02	14.29	02	03.17
11,000 –1 lakh	10	21.28	-	-	06	42.86	16	25.40
1-3 lakhs	26	55.32	02	100	05	35.71	33	52.38
> 3 lakhs	11	23.40	-	-	01	07.14	12	19.05
Total	47	100	02	100	14	100	63	100

A significant number of patients 33/63 (52%) had total leucocyte count between 1- 3 lakh /cu.mm. (Table 4). In the chronic phase, the predominant cells were myelocytes (10-28%) and polymorphs (22-55%). The basophil percentage ranged from 1-18% (Figure 1). Eosinophilia was noted in most cases with the highest ranging at 12%. In the accelerated phase, blasts were increased to a maximum of 16%. Of the 13 patients with medullary blast crisis, three were of lymphoblastic morphology and the remaining 10 were of the myeloblastic type. One case of extramedullary (localized) blast crisis in lymphnode had 2% blasts note in the peripheral blood.

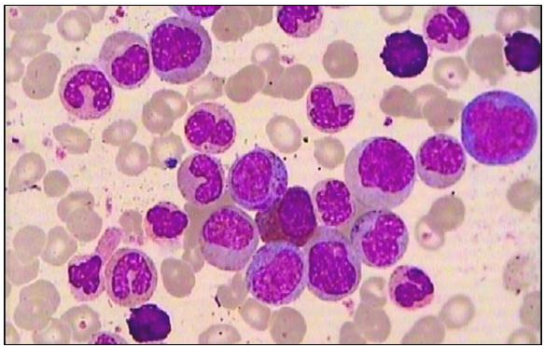

Figure 1: Peripheral smear of CML- chronic phase with cells of myeloid series with increased basophils.

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Table 5: Platelet counts

Platelet count per cmm	Chronic phase (n = 47)		Accelerated phase (n = 2)		Blast crisis (n = 14)		Total (n = 63)	
	No	%	No	%	No	%	No	%
< 1.00 lakh	02	04.25	01	50	11	78.57	14	22.22
1– 4 lakhs	20	42.55	01	50	02	14.29	23	36.51
4 – 10 lakhs	22	46.81	-	-	01	07.14	23	36.51
>10 lakhs	03	06.38	-	-	-	-	03	04.76
Total	47	100	02	100	14	100	63	100

In the chronic phase, 25 of the 47 patients had increased platelet count and 3 among those had platelet count over 10 lakhs. (Figure 2).

Among the blast crisis patients, 11 of the 14 patients had platelet count less than 1 lakh and among them 7 had the count less than 20,000/cu. Mm. (Table 5, Figure 3).

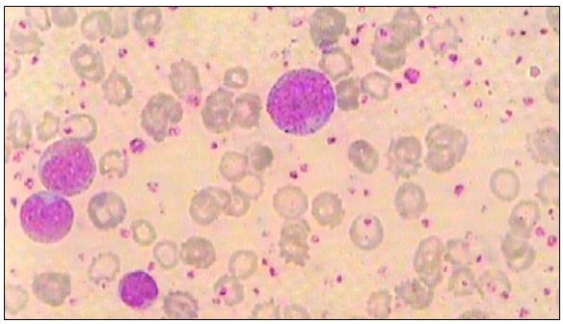

Figure 2: Peripheral smear of CML-chronic phase showing thrombocytosis with few platelets in giant forms.

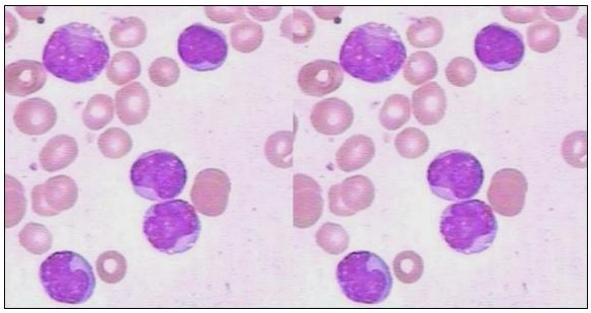

Figure 3: Peripheral smear of CML-blast crisis showing blasts with decreased platelets.

