

Non-hematological Adverse Events of Imatinib in Patients with Chronic Myeloid Leukemia in Chronic Phase (CML-CP)

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ARTICLE INFO

Article history:

Received on: 06/11/2014

Revised on: 24/12/2014

Accepted on: 17/01/2015

Available online: 27/02/2015

Key words:

Chronic myeloid leukemia,
Fatigue, Imatinib, Myalgia

ABSTRACT

The aim of this study is survey of effects of Imatinib with dose 400 mg per day after 6 months in the patients with CML chronic phase. Between of 2010 - 2014, fifty four patients with high risk CML referred to Taleghani hospital in Kermanshah, Iran. We used the questionnaire about adverse events (AEs) of Imatinib capsule (Cipla manufacture, India) in these patients. For grading AEs, We used Common Terminology Criteria for AEs (CTCAE) manuscript (low AE equals grade 1, 2; high AE equals 3, 4 and grade 5 is optional) that diagram related to them was plotted with Excel 2007 software. 54 patients that referred to hospital, 27 patients were female and 27 patients were male. Mean of age for the patients was 45.7 ± 13.8 years (range, 23 to 78 years). Fatigue, (66.7%), myalgia (61.6%), joint pain (61.6%) and cramp (57.4%) are the most AEs in the patients after treatment of Imatinib. In the future studies we should evaluate non-hematological AEs for Imatinib in a lot of CML patients and apply to CTCAE manuscript exactly.

INTRODUCTION

Chronic myeloid leukemia (CML) is a chronic disease that about 50% of patients are more than 60 years old, and about 50% of patients are asymptomatic (Baccarani *et al.*, 2013). In the patients with CML, the introduction of targeted therapy using tyrosine kinase inhibitors (TKI), the majority of patients remain in long-term complete remission. However, the discontinuation of the therapy usually leads to disease relapse which indicates that the residual disease remains to be a major issue in CML management (Mauro, 2013) The first approved TKI was Imatinib Mesylate (Glivec or Gleevec), that is still the CML standard treatment for many-patients and the structure of Imatinib has been shown in **Fig. 1** (Baccarani *et al.*, 2013). Imatinib, a tyrosine kinase inhibitor, was called as "magical bullet," when it revolutionized the treatment of chronic myeloid leukemia (CML)

in 2001, and it was invented in the late 1990s by biochemist Nicholas Lyndon and its use to treat CML was driven by Brian Druker. Encouraged by the success of Imatinib in treating CML patients, scientists explored its effect in other cancers and it was found to produce a similar miracle effect in other cancers where tyrosine kinases were over expressed. (Iqbal and Iqbal, 2014) In other hand, Imatinib was one of the first cancer therapies to show the potential for such targeted action, and is often cited as a paradigm for research in cancer therapeutics (Stegmeier *et al.*, 2010). Imatinib(Indian generic) was started at a dose of 400 mg in our patients with CML chronic phase. The most commonly observed non-hematologic AEs include nausea, vomiting, diarrhea, muscle cramps, fluid retention, skin rash, and fatigue other less common AEs, such as liver and kidney toxicity, have also been reported in the literature (Foringer *et al.*, 2005). The side effects of TKIs are reported as 'tolerable' and 'manageable', but when the AEs, even minimal, even mild, are chronic, the quality of life and the compliance to treatment will be affected (Talpez *et al.*, 2013). To optimize Imatinib treatment and the understanding of CML, the European treatment and outcome study for CML

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(EUTOS) was launched as a scientific collaboration between the Euro-pean LeukemiaNet (ELN) and the manufacturer of the drug. (Anonyms, 2008) In this study, we reported non-hematologic AEs (AEs) of Imatinib in CML chronic phase patients in Kermanshah province, Iran.

