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Full Length Article

Impact of imatinib interruption and duration of prior hydroxyurea on the treatment outcome in patients with chronic myeloid leukemia: Single institution experience

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KEYWORDS

Chronic myeloid leukemia;
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Abstract *Background:* Optimal response requires that patients should be maintained on the drug continuously.
Objectives: To evaluate the influence of imatinib interruption and prior hydroxyurea use on the outcome of patients with chronic myeloid leukemia.
Materials and methods: Between January 2010 and November 2013, patients with chronic phase who received imatinib at the Kasr Al-ainy Center of Clinical Oncology were included.
Results: Sixty patients were included in this study, thirty three patients (55%) received imatinib upfront, while 27 (45%) received imatinib post hydroxyurea. Imatinib was not given regularly in 50% of patients. In terms of response, only major molecular response and complete molecular response were statistically significant in favor of patients who were receiving imatinib regularly compared to those who had interruption ($p < 0.001$, $p < 0.001$, respectively) , while there was no difference in patients stratified according to prior hydroxyurea. The median progression free survival was 30.3 months (95% CI 24.3–36.3). Among the group of patients who received imatinib regularly, progression free survival was longer ($p = 0.049$), there was no difference between those who received prior hydroxyurea versus those who did not ($p = 0.67$).
Conclusion: Duration of prior hydroxyurea had no impact on response or progression free survival, while patients regular on imatinib had statistically significant difference with respect to major

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molecular response, complete molecular response and progression free survival compared to those who had periods of drug interruption, thus we need more governmental support to supply the drug without interruption to improve the outcome of therapy.

Introduction

Chronic myeloid leukemia (CML) accounts for approximately 15 to 20 percent of leukemias in adults [1]. It has an annual incidence of 1 to 2 cases per 100,000, with a slight male predominance [2–4].

CML is a myeloproliferative neoplasm characterized by the BCR-ABL1 fusion gene located in the Philadelphia chromosome (Ph+), and uncontrolled proliferation of mature and maturing granulocytes with fairly normal differentiation [5].

The management of Ph+, BCR-ABL1 + CML has undergone a profound evolution over a relatively short period of time, starting with allogeneic stem cell transplantation and recombinant Interferon-alfa, and more recently and most significantly, with the tyrosine kinase inhibitors (TKIs) [6–8].

The first trials of TKIs in BCR-ABL-positive disease evaluated imatinib in patients refractory or intolerant to interferon therapy, which had been the standard of care prior to the availability of imatinib. Subsequently, the randomized IRIS trial (International Randomized Study of Interferon and STI571) compared imatinib to interferon therapy in previously untreated patients in chronic phase [9]. Imatinib produced significantly higher hematologic and cytogenetic response rates with deeper, more durable responses, and much less toxicity. No survival benefit has been demonstrated due to the large number of patients allowed to switch from Interferon to imatinib. However, several historical/retrospective comparisons have shown significantly better overall survival following treatment with imatinib than with interferon-containing regimens [10,11]. Thus, imatinib was the first approved TKI in the management of CML.

Here, we retrospectively reviewed patients referred to the Kasr Al-ainy Center of Clinical Oncology and Nuclear Medicine (NEMROCK) with the diagnosis of chronic phase CML and treated with imatinib aiming at evaluation of the influence of imatinib interruption and prior hydroxyurea use on the response and progression free survival.

Patients and methods

Between January 2010 and December 2013, all patients with chronic phase CML who received imatinib at NEMROCK were included in a retrospective analysis. All patients started on imatinib 400 mg daily. Patients were assessed every 2 weeks in the first 2 months then on monthly basis.

The patients were analyzed with respect to the demographic profile, European Treatment and Outcome Study (EUTOS) scoring system for CML, molecular response, safety and survival. Cytogenetic analysis was not performed routinely in our institution. A baseline qualitative PCR test was done to confirm the type of BCR-ABL transcripts. Molecular response was performed using real time quantitative polymerase chain reaction (RT Q-PCR) every 3 months.