Table 6: Bone marrow aspirate assessment

		Chronic phase (n= 31)		Accelerated phase (n= 1)		Blast crisis (n = 7)		Post treat (n = 2*)	
		No	%	No	%	No	%	No	%
Cellularity	Hypercellular	31	100	01	100	07	100	01	50
	Hypocellular	-	-	-	-	-	-	-	-
	Normocellular	-	-	-	-	-	-	01	50
Myeloid	Normal	-	-	-	-	-	-	02	100
	Hyperplasia	31	100	01	100	07	100	-	-
	Normal maturation	31	100	-	-	-	-	02	100
	Increased blasts	-	-	01	100	07	100	-	-
	Increased eosinophils	05	16.13	-	-	-	-	-	-
Erythroid	Increased	-	-	-	-	-	-	-	-
	Decreased	31	100	01	100	07	100	-	-
	Normal	-	-	-	-	-	-	02	100
Megakaryocytes	Increased	07	22.58	-	-	01	14.29	-	-
	Decreased	02	06.45	01	100	06	85.71	-	-
	Normal	22	70.97	-	-	-	-	02	100
	Dysplasia	03	09.68	-	-	-	-	-	-
	Micro megakaryocytes	07	22.58	-	-	-	-	01	50

Bone marrow aspirates were available in 44 cases(Table 6). *Three cases of post treatment aspirates were not included in this analysis as they were diluted with sinusoidal blood. Image showing bone marrow imprint in CML-CP showing myeloid hyperplasia with increased megakaryocytes (Figure 4).

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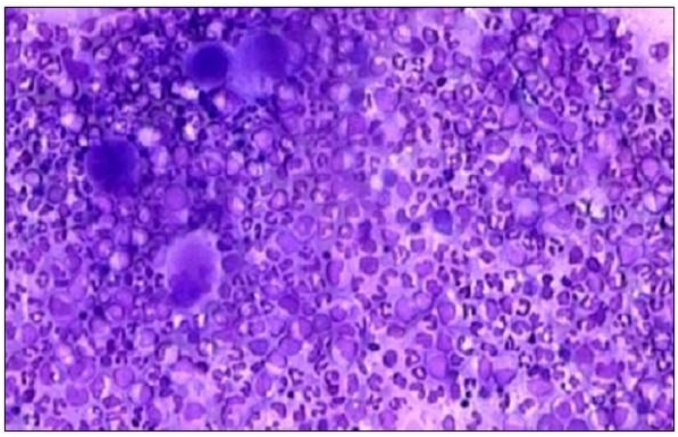

Figure 4: CML-chronic phase: Bone Marrow imprint showing myeloid hyperplasia with increased megakaryocytes.

Table 7: Bone marrow biopsy

		Chronic phase (n=5)		Blast crisis (n=2)		Post treat (n=4)*	
		No	%	No	%	No	%
Cellularity	Hypercellular	5	100	2	100	1	25
	Hypocellular	-	-	-	-	1	25
	Variable	-	-	-	-	2	50
Myeloid	Increased	5	100	2	100	3	75
	Decreased	-	-	-	-	1	25
	Normal	-	-	-	-	-	-
	Normal maturation	5	100	-	-	4	100
	Increased blasts	-	-	2	100	-	
	Prominent eosinophils	2	40	-	-	-	
Erythroid	Increased	-	-	-	-	1	25
	Decreased	5	100	2	100	2	50
	Normal	-	-	-	-	1	25
	Normoblastic	5	100	2	100	2	50
	Megaloblastic	-	-	-	-	2	50
Megakaryocytes	Increased	4	80	1	50	2	50
	Decreased	-	-	1	50	1	25
	Normal no.	1	20	-	-	1	25
	Clustering	1	20	1	50	-	
Sinusoids	Dilatation	-	-	-	-	1	25
Reticulin	Grade 1	-	-	-	-	2	50
	Grade 1-2	2	40	-	-	-	
	Grade 2-3	1	20	2	100	2	50
	Grade 4	1	20	-	-	-	

*Bone marrow biopsy was available in 12 cases only (Table 7). One case of post treatment marrow showed ischemic necrosis and only few viable myeloid cells along with lymphocytes, hence not included in the analysis. Reticulin stain showed fibrosis in 8 cases.

