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Original article

Evaluation of anemia after long-term treatment with imatinib in chronic myeloid leukemia patients in chronic phase

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ABSTRACT

Introduction: The incidence of grade 3–4 anemia was reported to be 3% with imatinib therapy for newly diagnosed chronic myeloid leukemia (CML) in the chronic phase (CP). However, there are few data regarding the causes and the development of anemia after long-term treatment. This study aimed to evaluate the incidence of anemia after at least two years of imatinib treatment of CML patients in the CP and to identify other contributing causes of anemia in this population.

Patients and methods: We performed a retrospective analysis of 97 CML patients in the CP treated with imatinib for at least two years. We analyzed the hemoglobin (Hb) levels of CML patients at diagnosis, upon initiation of treatment with imatinib and after two years of imatinib treatment, and investigated other causes of anemia in this population.

Results: Most of the patients presented Hb levels below the normal range (80.4%) after the second year of treatment, 17.9% grade 2 and 1.3% grade 3. In 13 cases (16.7%), anemia was attributed to resistance and in 13 cases (16.7%) the following causes were identified: iron deficiency ($n = 5$), hypothyroidism ($n = 2$), vitamin B12 deficiency ($n = 3$), acquired immune deficiency syndrome (AIDS) ($n = 1$), pulmonary tuberculosis ($n = 1$) and renal toxicity ($n = 1$). In 52 patients (66.6%), there were no other factors contributing to anemia, except imatinib treatment.

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Conclusion: Regular follow-up is required to identify the causes of anemia not related to CML or imatinib toxicity. The importance of investigating secondary causes of anemia should be emphasized, especially in patients with good adherence to treatment and satisfactory therapeutic response.

Introduction

Imatinib mesylate is a potent and specific inhibitor of prototypic cytoplasmic tyrosine kinases (ABL kinases), and its introduction as first-line treatment of CML increased the survival of these patients.[1,2] Currently, imatinib is the first-line treatment for CML in Brazil for all stages of the disease.[3] In general, imatinib therapy is well-tolerated, but several dose-dependent side effects have been reported in 2–5% of the patients.[4] Most side effects are mild (less than grade 2) and do not require treatment interruption. Most of the symptoms resolve within a short period after drug discontinuation.[5] Low-grade chronic toxicities are emerging as a frequent concern for patients who have been receiving this therapy for several years.[5] Myelosuppression is the most common grade 3–4 adverse event, presented by 35–45% of the patients.[6,7] The overall incidence of neutropenia, thrombocytopenia and anemia by 12 months were 43, 48, and 38%, respectively, and grades 3–4 were 12, 10, and 3%, respectively, in early CP patients with imatinib as the first-line treatment.[8] Anemia, neutropenia, and thrombocytopenia can lead to treatment interruptions or imatinib dose reductions.[9] Myelosuppression during therapy for CML with imatinib has been associated with a poor response to therapy and with a worse prognosis[10] and may reflect a reduced reserve or a delayed recovery of normal hematopoietic stem cells present at diagnosis.[11] Cortes et al. studied 338 patients receiving imatinib. Sixty-eight percent developed anemia (Hb levels $\leq$ 11 g/dL). Patients with anemia showed a trend of worse complete cytogenetic response rates and worse survival.[9] In the 6-year follow-up of the Insulin Resistance Intervention After Stroke (IRIS) trial, imatinib was discontinued in about one-third of patients with CML in the CP due to resistance or intolerance.[12] Grade 3 or grade 4 anemia (Hb level < 6.5 g/dL) was observed in 3% of the patients with newly diagnosed CML in the chronic phase (CP) treated with imatinib in a median follow-up of 19 months and in 7% after IFN-α failure. However, there are few data concerning anemia development after long-term treatment with imatinib.

Objective

The primary purpose of this study was to evaluate the incidence of anemia in patients with CML in the CP after two or more years of treatment with imatinib and to investigate other causes of anemia in this population.

