IMATINIB IN CHRONIC MYELOID LEUKEMIA: PATIENT-REPORTED SIDE EFFECTS AND THEIR INFLUENCE ON QUALITY OF LIFE

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ABSTRACT

Objective: To evaluate side effects of Imatinib by patients of chronic myeloid leukemia and their influence on quality of life.

Study Design: Descriptive & analytic study.

Place and Duration of Study: The study was carried out at department of oncology CMH Rawalpindi, from Jan 2015 to Dec 2015.

Material and Methods: The study was carried out at department of oncology CMH Rawalpindi from Jan 2015 to Dec 2015. Patients who had been using Imatinib orally for at least 6 months participated in the study. Patients under 18 years of age were excluded from the study. A questionnaire was developed to record adverse effects. This questionnaire included demographic details and quality of life issues like effects on their mood, daily life activities, work, walking and relationships.

Results: Ninety two patients participated in the study. Mean age of the participants was 42.05 years (range 22 to 68 years), 52% were males. Among the study population eighty-seven percent had suffered from at least one adverse reaction. The most commonly complained adverse events were muscle cramps (67 out of 92, 72.8%); fatigue (58 out of 92 63.04%), gastro intestinal upset (44 out of 92 47.82%) and skin rashes (30 out of 92 32.60%). More than half of the patients felt that the adverse effect had a negative influence on their daily quality of life.

Conclusion: Adverse drug effects were common among CML patients receiving Imatinib therapy. These adverse drug reactions had negative impact on patients' daily life.

Keywords: Adverse effects, CML, Imatinib, Patient-reported symptoms, Quality of life.

INTRODUCTION

Chronic Myeloid Leukemia (CML) accounts for 15% of adult leukemias[1]. It is characterized by Philadelphia chromosome (Ph) which results from a reciprocal translocation between chromosomes 9 and 22. Translocation t (9;22) leads to fusion of breakpoint cluster region (BCR) gene on chromosome 22 and Abelson murine leukemia (ABL1) gene located on chromosome 9[2]. The product of the BCR-ABL1 fusion gene plays a central role in the pathogenesis of CML[3]. Imatinib and other tyrosine kinase inhibitors (TKIs) has markedly improved the prognosis for CML patients. CML chronic phase patients treated with TKIs have good survival rates. Estimated overall survival rate for patients treated with Imatinib is 85% after 8 years' follow-up[4]. However patient has to take this therapy for life long. In CML patients Imatinib treatment is indicated for the whole life, and is usually very well tolerated. As the treatment is life long, many of the patient's experience some drug-related side effects at some point during the treatment course[5]. Oral Imatinib therapy is associated with a number of adverse events, inclusive of but not limited to bone marrow suppression, gastrointestinal upset, skin rashes, fatigue, and muscle pains. These adverse effects occur at varying frequencies[6]. Over the past 15 years, evidence has proved that self-reporting of adverse drug effects by patients is both feasible and much more useful. Many of the recent studies have described programmes in which self-reporting by patients has been used to collect data rather than using the system of reporting by health care providers[7].

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Standardized collection of patient reported outcomes and data for health related quality of life in solid tumours has led to better understanding of treatment effectiveness, but similar evidence is lacking in leukemia cases[8]. FDA has defined patient reported outcomes as "measurement of different aspects of patient's health status directly from the patient without any interpretation of a doctor or health care provider)[9]. In chronic myeloid leukemia patients treated with Imatinib (or other tyrosine kinase inhibitors) documentation of side effects of therapy from the patients' perspective is useful to evaluate efficacy of treatment and overall clinical benefits of newer treatment options. An approach which is patient-centred is more useful and this concept is supported by recent research showing that physicians are more likely to underestimate the intensity of symptoms felt by patients with advanced malignany[10]. At this point in time, however there is lack of availability of validated instruments to measure patients' quality of life in CML We developed a questionnaire to record patient reported adverse effects and quality of life issues for chronic myeloid leukaemia patients.

The aim of this study was to use this questionnaire to evaluate patient reported side effects of treatment and their impact on daily living of CML patients taking Imatinib.

PATIENTS AND METHODS

This descriptive study was conducted at Oncology Department, Combined Military Hospital Rawalpindi from 1st January 2015 to 31st December 2015.

Ninety two adult patients suffering from chronic-phase CML who had been on Imatinib treatment for at least 6 months were included in the study. Informed consent was obtained from all the patients participating in the study. The study protocol was approved by hospital's ethics committee. All patients were interviewed by a member of the research team and findings were recorded using a structured form. The questionnaire was developed after searching the literature for adverse effects of imatinib. It was reviewed by a panel of experts and was finalized after piloting on 10 patients. The collected data was analysed using SPSS version 17. Patient-reported side effects of drug were assessed during the interview with the help of a structured questionnaire. The questionnaire comprised of two demographic items, a list of ten treatment-specific adverse effects, and five questions determining the symptoms' effect on patient's daily life.

This interview also included five specifically designed questions to assess functional impairment of daily life associated with Imatinib therapy. The effect of drug's side effects on patient's mood, daily life activities, work, walking and relationships in general were documented. Each positive answer had one point (i.e. the patient answering "yes" will get one point), leading to a maximum 5 points. If the patient did not have any negative effect on his/her daily life, then the score was "0". The statistical analysis was performed using SPSS Statistics. Descriptive statistics were recorded as means, medians, frequencies and percentages.

