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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