Complete hematological response (CHR) was defined as white blood cell count $< 10 \times 10^9$/L, platelet count $< 450 \times 10^9$/L, presence of $< 5\%$ myelocytes plus metamyelocytes, $< 20\%$ basophils and absence of blasts or promyelocytes in the peripheral blood, or extramedullary involvement. Major molecular response (MMR) was defined as BCR-ABL: ABL $\leqslant 0.1\%$, while complete molecular response (CMR) or molecularly undetectable leukemia refers to no detectable BCR-ABL transcripts by RTQ-PCR.

The 2009 European Leukemia Net (ELN) response criteria was adopted to define chronic, accelerated, blastic phases and to assess the response [12]. An optimal response to imatinib is defined by CHR at 3 months, BCR-ABL: ABL < 10% at 6 months, BCR-ABL: ABL < 1% at 12 months and MMR at 18 months. Failure is defined by incomplete HR at 3 months, no CHR at 6 months, BCR-ABL: ABL > 10% at 12 months, and BCR-ABL: ABL > 1% at 18 months. In any other situation, the response is defined suboptimal.

Adverse events were assessed according to common terminology criteria for adverse effects (CTCAE) version 3.0 [13].

Statistical analysis

Descriptive statistical analysis was carried out to assess the patients' demographics and clinical characteristics. Patients were divided into 2 groups according to prior hydroxyurea administration or imatinib interruption. The comparison between the 2 groups and the response was assessed using the Chi-square test. Survival plots were drawn using the Kaplan–Meier method [14]. The log-rank test was used to assess the survival difference between groups. Univariate analysis using Cox regression module was performed to test the power of relation between variables and survival. Differences were considered significant if p value was less than 0.05 [15]. All analyses were performed using SPSS statistical software (version 20.0).

Progression free survival (PFS) was defined as the time from the start of imatinib to the onset of an accelerated or blastic phase, discontinuation of imatinib due to failure, suboptimal response or death.

Results

During the study period, 60 patients were included. Thirty-three patients (55%) received imatinib upfront, while 27 (45%) received imatinib post hydroxyurea. Of the latter group, patients were shifted to imatinib as soon as the drug was available through the ministry of health. Hydroxyurea was used

Table 1 Baseline characteristics of whole group patients included in the study.

Characteristics		*n* (%)
Age (years)	Median	46
	Range	18–86
	>60 years	10(17)
Gender	Male	30(50)
	Female	30(50)
EUTOS[†] score	Low	45(75)
	High	15(25)
White cell count (10^9/L)	Median	150
	Range	29.8–500
Hemoglobin (g/dl)[‡]	Median	10
	Range	6.4–12.6
Platelet count (10^9/L)	Median	271
	Range	93–797

[†] EUTOS: European Treatment and Outcome Study for CML.
[‡] Gram/deciliter.

Table 2 Response to imatinib therapy in whole group patients included in this study according to prior hydroxyurea.

Variable	Imatinib upfront *n*:33	Imatinib post hydroxyurea *n*:27	*P* value
Complete hematologic response	31 (94%)	24 (89%)	0.234
Major molecular response	19 (57.5%)	15 (55.5%)	0.757
Complete molecular response	9 (27%)	6 (22%)	0.462

with a range of treatment duration between 1 month and 60 months prior to imatinib.

The median age of the patients was 46 years, with no gender predominance (Male:Female ratio 1:1). The majority of the cases had low risk (75%) according to EUTOS scoring system. Baseline patients' characteristics are summarized in Table 1.

At a median follow up of 22 months, the rate of CHR, MMR and CMR was not statistically different in the group who had imatinib upfront compared to those who had hydroxyurea, Table 2. By comparing those who were regular on imatinib to those who had interruption, there was a statistically significant difference observed in both MMR ($p < 0.001$) and CMR ($p < 0.001$) while CHR was similar ($p = 0.348$) (Table 3).

Imatinib dose and safety

All patients started on imatinib 400 mg daily. The dose was reduced to 300 mg/day in 7 patients (11.6%) due to recurrent neutropenia or thrombocytopenia.

The median treatment duration was 14.6 months (range: 1–64). Imatinib was not given regularly in 50% of patients due to financial and logistic reasons, with median treatment interruption of 21 days (range 7–50 days), with most of the treatment delay encountered after the first year of therapy.

Table 3 Response to imatinib therapy in whole group patients included in this study according to drug interruption.

