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ASSESSMENT OF ADVERSE EFFECTS OF IMATINIB IN CHRONIC MYELOID LEUKEMIA PATIENTS AT CIVIL HOSPITAL OF KARACHI, PAKISTAN

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Abstract

Background:
The original etiologic agent, imatinib mesylate, the first-in-class tyrosine kinase inhibitor (TKI), remains the leading therapeutic weapon in Chronic Myeloid Leukemia (CML) especially in the low- and middle-income countries. Despite the unquestionable effectiveness, the negative effects of the long-term use of this agent are often characterized by all the factors that can reduce patient compliance and decrease the quality of life. Based on this, the current study aimed to establish the frequency, typology as well as severity of imatinib related adverse events in patients with CML who are under the care of a publicly funded tertiary referral centre in Karachi, Pakistan.

Methods:
The design was cross-sectional descriptive and used in Civil Hospital Karachi in the period between January and December 2023. A total of 385 patients with CML diagnosed and put under imatinib treatment of ≥ six months were recruited. A structured proforma was used to record demographic data, disease stage, period of therapy and adverse events that had been documented. The grading was based on the Common Terminology Criteria of Adverse Events (CTCAE v5.0). Statistical examinations were conducted using SPSS v26.0, and Chi-square and t-tests were conducted to evaluate the relationships (p below 0.05 was taken to be significant).

Results:
Among all the 385 participants, 94% stated that they had had at least one adverse event. The most frequent non-hematologic toxicity were fatigue (67.8%), peripheral oedema (58.2%), and nausea (50.1%). Hematologic toxicities were reported as anemia (29.6%) thrombocytopenia (14.5%) neutropenia (8.8%)). Patients with elevated levels of alanine aminotransferase (ALT) were reported 21.3%. The significant predictive factors of increased toxicity were female gender,

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high disease stage and treatment duration over three years. The proportion of adverse events that affected daily functioning was 39.2% and several concurrent toxicities were found in 56.1% of the cohort.

Conclusion:

The use of imatinib in the treatment of CML has a high rate of hematologic, as well as non-hematologic side effects. Other independent predictors of toxicity include female sex, long term exposure, and advanced stage of the disease. Frequent monitoring and personalized intervention plans are a necessity to maximize treatment and make sure the patients have a good quality of life.

INTRODUCTION

Chronic Myeloid Leukemia (CML), is a haematopoietic stem between malady that has a global occurrence of around 1 to 2 cases every 100,000 individuals each year [1]. The Philadelphia chromosome that creates a continuously active tyrosine kinase and forms a t(9;22)(q34;q11) translocation bleaching characterizes the disease, resulting in the formation of BCR-ABL1 fusion gene [2, 3]. The incidence of a new selective BCR -ABL1 inhibitor, imatinib mesylate, has reduced CML into a chronic illness and not a terminal illness [4-6].

Imatinib has resulted in long-term haematologic and cytogenetic remission [7]. Imatinib has produced prolonged haematologic and cytogenetic remission in more than However, chronic intervention with this agent is also accompanied by a range of events such as fatigue, gastrointestinal dysfunctions, oedema, cytopenias and hepatotoxicity that may hamper compliance may undermine the therapeutic outcome [8-11].

In the resource-limited conditions of countries like Pakistan, imatinib is still the major TKI due to the relative cost-effectiveness of this method and its accessibility through governmental and donor programs. However, there are few local data on its adverse profile of effect, and therefore tight control and pharmacovigilance cannot be underrated.

The current study aim is to fill the gap in the literature evaluation of the occurrence, frequency, and risk factors of imatinib-linked toxicities in a large tertiary care setting Karachi.

MATERIALS AND METHODS

Study Design and Setting

It is a cross-sectional observational study that was conducted at the Department of Oncology, Civil Hospital Karachi in the period between January 2023 and December 2023.