Patients and Methods

The study was conducted from 2010 to 2014; during this period, fifty four patients with high risk CML referred to Taleghani hospital in Kermanshah, Iran. We gathered data with using the questionnaire about AEs of Imatinib capsule (Cipla manufacture, India) that medical oncologist prescribed to them for a period of time sex months with dose 400 mg per day as first line therapy. Non-hematologic AE of Imatinib includes: fatigue(most), weakness and lethargy, myalgia, joint pain(knee-ankle-elbow), cramp, bone pain, swelling of face, insomnia, depression, abdomen pain, nausea, swollen hands and feet, constipation, weight loss, vomiting, cough, weight gain, fever, rash and hives, weld, throat infection, diarrhea, sinusitis, blood in the stool-vomiting blood and urinary retention(lowest). Grade refers to the severity of the AE: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated (Grade 1 or Mild). Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)(Grade 2 or Mild). medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL(Grade 3 or severe). Life-threatening consequences; urgent intervention indicated (Grade 4). We regardless grade 5 based on CTCAE. In our study, the patients with low AE are located in grade 1 or 2 and the patients with high AE are located in grade 3 or 4. We used Excel 2007 software for drawing of diagram.

RESULTS

In this study, 54 patients with CML in the chronic phase were included; 27 patients were female and 27 patients were male. Mean of age for the patients was 45.7 ± 13.8 years (range, 23 to 78 years) (**Table 1**). The **Table 2** shows different AEs of Imatinib capsule that and also **Fig. 2** shows grading of AEs that we separate them two level, low AE and high AE.

The **Table 2** shows that fatigue, weakness and lethargy, myalgia, joint pain (knee-ankle-elbow) and cramp observe in more of 50% of patients.

DISCUSSION

Imatinib produces a high effect in the course of CML (Baccarani *et al.*, 2014). It is a very powerful medication, so AEs can be expected to occur (Valizadeh, 2011). A study (Mozaheb, 2014) in Iran showed that fluid retention (64%), fatigue (43%), musculoskeletal pain (41%), skin rash (35%), nausea (21%) were the most common non-hematologic side effects for

Imatinib in the CML patients but in our study were fatigue, weakness and lethargy (66.7%), myalgia (61.6%), joint pain(knee-ankle-elbow)(61.6%) and cramp (57.4%). A study in India (Gupta and Prasad, 2007) reported edema and arthralgia as their predominant adverse effects (Moshfeghi *et al.*, 2013). reported that the most prevalent adverse effects of Imatinib in previous studies were edema, nausea, cramp, rash, and diarrhea, which occurred in 29-60% of the patients with CML, and other study in Iran reported frequency of common adverse effects observed for the Indian and Iranian kinds of the drug in the study were as follows: edema (facial edema was more prevalent) (62.7 vs. 63.7%), GI symptoms (41.9 vs. 39.1%), fatigue and headache (40.6 vs. 43.2%), mood symptoms (11.6 vs. 15.6%), and hematological complications (9.3% in both kinds) (Moshfeghi *et al.*, 2013; Hattab, 2013). Is reported skin rash was 19.9%. In the IRIS (international randomized study of interferon) study, 30% of the patients had grades 3/4 AEs that included fatigue, depression, myalgia, arthralgia,(O'Brien *et al.* , 2003) whereas in our study 24%,5.5%, 13% and 11% of the patients had those signs in high AEs, respectively. Also in low AEs we observed them with more density, 42.5%, 24%, 48%, 50%, respectively and other study reported just fatigue (43%) (Talpez *et al.*, 2013). There were no reports of nausea, muscle cramps, joint pain, and skin hypo pigmentation (Jalaeikhoo *et al.*, 2011) whereas in our study was reported nausea (25.9%), cramp (57.4%), joint pain(61.6%) and skin hypo pigmentation(31.5%) that it is apposite of report of Jalaeikhoo *et al.* (Jalaeikhoo *et al.*, 2011). but approximately was similar to report of O'Brien SG *et al.*[O'Brien *et al.*, 2003] In a Iranian study which were used generic Imatinib, like our study, AEs were: edema (63%), GI symptoms (40%), fatigue and headache (40%) and mood symptoms (13%)(Moshfeghi *et al.*, 2013). Elderly female patients had higher Imatinib concentrations and more AEs (Gotta *et al.*, 2014). There is reduction in the risk of non-hematological AEs with early treatment, including weight gain (11%), periorbital edema (12%), rash (9%), diarrhea (11%), and bone pain (8%)(Breccia *et al.*, 2008). Common AEs of Imatinib were relatively similar and comparable to others. All these differences may be due to the effect of biological, environmental, or socioeconomic factors, and/or the Imatinib which was used. we showed a higher efficacy and safety of Imatinib therapy among Iranian patients with CML (Jalaeikhoo *et al.*, 2011). In **Table 2**, we observed 24 AEs related to Imatinib capsule that some of them is observed in CML chronic phase patients rarely like Sinusitis(5.6%), blood in the stool-vomiting blood(3.7%), urinary retention(1.9%). We saw constipation in 12 patients from all patients were under our study so based on our knowledge, it is a new AE for Imatinib. As we can see in **Table 1** the mean age of our patients (Kermanshah, Iran) was 45.7 (range 23- 78) years at diagnosis but is more than some reports from eastern. In a study, age at diagnosis differed within Asia, in western Asia 44.4 years, southeastern Asia 39.5, eastern Asia 38.4, south-central Asia 37.8 were reported (Mendizabal *et al.*, 2013).