Variable	No interruption (*n*:30)	Interruption (*n*: 30)	*P* value
Complete hematologic response	38 (95%)	17 (85%)	0.348
Major molecular response	28(70%)	6(30%)	<0.001
Complete molecular response	13(32%)	0(0%)	<0.001

The predominant grade 1 and 2 hematological toxicity of imatinib included neutropenia (27%), followed by anemia (24%) and thrombocytopenia (15%). None of the patients developed grade 3 or 4 hematological adverse events.

The most commonly reported non hematological adverse event of imatinib included peripheral edema (31%), muscle cramps (30%), fatigue (26%), and skin rash (10%), these events were mostly grade 1 or 2 toxicity. Only one patient discontinued imatinib due to grade 3 arthralgia.

Survival analysis

The median PFS was 30.3 months (95% CI 24.3–36.3) (Fig. 1). No statistically significant difference was observed in PFS according to EUTOS score ($p = 0.334$) (Fig. 2) or duration of prior hydroxyurea administration ($p = 0.224$), (Fig. 3).

Patients regular on imatinib had longer PFS compared to those who had periods of drug interruption ($p = 0.049$), (Fig. 4 and Table 4).

Discussion

Philadelphia-positive, BCR-ABL1-positive CML is a simple model of cancer driven by a single, specific, chromosome translocation, the t(9;22)(q22;q11), that leads to the formation of a new, hybrid, leukemia-specific gene (BCR-ABL1) that codes for a unique protein that drives the leukemic transformation of hematopoietic stem cells. This makes CML an ideal model for true targeted therapy [6].

In the current analysis, we reviewed the response and safety of imatinib in our institute from January 2010 to November 2013. Before 2009, hydroxyurea was the main treatment line for our patients with chronic phase CML, while interferon alpha was used only for few patients due to the cost and side effects.

The median age of our patients was 46 years. CML has a slight male predominance [3,4], however, in the present study, cases were distributed equally in both genders. Various scoring systems have been devised in an attempt to predict disease outcome, Sokal [16] and Euro (Hasford) [17] scores were developed prior to the discovery of imatinib, the EUTOS score was developed and validated using data from 2060 patients enrolled in prospective studies of imatinib [18]. In our analysis, the majority of the cases ranked in the low risk group (75%).

In the major studies testing the efficacy of imatinib 400 mg daily in CML, the proportion of patients who achieved MMR after 1 year of therapy ranged from 18% to 58% [19–25]. In a

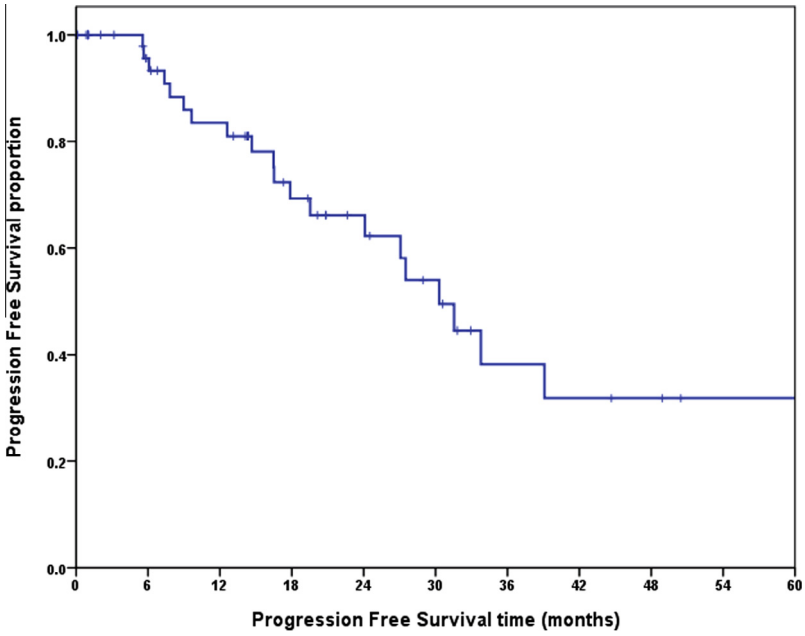

Figure 1 Progression-free survival of the whole group patients included in this study.