Patients and methods

In this observational and retrospective study, we included patients with CML in the chronic phase at diagnosis, treated with imatinib for at least 24 months. Exclusion criteria: Patients who presented accelerated and blast phase at diagnosis and patients in the CP treated with imatinib for less than two years were excluded from the study. Between 2003 and 2010, 153 patients with CML received imatinib 400–800 mg at our center. Fifty-three patients were excluded from the analysis because they discontinued imatinib before 24 months (n = 53) due to the following reasons: intolerance (n = 11), resistance (n = 23), poor adherence (n = 5), death (n = 11) and allogeneic transplantation (n = 3). Three additional patients had still not completed 24 months of treatment. Ninety-seven patients were analyzed. We reviewed their records until February 2014 and collected clinical data (gender, age and comorbidities), laboratory results (Hb levels and renal function) and response to imatinib. Anemia was defined as Hb levels less than 12 g/dL for women and below 14 g/dL for males. After initiating imatinib treatment, anemia was graded according to the Common Terminology Criteria for Adverse Events (National Cancer Institute – Version 4.0): Grade 1 (Hb level < lower limit of normality −10 g/dL), grade 2 (Hb level < 10–8 g/dL), grade 3 (Hb level < 8.0 g/dL), grade 4 (fatal consequences; need for urgent action), grade 5 (death).[13] We considered the lowest level observed until the date of the last follow-up. Renal function was analyzed at diagnosis, after two years of treatment and at the last follow-up and classified as: Grade 1 (creatinine increase in 0.3 mg/dL; 1.5–2× above the baseline), grade 2 (creatinine 2–3× above baseline), grade 3 (creatinine 3× the baseline or >4 mg/dL; need for hospitalization); grade 4 (fatal consequences; hemodialysis indication), grade 5 (death). Response criteria were based on the European LeukemiaNet recommendations.[14] Patient characteristics comparisons were performed using the Fisher's exact or Chi Square Tests.

Results

We analyzed 97 patients with CML in the CP. The median follow-up was 85 months (26–128 months). Thirty-seven patients (38.1%) did not present any comorbidity and 61.9% had one or more comorbidities: hypertension (33.4%), diabetes mellitus (26.7%), heart disease (11.7%), hypothyroidism (10%) and chronic renal failure (13.3%). The clinical characteristics at diagnosis are shown in Table 1. Treatment and responses: Ninety-five patients used hydroxyurea for initial

Table 1 – Main characteristics at diagnosis of 97 patients with CML in chronic phase treated with imatinib.

Characteristics		Patients (*n*)
Age (year)		
Mean	47	–
Range	17–79	–
Sex (%)		
Male	55.7	54
Female	44.3	43
Comorbidities (%)		
Any	38.1	37
One or more	61.9	60
Risk assessment – Sokal (%)		
Low	38.8	31
Intermediate	36.3	29
High	25.0	20
Not evaluated (missing data)	–	17
Leukocytes ($\times 10^9$/L), median and range	152.1 (33–483)	–
Platelets ($\times 10^9$/L), median and range	461.4 (129–1750)	–
Hb (g/dL), median and range	11.7 (5.9–15.8)	–
Previous use of IFN (%)	21.6	21
Initial dose of imatinib (%)		
300 mg	2.1	2
400 mg	89.7	87
600 mg	1.0	1
800 mg	7.2	7

cytoreduction, and 21 patients (21.6%) used interferon (IFN) prior to imatinib, with a mean treatment duration of 96.1 days. One patient used bosutinib before imatinib. The initial dose of imatinib ranged from 300 to 800 mg: 89.6% used 400 mg. In 38.1%, the dose was increased during the treatment course. The median time between diagnosis and the initiation of imatinib treatment was 2 months (0–29). Responses to imatinib are described in Table 2.

Eighty-seven patients (91.5%) achieved complete cytogenetic response (CCyR), 41 (42.3%) had major molecular response (MMR) and 41 (42.3%) cases showed complete molecular response (CMR). At the last follow-up, 41 (42.2%) presented CMR, 37 (38.1%) MMR, 9 (9.3%) maintained CCyR, but without MMR, 3 (3.1%) (PCyR), 1 (1%) minor cytogenetic response, 4 (4.1%) only CHR and 1 (1%) in the CP without hematologic response. One patient progressed to the accelerated phase. Six patients died due to sepsis, murder, pulmonary infection and arterial aneurysm rupture.