Table-I: Characteristics of CML patients on imatinib therapy (n=92).

Variables	n (%)
Sex	
Male	58 (63%)
Female	34 (37%)
Age	
Median	39.50
Range	22-68

RESULTS

A total of 110 CML patients in chronic phase reporting at Department of Oncology Combined

Military Hospital of Rawalpindi between January 2015 and December 2015 were contacted. Of these, 92 gave consent for participation in our study. The mean age of participants in our study was 42.05 years (range 22-68 years) and 58 (63%) of them were male. Patient characteristics are shown in table-I.

The frequency of patient-reported drug side effects was high. In our sudy 87% of the patients stated suffering from at least one side effect which had started after initiation Imatinib treatment. The most commonly reported side effect was muscle cramps (that was reported by 67 out of 92 (72.8%) patients, fatigue was experienced by 58 out of 92 (63.04%) patients, gastrointestinal upset was third most commonly reported side effect (44 out of 92 patients or 47.82%). Other side effects were skin rashes (30/92 32.60%), swelling of hands, feet, or face (28/92 30.43%), loss of appetite (19/92 20.65%), shortness of breath (16/92 17.39%), feeling sad/ depression (12/92 13.04%), problem with remembering things (12/92 13.04%) and loss of sleep (10/92 10.86%). More than half of the study population reported that these side effects had a negative impact on their daily life (table-II). A significant number of patients reported that the side effects had a negative impact either on their mood, daily life, walking, relationships and work (table-III). Women were effected more than men (63% vs 54%).

Table-II: Frequency of patients' self-reported side effects with Imatinib use.

S. No	ADRs	n (%)
1	Muscle cramps	67 (72.8%)
2	Fatigue	58 (63.04)
3	Gastrointestinal upset	44 (47.82)
4	Skin rashes	30 (32.60)
5	Swelling of hands, feet, or face	28 (30.43)
6	Loss of appetite	19 (20.65)
7	Shortness of breath	16 (17.39)
8	Feeling sad	12 (13.04)
9	Problem with remembering things	12 (13.04)
10	Loss of sleep	10 (10.86)

Table-III: The negative impact of drug toxicity on patients' quality of life.

S. No	Effects on	n (%)
1	Mood	78 (84.78)
2	Daily life	60 (65.21)
3	Walking	52 (56.52)
4	Relationship	42 (45.65)
5	Work in general	34 (36.95)

DISCUSSION

In our study, the frequency of patient-reported side effects during Imatinib treatment was high. These side effects had a significant impact on patients' quality of life.

Studies have shown that adverse effects associated with Imatinib and other tyrosine kinase inhibitors could be a primary reason for poor compliance which can lead to inadequate treatment responses[11]. However in our study patients were willing to continue the treatment despite of the side effects. So we were unable to find any negative impact of these adverse symptoms on patient's compliance. However, the higher number of side effects definitely had a negative impact on the patient's quality of life. Same results have been shown in a study by Meri K and colleagues[12].

Important aspects of our study is that it focusses on the patients' reported adverse events

and not on the already documented list of adverse drug reactions. As documented by the FDA, some "treatment effects are known only to the patient, and such information can be lost when the patient's perspective is filtered through a doctor's evaluation of the patient's response"[13]. These kind of studies can help the physicians to make more tailored treatment decisions for their patients. In general, patients report symptoms more accurately, more early and more frequently than the physicians. From these studies, physicians will get a better understanding of patients' perspectives and will be able to provide better clinical care.

The treatment related toxicities, although sometimes very disturbing for the patients, can be effectively managed in most cases if detected earlier. Furthermore, as there are different newer tyrosine kinase inhibitors available in the market it is more likely that patients intolerant to one drug can be offered some other better tolerated alternative drug. In future studies should be carried out that address the comparison of imatinib to other tyrosine kinase inhibitors to find out to use the tyrosine kinase inhibitor that best suites a patient. There is a need to develop instruments which are leukemia and CML-specific.

Treatment of CML has evolved during the last decade. With improvement in treatment, CML patients now expect longer survival. The importance of managing side effects related to therapy cannot be underestimated. Continuous and adequate dosing of medication is considered backbone for success in CML therapy; however, many patients still struggle to remain adherent to treatment. Among CML patients, good compliance to treatment is related with improvement in long term clinical outcomes[14]. Our study aims to provide a model to link the relationship between goals of patient treatment satisfaction, disease related side effects, and quality of life outcomes among a diverse sample of patients with chronic-phase CML in Pakistan. Many patients are asymptomatic at diagnosis and therefore may be irritated by the adverse drug toxicities caused by the treatment. The toxicities which had the most negative influence on patients' quality of life in the present study were muscle cramps, fatigue and skin rashes. Addressing these symptoms in time could help in a better treatment compliance which ultimately may transmit into better outcome.

CONCLUSION

Imatinib related ADRs were common among CML patients. These drug related adverse effects had a negative influence on quality of life of these patients.

LIMITATIONS OF STUDY

The limitation of our study was instruments used for assessing drug toxicities and quality of life were not validated specifically for leukemia patients. The study was a cross-sectional study. The patients' reported side effects were not compared with physician's assessment. It was single institution study with limited number of patients.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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