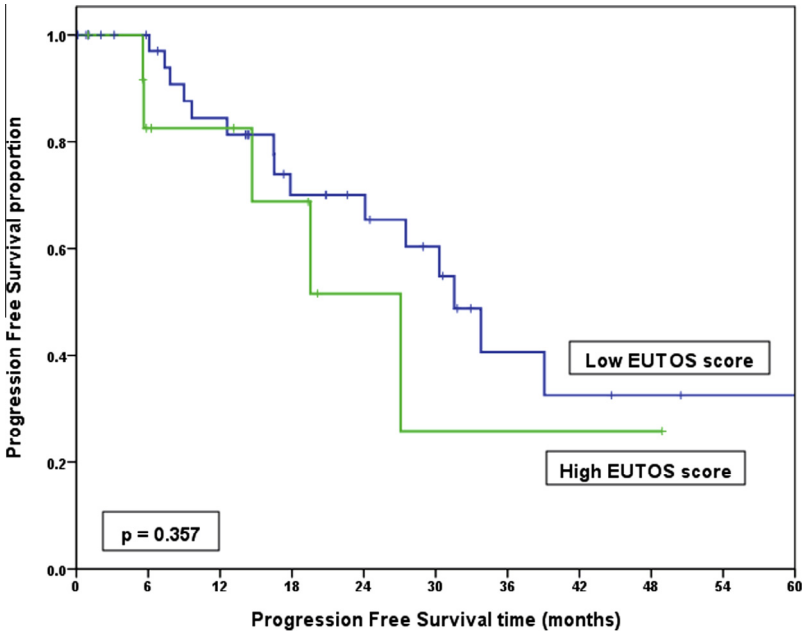

Figure 2 Progression-free survival of the whole group patients included in this study according to EUTOS score.

recent Egyptian study of 55 patients, CHR at 3 months and MMR at 18 months was achieved by 98.2%, and 51% respectively [26]. In the present study, the rate of CHR and MMR according to prior hydroxyurea or imatinib interruption was 91.6%, 56.6% respectively, CMR was 25% and 21.6% for the patients stratified according to prior hydroxyurea and imatinib interruption respectively. These figures are somewhat lower than those of the international studies while similar to the Egyptian one. The importance to maintain patients regularly on imatinib was addressed in SPIRIT2 study, in which treatment interruption or dose reduction of imatinib or dasatinib in newly diagnosed CML within first 3 months was associated with poorer molecular response at 3 and 12 months [27]. In our analysis, the MMR and CMR were statistically significant in favor of those who were receiving imatinib regularly.

In the published literature, PFS ranged between 83% and 94% and the number of patients still receiving initial imatinib treatment was reported at 63% to 79% after 3 to 5 years [28–37]. In our analysis, the PFS, and the percentage of those who are still receiving imatinib, were inferior to the previously

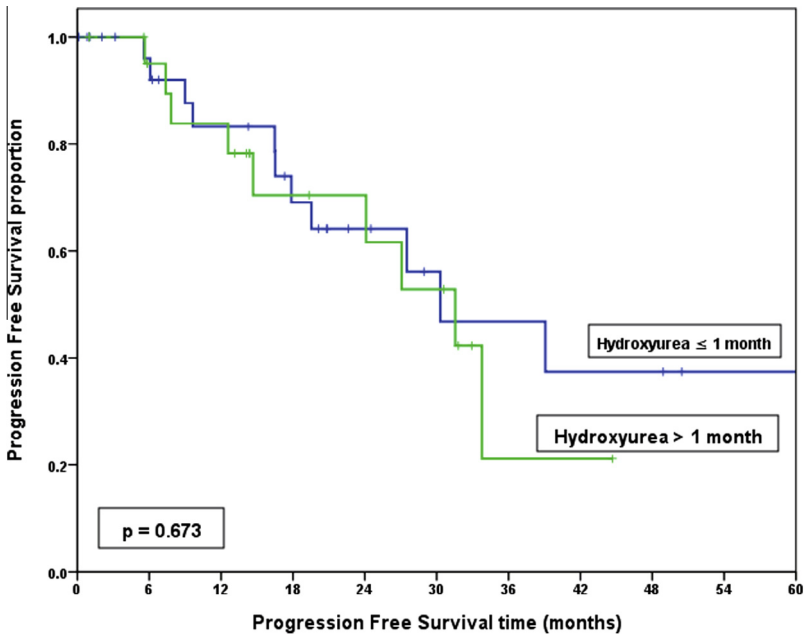

Figure 3 Progression free survival according to duration of hydroxyurea therapy (< 1 month versus > 1 month).