Anemia evaluation

At diagnosis, 63 of 92 patients (68.5%) presented anemia. Five patients were treated at other centers at the beginning of the treatment and initial blood cell counts were not available. On the first day of imatinib administration, 53 patients had anemia (54.6%). Fifty-six of the 63 patients who had anemia at diagnosis persisted with this finding. Among 29 patients with hemoglobin levels within the normal range at diagnosis, 18 (62%) had anemia after two years of treatment. Table 3 shows the mean hemoglobin values at diagnosis, at imatinib initiation and after two years of therapy. After two years of treatment with imatinib, 80.4% ($n = 78$) of the patients presented anemia Pl. Table 4 shows the characteristics of patients with anemia compared to those without anemia after two years of treatment. Only anemia at diagnosis was a statistically significant factor ($P < 0.001$). In 52 patients (66.6%), we did not identify other causes for anemia, and in 13 cases (16.7%) anemia was attributed to the disease. All of them switched to a second-generation inhibitor (nilotinib or dasatinib). Six of them presented the resolution of anemia after switching. In 13 cases (16.7%), the etiology was defined as: iron deficiency ($n = 5$), hypothyroidism ($n = 2$), B12 vitamin deficiency ($n = 3$), AIDS ($n = 1$), pulmonary tuberculosis ($n = 1$) and chronic renal failure ($n = 1$). During the follow-up, 27 patients (34.6%) had normalization of Hb levels without medical intervention, but the majority (51.3%) persisted with anemia until the date of the last follow-up. Five patients showed clinical improvement after treatment of the underlying condition: three patients with iron deficiency received iron replacement, one case received treatment for pulmonary tuberculosis and one patient with chronic renal dysfunction received erythropoetin. Table 5 shows the evaluation of patients who developed anemia after two years of imatinib treatment and the causes were found to be related to the development of anemia. In patients with anemia, 37.2% had CCyR, 29.5% MMR and 15.4% CMR. Considering the assessment of the status of patients with anemia at last follow-up, 8.9% ($n = 7$) were in CCyR, 41% ($n = 32$) in MMR and 41% ($n = 32$) in CMR. Renal toxicity: The mean values of creatinine at diagnosis, after two years of therapy and last follow-up are shown in Table 6. In the assessment of renal toxicity after two years of imatinib treatment, 7 of 83 patients (8.4%) developed it. Six patients (85.7%) had grade 1 toxicity, and one patient (14.3%) had grade 2 toxicity. In 76 cases (91.6%) there was no change in creatinine values. Fourteen patients were not evaluated due to lack of data. In the last evaluation of renal function, 19 of 84 (22.6%) patients had renal impairment: 18 (94.7%) had grade 1 toxicity and 1 (5.3%) had grade 3 toxicity. Sixty-five of the cases (77.4%) maintained stable creatinine levels, in comparison with diagnosis levels. It was not possible to evaluate the renal function of 13 patients due to lack of data.

Table 2 – Responses to treatment with imatinib in patients with CML in chronic phase.

Response	Patients ($n = 97$)	*n* (%)	Loss of response (*n*)	*n* (%)
Hematological	97	100	1	1
Cytogenetics				
Complete	87	91.5	4	1.14
Molecular				
Complete	41	42.3	2	4.9
Major	41	42.3	6	14.6

Table 3 – Hemoglobin evolution at diagnosis and over imatinib therapy (g/dL).

	Minimum	Maximum	Mean
At diagnosis	5.9	15.8	11.7
Imatinib initiation	4.0	17.1	12.6
Two years after imatinib	8.7	16.0	12.9

Table 4 – Patient characteristics according to the presence or not of anemia after two years of imatinib treatment (*n* = 97).

Baseline characteristics	Presence of anemia after two years of imatinib treatment (%)		
	Yes (*n* = 78)	No (*n* = 19)	*P*
Age (years)			
≥60	28 (36)	3 (16)	0.1[a]
≤60	50 (64)	16 (84)	
Gender			
Female	31 (40)	12 (63)	0.06[b]
Male	47 (60)	7 (37)	
Anemia at diagnosis (n = 92)			
Yes	56 (75.6)	7 (38.9)	0.002[b]
No	18 (24.4)	11 (61.1)	
Sokal score (n = 80)			
Low	21 (33.3)	10 (58.8)	0.06[b]
Intermediate	23 (36.5)	6 (35.3)	
High	19 (30.2)	1 (5.9)	
Previous use of INF			
Yes	19 (24)	2 (1.5)	0.23[a]
No	59 (76)	17 (89.5)	
Initial dose of imatinib			
300 mg	2 (2.5)	0	
400 mg	69 (88.5)	18 (94.7)	0.66[b]
600–800 mg	7 (9)	1 (5.3)	

[a] Fisher test.
[b] Chi-square test.

Table 5 – Evaluation of responses to imatinib therapy in patients who developed anemia (*n* = 78).

		Status after 2 years of imatinib treatment							Total (%)	Total (*n*)
		CHR	CCyR	PCyR	Minorcyr	CMR	MMR	PH		
Cause of anemia	No cause identified	2	21	1	0	9	19	0	52	66.6
	Resistance	5	4	2	1	0	0	1	13	16.7
	Others	0	4	2	0	3	4	0	13	16.7
Total (*n*)		7	29	5	1	12	23	1	78	–
Total (%)		8.9	37.2	6.4	1.3	15.4	29.5	1.3	–	–

Table 6 – Creatinine levels at diagnosis and during therapy with imatinib.