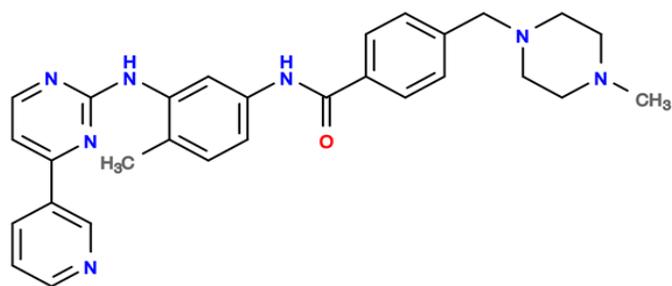


Fig. 1: Chemical structure of Imatinib.

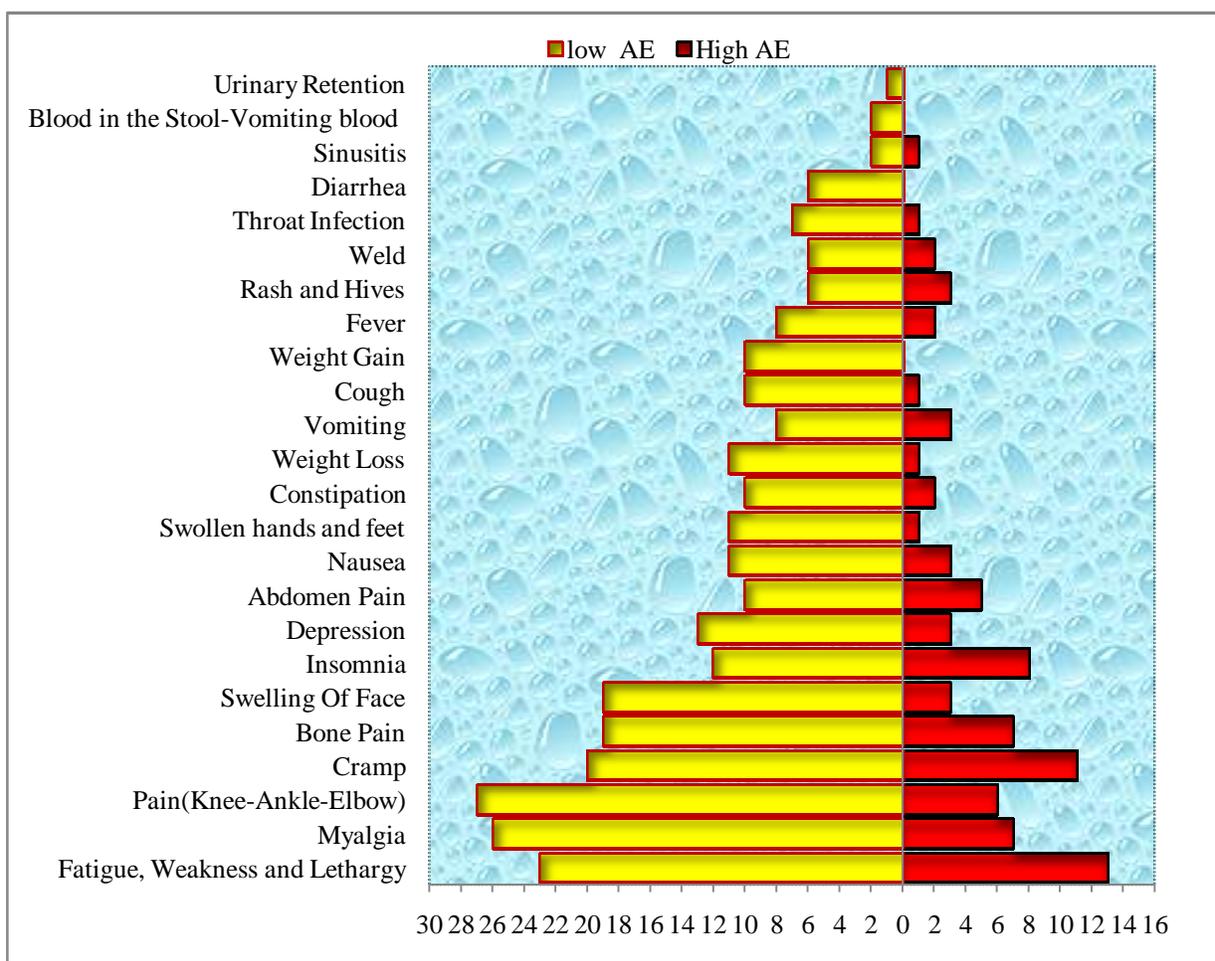


Fig. 2: Tow grading for AEs of Imatinib in CML chronic phase patients.

Table 1: Characteristic of the 54 patients with CML

Characteristic	n(%)
Sex	
Male	27
Female	27
Age(year)	
Min	23
Max	78
Mean	45.7±13.8

Table 2: Common non-hematologic side effects of Imatinib (n=54).

<i>Non-hematologic AE</i>	<i>n(%)</i>	<i>Non-hematologic AE</i>	<i>n(%)</i>
Fatigue, Weakness and Lethargy	36(66.7)	Weight Loss	12(22.2)
Myalgia	33(61.6)	Vomiting	11(20.4)
Joint Pain (Knee-Ankle-Elbow)	33(61.6)	Cough	11(20.4)
Cramp	31(57.4)	Weight Gain	10(18.5)
Bone Pain	26(48.1)	Fever	10(18.5)
Swelling Of Face	22(40.7)	Rash and Hives	9(16.7)
Insomnia	20(37.0)	Weld	8(14.8)
Depression	16(29.6)	Throat Infection	8(14.8)
Abdomen Pain	15(27.8)	Diarrhea	6(11.1)
Nausea	14(25.9)	Sinusitis	3(5.6)
Swollen hands and feet	12(22.2)	Blood in the Stool-Vomiting Blood	2(3.7)
Constipation	12(22.2)	Urinary Retention	1(1.9)

CONCLUSIONS

Fatigue and Myalgia are the most AEs for Imatinib in the patients of CML. Therefore, in the future studies we should evaluate AEs for Imatinib in a lot of CML patients and express grading more accurate.

ACKNOWLEDGMENT

There is no acknowledgment.

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How to cite this article:

Mehrdad Payandeh, Edris Sadeghi, Masoud Sadeghi. Non-hematological Adverse Events of Imatinib in Patients with Chronic Myeloid Leukemia in Chronic Phase (CML-CP). *J App Pharm Sci*, 2015; 5 (02): 087-090.