TYPES OF ANEMIA IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA-CHRONIC PHASE ON IMATINIB MESYLATE

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Abstract:

Background: Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of pluripotent hemopoietic stem cells, resulting from t(9;22)(q34;q11) producing Bcr-Abl1 fusion transcript. Imatinib mesylate is a specific Bcr-Abl tyrosine kinase inhibitor which is well tolerated but may cause a myelosuppression which results in treatment interruptions and poor outcome.

Aim of the study: To evaluate the types of anemia in patients with CML-chronic phase on imatinib mesylate.

Patients and methods: This is a cohort prospective study which included 200 patients with CML-chronic phase attending the National Center for Hematology from October 2009 to April 2010. These patients are already on imatinib mesylate and having documented normal hemoglobin (Hb) concentration and/or packed cell volume (PCV) % at time of diagnosis.

Results: Male:female ratios are 1:2, 1:1 and 1.04:1 for iron deficiency anemia, megaloblastic anemia and anemia of chronic disorder respectively, Out of the total 200 patients enrolled in this study, 59 patients (29.5%) were having anemia, 43 patients (21.5%) with anemia of chronic disorder and 16 patients (8%) with nutritional anemia divided into 12 patients (6%) with iron deficiency anemia and 4 patients (2%) with megaloblastic anemia, Forty two patients were having mild anemia, 13 patients with moderate anemia and only 4 patients were facing severe anemia There was non-significant difference in the degree of anemia, evaluated by Hb concentration and PCV % with p-value 0.294 and 0.712 respectively, between iron deficiency anemia, megaloblastic anemia and anemia of chronic disorder.

Conclusions: Incidence of anemia in CML patients is not affected by sex, except for iron deficiency anemia which is more prevalent in menstruating females. The incidence of anemia of chronic disorder is expectedly high because its preventive and therapeutic measure which is the administration of erythropoietin is usually not available. The incidence of both types of nutritional anemia, iron deficiency and megaloblastic, are unacceptable due to the facts that the treatment is available and these patients are already under close follow up, so early diagnosis and treatment of this anemia should be an easy routine. The percentage of severe anemia is within the accepted limits.

Introduction:

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of pluripotent hematopoietic stem cells, characterized by increased proliferation and decreased apoptosis of myeloid progenitor cells [(1)].

CML is a malignant disorder of the stem cell due to reciprocal balanced translocation of genetic material between the long arms of chromosomes 9 and 22 t(9;22)(q34;q11) producing a shortened chromosome 22, the Philadelphia (Ph) chromosome, which is the cytogenetic hallmark of the disease and the molecular hallmark is the Bcr-Abl1 fusion transcript [(2)].

Imatinib mesylate (Glivec or Gleevec) is a specific Bcr-Abl tyrosine kinase inhibitor that rapidly reverses the clinical and hematological abnormalities and induces major cytogenetic responses in over 80% of previously untreated CML [(3)].

At present it is advisable to maintain treatment with it indefinitely until the criteria for cessation can be established [(1)].

Overall, imatinib therapy is well tolerated, but severe dose-limiting side effects are reported to occur in 2–5% of patients, including fatigue, skin rashes, bone aches, muscle cramps, fluid retention, edema, liver dysfunction and myelosuppression [(4)].

Myelosuppression is the most common adverse event, reportedly occurring in 35 - 50 % of CML patients and it develops less frequently in patients with newly diagnosed CML compared with patients treated for chronic phase CML.

The resulting anemia, neutropenia, and thrombocytopenia lead to treatment interruptions that may be prolonged and necessitate dose reductions of imatinib [(5)].

Myelosuppression during imatinib therapy for CML has been associated with a poor quality of life and fatigue, poor response to therapy and poor prognosis. This is a manifestation of an intrinsically worse disease and also of inadequate delivery of imatinib [(6)].

Averting myelosuppression can improve treatment efficacy and prognosis [(7)].

Unlike both neutropenia and thrombocytopenia which can be inevitable and yet non-preventable in many patients with CML on treatment, anemia should be a predictable and to a great degree a preventable type of myelosuppression [(8)].

Aim of the study:

To evaluate the types of anemia in patients with CML-chronic phase on imatinib mesylate.

Patients and methods:

This is a cohort prospective study which included 200 patients with CML-chronic phase on imatinib and having a documented normal hemoglobin (Hb)

concentration and/or packed cell volume (PCV) at time of diagnosis. These patients were attending the National Center for Hematology from October 2009 to April 2010.

For each patient, after explanation and verbal consent for participation in the study, the following tests were requested: Full blood count using the Abbott hematology autoanalyser CELL-DYN 1700 and peripheral blood smear. Later, if the primary results revealed the presence of anemia then the patient is asked to perform a serum iron, total iron binding capacity and transferrin saturation for confirmation of the initial diagnosis.

Patients with macrocytic anemia could not be further investigated due to unavailability of serum B12 and serum and red cell folate tests. However, characteristic peripheral blood smear features plus adequate response to vitamin B12 and folic acid therapeutic trial were the findings used to entitle those patients as having megaloblastic anemia [9].

Anemic patients at time of diagnosis were excluded from the study.

All patients included in this study are adult males and non-pregnant females, for whom anemia is defined as Hb less than 13 g/dl and/or PCV less than 40 % for males, and Hb less than 12 g/dl and/or PCV less than 36 % for females [10].

In this study anemia is classified as mild (Hb level of ≥ 10 g/dl), moderate (Hb level of 8-9.9 g/dl) and severe (Hb level ≤ 7.9 g/dl), in correspondence to grades 1, 2, and 3 of the National Cancer Institute (NCI) Common Toxicity Criteria, respectively [11].