Creatinine (mg/dL)	Minimum	Maximum	Median
Before imatinib	0.31	1.31	0.85
After 2 years of imatinib	0.57	1.39	0.96
Until last follow-up	0.51	4.17	1.05

Discussion

We observed a high frequency of anemia after long-term treatment with imatinib, most of these cases being treatment-related, as most of the patients exhibited satisfactory cytogenetic and molecular responses. It is not clear why some patients develop myelosuppression during this therapy. Along with its potent inhibitory effect on the tyrosine-kinase inhibitors BCR-ABL, imatinib also inhibits the proto-oncogene c-kit, which is involved in hematopoiesis. Thus, myelosuppression may be a result of the unwanted progenitor cell suppression.[10,11] In the present study we analyzed the hematological toxicity of red blood cells caused by imatinib. Seventy-eight patients (80.4%) presented anemia after two years of therapy, and 19.2% of the patients had grade 2–3 toxicity (only one had grade 3). In the IRIS trial, the use of imatinib a as first-line treatment for the CP, anemia occurred in 45% of the patients and grade 3–4 anemia occurred in 3% of them.[4] However, few studies have evaluated the toxicity during

long-term treatment. In most of the patients (66.6%), we found no etiological factor for the anemia, whereas 94.2% ($n = 49$) of the cases had CCyR and MMR. Only 6 of the 52 patients without a defined cause for anemia showed no cytogenetic and molecular responses and therefore anemia could only be attributed to the disease. We also found that toxicity was transient in 35.9% of the patients, as there was resolution without treatment, but its persistence in 51.3% of cases suggests that the degree of myelotoxicity appears to be irreversible during continued therapy (7.7% had resolution of anemia and 5.1% improvement in Hb levels after changing to a second-generation inhibitor). Sneed et al. demonstrated that myelosuppression during therapy with imatinib adversely affected the results of patient care, mainly the achievement of CCyR, independent of other variables prior to treatment.[10] However, it is difficult to evaluate if the worst prognosis is related to the presence of a limited pool of normal stem cells that is unable to produce the normal hematopoiesis after the suppression of the abnormal clone or the low-dose intensity of imatinib due to treatment interruptions and dose adjustment. In a multivariate analysis, in 68% of the cases, the following pre-treatment factors were associated with an increased independent risk of developing anemia during treatment with imatinib: basal Hb levels < 12 g/dL, age ≥ 60 years, female gender, higher starting dose and intermediate- or high-risk Sokal score.[9] The development of anemia during the use of imatinib has been associated with worse rates of CCyR (68% vs. 77%) and worse survival.[9] On the other hand, a recent study showed that the presence of persistent/late chronic anemia (about 30% of 128 patients) did not seem to affect the event-free survival (EFS) and overall survival (OS).[15]

In the management of adverse events related to therapy with imatinib, treatment interruption and dose reduction should be avoided when managing anemia. In this context, erythropoietin (EPO) can be used to improve Hb levels and to allow an effective dose of imatinib.[16] Cortes et al. used EPO in 102 of 230 patients (68%) who developed anemia with the use of Imatinib. They received 40,000 U of weekly subcutaneous EPO. An increase in Hb ≥ 2 g/dL was found in 69 patients (68%) and 22 patients (22%) had an increase of 1–1.9 g/dL. The authors concluded that EPO is safe and effective in CML patients in the CP.[9] The long-term safety of EPO was analyzed in a cohort of 608 CML patients. Anemia grades 3–4 occurred in 10%. Patients who received EPO presented a higher rate of thrombosis, in comparison with patients who did not (8.5% vs. 2.6%, $P = 0.0025$). There was no difference in the cytogenetic response rate and survival.[17] In our cohort, EPO was not routinely available and was used only in one patient with renal impairment. In the present study, there was an incidence of renal toxicity of 8.9% and most of the patients developed mild toxicity (7.6%). However, at the last follow-up, 23.2% of the patients presented renal dysfunction, which suggests that the incidence of renal toxicity increases with the time of exposure to imatinib. The IRIS trial did not report acute renal failure as an imatinib-related adverse effect.[18] Marcolino et al. evaluated the renal function in CML patients receiving long-term treatment with imatinib and reported an incidence of 7% of acute kidney injury with imatinib, which was most often irreversible. In the long term, imatinib was related to a clinically significant decrease in the glomerular filtration rate (GFR), which can lead to chronic renal failure.[19] Considering that CML is more common in elderly patients, and that the prevalence of the GFR can be as high as 60% in individuals 60–69 years old and up to 74% in older individuals, the exact incidence of this adverse effect in patients is still uncertain.[19,20] Furthermore, the current study did not consider other conditions that can contribute to progressive renal dysfunction, such as the association with hypertension and diabetes mellitus, which was present in 34% and 16.4% of the study population, respectively.

Conclusions

We conclude that despite the high incidence of anemia in long-term treatment with imatinib in CML patients, most cases are mild or moderate and hence symptomatic treatment continues to be the preferred option prior to switching the therapy. In the absence of secondary causes that justify the anemia, myelosuppression caused by imatinib should be considered. Regular monitoring and additional investigation are necessary to identify causes unrelated to CML that can be treated, especially in patients with good adherence and satisfactory therapeutic response. Long-term treatment with imatinib may also result in a significant reduction in the glomerular filtration rate and chronic renal failure. Therefore, it is important to monitor renal function regularly in patients on imatinib treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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