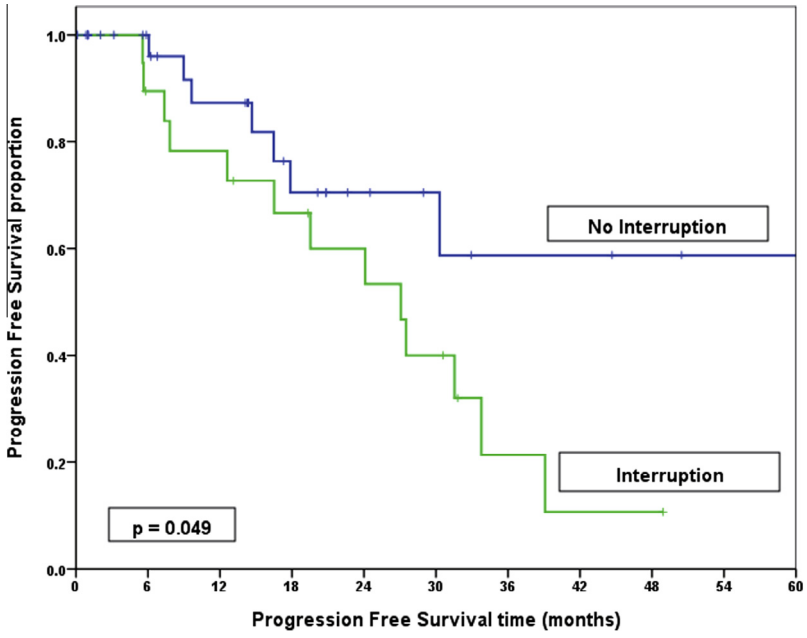

Figure 4 Progression-free survival according to imatinib interruption.

published trials, including some studies in other developing countries [38,39]. These results could be attributed to small number of patients, retrospective nature of the study, and irregular intake of imatinib.

In our study, there was no significant difference in response or PFS in the group of patients who received imatinib as the initial treatment compared to those who received it after hydroxyurea. On the contrary, there was a significant lower median PFS in patients with irregular administration of imatinib compared to those who were regular on the drug. Thus, a short delay in starting imatinib is better than starting earlier then had to interrupt the drug due to unavailability.

In the present analysis, half of the cases received imatinib irregularly. The cost of imatinib is high, particularly because treatment needs to be continued for life. In Egypt, imatinib is provided through the ministry of health, and similar to other developing countries; we have financial problems to maintain our patients on imatinib continuously without interruption.

The introduction of imatinib was celebrated as the beginning of a new era of cancer treatment, in which therapy was

Table 4 Univariate analysis for factors affecting Progression Free Survival.

Variable		Number of cases	2 years PFS (%)	*P* value	HR	95% CI
Prior hydroxyurea	No	33	65	0.673	1.21	0.49–2.96
	Yes	27	62			
Imatinib interruption	No	30	70	0.049	2.38	1.01–5.99
	Yes	30	60			
EUTOS score	High	15	50	0.360	1.61	0.58–4.48
	Low	45	70			

HR: hazard ratio; EUTOS: European Treatment and Outcome Study.

finally nontoxic, safe and well-tolerated [40]. After more than 10 years, these promises were largely fulfilled because the side effects of imatinib are usually mild, with only rare severe, life threatening complications [41]. Overall, imatinib was tolerable in our patients, most of the adverse events were manageable, only one patient stopped therapy due to grade 3 arthralgia.

In conclusion, duration of prior hydroxyurea had no impact on response or PFS, while patients regular on imatinib had statistically significant difference of MMR, CMR and PFS, compared to those who had periods of drug interruption. Thus, we need more governmental support to supply the drug without interruption to improve treatment outcome for our CML patients.

Conflict of interest

None.

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