DISCUSSION

CML is a clonal stem cell disorder the hallmark of which is increased proliferation of myeloid elements. It has two distinct clinical phases - chronic phase characterized by proliferation of myeloid cells with maturation and an advanced phase comprising of accelerated phase and blast crisis.[7]

The distribution of cases in our study was in the chronic phase, accelerated phase and blast crisis. When compared with other Indian studies, the percentage of patients in the blast crisis phase was more.[8] This could be attributed to the fact that the tertiary care center where the study was conducted was a referral center for such cases.

The median age group of the study sample population was 31-40 years which is consistent with Indian literature (35-40 yrs) while the presentation was early when compared to European literature (55 yrs). Most common symptoms in our study were weakness, anorexia and easy fatiguability which were similar to the Indian Literature. Indian patients were symptomatic and most present with weakness and dull aching pain in the left hypochondrium .[6,9]

CML patients in chronic phase usually have anaemia of normocytic normochromic type at the time of diagnosis, although normal or elevated levels of hemoglobin have been reported. The severity of anemia was directly proportional to the degree of leucocytosis. In the study by Kumar *et al.*, the average Hb concentration ranged from 4.5-

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11.3 gm% with a mere 14.4% presenting with Hb less than 7 gm%. The median value was 9 gm%.[10]
In this study, among 47 patients in the chronic phase, the median Hb value was 9.1gm%. Only 8 patients (16.33%) had Hb concentration less than 7gm% and these results were comparable to the results of Kumar *et al.*.[10] Anemia and thrombocytopenia were reported as the commonest early findings in the advanced phase of CML.[11] In this study, both the patients in accelerated phase had anemia. Among patients in blast crisis, 12 patients (85.71%) had Hb concentration less than 10gm% and these values were comparable with the study by Kumar *et al.* where all patients had Hb less than 10gm%.[12] These findings demonstrate that the severity of anemia was directly proportional to disease progression.
In this study, RBC morphology in a majority of the patients with anemia varied from normocytic normochromic type to microcytic hypochromic type with mild anisopoikilocytosis. Polychromasia & nucleated RBC's also noted in most cases.
In this study the leucocyte count in chronic phase had a median range of 1-3 lakhs/cu.mm. which was comparable to most of the studies reviewed, where the mean range was 1,34,000 to 2,25,000/cu.mm.[13] The highest total leucocyte count in this study was 6,00,000/cu.mm. A Majority (57%) of the patients in blast crisis had leucocyte count below 1 lakh and this could be explained by the fact that most of these patients were on treatment with Gleevac. Of the 13 medullary blast crisis cases, 3 (23.08%) had lymphoblastic morphology and ten (76.92%) had myeloblastic morphology. This was comparable to the findings of Bhatti *et al.*[13]
In this study, among 47 patients in chronic phase, 53.19% had increased platelet count (> 4 lakhs /cu.mm.) which was higher than the findings of Kumar *et al.* (13.1% cases).[10] Out of these, 3 patients (6.38 %) had count more than 10 lakhs/ cu.mm.
Among the cases in chronic phase, 42.55% had counts between 1-4 lakhs/cu.mm. and the remaining 4.25% had a count less than 1 lakh/cu.mm. which was similar to the findings of Kumar *et al.* (4.4%).[10]
Mason *et al.* studied the clinical significance of elevated platelet count in 111 previously untreated patients and concluded that the hemorrhagic complications of thrombocytosis (> 10 lakhs/cu.mm.) in CML are unusual. In this study, no such complications were noted.
Thrombocytopenia was the earliest finding in the terminal phase and was not related to treatment.[1] Among the 14 patients in blast crisis in this study, 11 cases (78.57%) had thrombocytopenia (<1 lakh/cmm) and 7 of these thrombocytopenia cases had counts less than 20,000/cu.mm.
In two cases of blast crisis (14.29%) platelet count was more than 1 lakh/cu.mm. and both had myeloid type of blast crisis. In contrast to this, Kumar *et al.* found thrombocytopenia in 35.7% cases of blast crisis.[12]
Bone marrow aspirate and biopsy showed marked hypercellularity with myeloid hyperplasia in all three phases. In the chronic phase, myeloid maturation was noted with increased eosinophils and basophils. In blast crisis, the blast count was more than 20%. These marrow findings were similar to the findings of Juliana *et al.*[14] The marrow of a single post treatment case showed ischemic necrosis and few viable myeloid cells along with lymphocytes which was consistent with the finding seen in the study by Joshi *et al.*[15]