Statistical analyses were performed by using Statistical Package for Social Sciences (SPSS) version 18.0.0 software. The results were expressed as mean ± standard error (SE), with the probability (p) value of less than 0.05 considered significant.

Results:

Male:female ratios are 1:2, 1:1 and 1.04:1 for iron deficiency anemia, megaloblastic anemia and anemia of chronic disorder respectively.

The sex distribution of patients according to type of anemia is illustrated in table 1.

Hb concentration and PCV % of patients according to type of anemia are summarized in table 2.

Grading of patients according to severity of anemia is presented in table 3.

Types of anemia in the patients with CML-chronic phase are listed in table 4.

Table 1: Sex distribution of patients according to type of anemia:

Parameter		Nutritional anemias				Anemia of chronic disorder		Total	
		Iron deficiency anemia		Megaloblastic anemia					
		No.	%	No.	%	No.	%		
Sex	Males	4	33.3	2	50	22	48.8	28	59
	Females	8	67.7	2	50	21	51.2	31	
Total		12		4		43			
		59							

Table 2: Hb concentration and PCV % of patients according to type of anemia:

Parameter	Nutritional anemias				Anemia of chronic disorder		P-value
	Iron deficiency anemia		Megaloblastic anemia				
	Range	Mean ± SE	Range	Mean ± SE	Range	Mean ± SE	
Hb concentration (g/dl)	**7.8 – 12.8**	**10.43 ± 0.423**	**9.1 – 11.7**	**10.13 ± 0.572**	**6.9 - 12.7**	**10.62 ± 0.214**	**0.294**
PCV (%)	**26 – 40.5**	**33.57 ± 1.33**	**30 – 37.1**	**32.78 ± 1.57**	**24.2 – 40.8**	**34.55 ± 0.567**	**0.712**

Table 3: Grading of patients according to severity of anemia:

Degree of anemia	Nutritional anemias		Anemia of chronic disorder	Total
	Iron deficiency anemia	Megaloblastic anemia		
Mild	8	2	32	42
Moderate	3	2	8	13
Severe	1	0	3	4
Total	12	4	43	59

Table 4: Types of anemia in 200 patients with CML-chronic phase:

Type of anemia		No.	%	Total			
				No.	%	No.	%
Nutritional	Iron deficiency	12	6	16	8	59	29.5
	Megaloblastic	4	2				
Anemia of chronic disorder		43	21.5	43	21.5		

Discussion:

CML is a clonal disease that results from an acquired genetic change in a pluripotential hemopoietic stem cell [1]. This altered stem cell proliferates and generates a population of differentiated cells that gradually displaces normal hemopoiesis and leads to a greatly expanded total myeloid mass [12]. The most important landmarks in the study of CML were the discovery of the Ph chromosome and the characterization of the Bcr–Abl1 chimeric gene and associated oncoprotein [13]. The introduction into clinical practice of the well tolerated treatment imatinib was an important therapeutic advance, as with this agent most patients achieved a complete cytogenetic response and prolongation of survival compared with other methods of treatment [14]. However, severe dose-limiting side effects are reported including myelosuppression which is the most commonly occurring severe adverse event [15]. The resulting anemia, neutropenia, and thrombocytopenia lead to treatment interruptions that may be prolonged and/or to dose reductions of imatinib resulting in lower probability of complete remission and poor outcome [5].

This study is aiming to evaluate the types of anemia in patients with CML-chronic phase on imatinib mesylate.

All patients included in this study were adults, i.e., one age group according to anemia definition and limits.

Both males and females were almost having the same incidence of anemia of chronic disorder and megaloblastic anemia. While the incidence for iron deficiency anemia was double in females, mostly because their usual iron requirements are more than the males [5, 16, 17]. Re-questioning the females with iron deficiency anemia revealed that 6 out of 8 patients were still menstruating.

Out of the total 200 patients enrolled in this study, 59 patients (29.5%) were having anemia, 43 patients (21.5%) with anemia of chronic disorder and 16 patients (8%) with nutritional anemia divided into 12 patients (6%) with iron deficiency anemia and 4 patients (2%) with megaloblastic anemia. The figure for the anemia of chronic disorder is expectedly high because its preventive and therapeutic measure which is the administration of recombinant erythropoietin is usually not available for the patients.

Anemia attributable to imatinib usually responds to administration of erythropoietin and should not, therefore, be more than temporary mild anemia in only small percentage of the patients [5].

The figures for both types of nutritional anemia, although much lower than that for anemia of chronic disorder, are unacceptable due to the facts that the oral replacement treatment is readily available and these patients are already under close follow up, so early diagnosis and treatment of this anemia should be an easy routine.

The percentage of severe anemia in this study (2%), which is a cause for treatment interruption, is accepted in comparison to other studies in which it is (3%) [16, 17].

There was non-significant difference in the degree of severity of anemia, evaluated by Hb concentration and PCV % with p-value 0.294 and 0.712 respectively, between nutritional anemias and anemia of chronic disorder, suggesting that the anemia itself, and not its specific cause, is the effective parameter in CML-chronic phase patients.

Conclusions:

1. Incidence of anemia in CML patients is not affected by sex of patients, except for iron deficiency anemia which is more prevalent in menstruating females.
2. The incidence of anemia of chronic disorder is expectedly high because its preventive and therapeutic measure which is the administration of recombinant erythropoietin is usually not available for the patients.
3. The incidence of both types of nutritional anemia, iron deficiency and megaloblastic, are unacceptable due to the facts that the oral replacement treatment is readily available and these patients are already under close follow up, so early diagnosis and treatment of this anemia should be an easy routine.
4. The percentage of severe anemia in this study is within the accepted limits.

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