Sample Size Calculation

Sample size was calculated using Cochran's formula [12]:

$n=Z^2 \cdot p \cdot (1-p)/d^2$

Where:

- Z=1.96 (95% confidence level)
- p=0.5 (expected prevalence)
- d=0.05 (margin of error)

$n=(1.96)^2 \cdot 0.5 \cdot 0.5/(0.05)^2=384.16 \Rightarrow$ Rounded to 385 patients

Inclusion and Exclusion Criteria

Inclusion:

- Age ≥18 years
- Confirmed CML diagnosis (chronic, accelerated, or blast phase)
- On Imatinib ≥6 months
- Informed consent provided

Exclusion:

- Use of second/third-generation TKIs
- Concomitant chemotherapy
- Pre-existing hepatic, renal, or cardiac disease
- Pregnant females

Data Collection

A structured proforma was used to collect:

- Demographics
- Disease phase and therapy duration
- Adverse effects (graded using CTCAE v5.0)
- Laboratory data: CBC, ALT, creatinine

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Statistical Analysis

The SPSS v26.0 was used in data analysis. Means and standard deviations were used in the summary of continuous variables but frequencies and percentages were used in summarizing the categorical variables. Statistical significance was calculated using chi-square and t-tests and $p>0.05$ was considered as significant.

RESULTS

Table 1: Demographic and Clinical Characteristics (n = 385)

Variable	Frequency (%)
Mean Age (years)	42.6 ± 11.2
Gender: Male	217 (56.4%)
Gender: Female	168 (43.6%)
Chronic Phase	313 (81.3%)
Accelerated Phase	49 (12.7%)
Blast Crisis	23 (6.0%)
Therapy Duration >3 years	154 (40.0%)

Table 2: Non-Hematologic Adverse Effects

Adverse Effect	Frequency (%)
Fatigue	261 (67.8%)
Peripheral Edema	224 (58.2%)
Nausea	193 (50.1%)
Myalgia	120 (31.2%)
Skin Rash	77 (20.0%)
Alopecia	47 (12.2%)
Diarrhea	38 (9.9%)

Table 3: Hematologic and Biochemical Adverse Effects

Parameter	Frequency (%)
Anemia	114 (29.6%)
Thrombocytopenia	56 (14.5%)
Neutropenia	34 (8.8%)
Elevated ALT	82 (21.3%)
Elevated Creatinine	17 (4.4%)

Table 4: Association of Gender with Selected Adverse Effects

Adverse Effect	Male (%)	Female (%)	p-value
Anemia	23.5%	37.5%	0.018
Edema	51.8%	66.7%	0.042
ALT Elevation	14.7%	30.4%	0.005

Table 5: Effect of Therapy Duration on Adverse Events

Therapy Duration	≥2 Adverse Effects (%)	ALT Elevation (%)
<3 Years (n=231)	41.1%	16.8%
>3 Years (n=154)	74.6%	28.6%
p-value	<0.001	0.019

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DISCUSSION

This study has revealed that there is high rate of Imatinib related adverse events on CML patients in an actual real world hospital environment. The most common prescription were non-haematologic toxicities especially fatigue, oedema, and nausea, with over half of the cohort being affected. These findings are reflective of comparable previous studies realized in other foreign countries [13-15].

Approximately 30 percent and 15 percent of patients developed hematologic toxicities with the development of anemia and thrombocytopenia, respectively. They are probably dose-dependent and occurrence is indicative of marrow suppressiveness or progression of illness [16, 17]. The safety of the ALT elevation (21.3%) supports previous results of hepatocellular damage that can be traced to the metabolism of Imatinib through cytochrome P450 [18].

The gender differences were statistically different: females had a higher incidence of anemia and hepatotoxicity that may represent pharmacokinetic differences, decreased baseline haemoglobin and hormonal effects [19, 20].

The length of treatment (>3 years) corresponded to toxicity and the importance of extended follow-up was stressed. These data are in line with the works of Tanaka et al. and Santos et al. stating cumulative toxicity following 36 months of treatment [21, 22].

The limitations of the study are the single center design and lack of pharmacogenetic data. However, the large sample and grading of toxicity would strengthen the results.

CONCLUSION

Imatinib is part of the CML management in Pakistan, but its application poses serious negative effects, including some cumulative effects. The indicators of increased toxicity include female sex, long therapy period, and late stage of the disease. A risk-based surveillance strategy and patient-centered management approach should therefore be adopted by the clinicians to reduce toxicity and ensure long-term therapeutic outcome.

Ethical Considerations

All participants provided written informed consent before enrollment. Confidentiality and anonymity were maintained throughout the research, and all procedures adhered to the Declaration of Helsinki (2013 revision).

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