CONCLUSION

The study was conducted to evaluate the cases of CML in Tertiary Care Centre. The study found a higher percentage of patients in the Blast crisis phase compared to other studies which could be attributed to the hospital being a referral center for such cases. Distribution of disease across age and sex were comparable to other Indian studies. Frequency and severity of anemia increased with the progression of the disease. Marked leukocytosis was a consistent finding in all phases of CML. Platelet counts were reduced in Blast crisis as expected.

REFERENCES

1. Rabinowitz I and Larson R S. Chronic Myeloid Leukemia. In Wintrobe's clinical hematology. 13th edition. Lippincott Williams & wilkins 2013 : 1705-1721.
2. Vardiman J W, Melo JV, Baccarani M *et al.* Chronic myelogenous leukemia. In WHO classification of tumours of haematopoietic and lymphoid tissues. IARC, Lyon (France) 2017:30-36
3. Mishra P, Seth T, Mahapatra M, Saxena R. Report of chronic myeloid leukaemia in chronic phase from All India Institute of Medical Sciences,1990-2010. Indian J Med Paediatr Oncol. 2013;34:159-63
4. Cervera E, Godínez F, Sosa R, Rivas R, Best C, Hernández J *et al.* Mexican Guidelines for the Diagnosis and Treatment of Chronic Myeloid Leukaemia. Journal of Cancer Therapy. 2013;04(03):747-764.
5. Minciacchi V, Kumar R, Krause D. Chronic Myeloid Leukemia: A Model Disease of the Past, Present and Future. Cells. 2021;10(1):117.
6. Bhutani M, Vora A, Kumar L, Kochupillai V. Lympho-hemopoietic malignancies in India. Med Oncol 2002;19:141-50.
7. Cortes J. Natural history & staging of Chronic myelogenous leukemia. Hematol oncol Clin North Am. 2004; 18 (3): 569 – 584.
8. Ruchi Sinha, Iffat Jamal, Priyamvada, Punam Prasad Bhadani. Clinico-haematological Profile of Chronic Myeloid Leukaemia: An Institutional Based Study from Bihar. National Journal of Laboratory Medicine. 2019, Jan, Vol-8(2):26-29.
9. Baccarani M, Pileri S, Steegnmann JL, Muller M, Soverini S, Dreyling M. Chronic myeloid leukaemia: ESMO

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Clinical Practice Guidelines for diagnosis, treatment and follow up. Ann Oncol.2012;23:72-75.
10. Kumar L, Sagar TG, Maitreyan V, Majhi U *et al.* Chronic granulocytic leukaemia: A study of 160 cases. J Assoc Physicians India. 1990; 38: 899-902.
11. Furtado V, Santos G, de Carvalho D, Staziaki P, Pasquini R, Funke V. Accelerated phase chronic myeloid leukemia: evaluation of clinical criteria as predictors of survival, major cytogenetic response and progression to blast phase. Revista Brasileira de Hematologia e Hemoterapia. 2015;37(5):341-347.
12. Kumar S, Gupta VK, Bharti A, Meena LP, Gupta V, Shukla J. A study to determine the clinical, hematological, cytogenetic, and molecular profile in CML patient in and around Eastern UP, India. J Family Med Prim Care 2019;8:2450-5
13. Bhatti FA, Ahmed S, Ali N. Clinical and hematological features of 335 patients of chronic myelogenous leukemia diagnosed at single centre in northern Pakistan. Clinical medicine insights. Blood Disord 2012;5:15-24
14. Hidalgo-López J, Kanagal-Shamanna R, Quesada A, Gong Z, Wang W, Hu S *et al.* Bone marrow core biopsy in 508 consecutive patients with chronic myeloid leukemia: Assessment of potential value. Cancer. 2018;124(19):3849-3855.
15. Joshi S, Sunita P, Deshmukh C, Gujral S, Amre P, Nair CN, *et al*. Bone marrow morphological changes in patient of chronic myeloid leukaemia treated with Imatinib mesylate. Indian J Cancer. 2008;45:45-49.

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