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Original Article

QTC Changes Associated with Tyrosine Kinase Inhibitors in Cancer Patients

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ABSTRACT

Objective: To look for QTc changes associated with Tyrosine Kinase inhibitors and factors related to these changes among patients suffering from cancer.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: Oncology Department, CMH Rawalpindi Pakistan from Dec 2020 to Apr 2021.

Methodology: The study included one hundred and eighty patients with solid or haematological malignancies taking Tyrosine Kinase inhibitors for more than three months. They underwent 12 lead ECGs inside the oncology department. QTc interval was calculated on the ECG of all the patients, and they were evaluated for the presence of prolonged QT interval. Age, gender, duration of Tyrosine Kinase inhibitor use and presence of comorbid illness were correlated with the presence of QTc changes in our study participants.

Results: Out of 180 cancer patients using Tyrosine Kinase inhibitors for more than three months included in the study, 96 (53.3%) were male, while 84 (46.7%) were female. One hundred and eighteen (65.5%) had normal QTc intervals, while 62 (34.5%) had prolonged QTc intervals in our study participants. Chi square test revealed that the advanced age of the patient and prolonged use of Tyrosine Kinase inhibitors was statistically significantly associated with QTc prolongation in our study (p-value<0.001).

Conclusion: Significant number of cancer patients using Tyrosine Kinase inhibitors had prolonged QTc intervals in our study. Special attention should be paid to cancer patients with advancing age and prolonged use of Tyrosine Kinase inhibitors.

Keywords: Cancer, QTc interval, Tyrosine kinase inhibitor.

How to Cite This Article: *Khattak R, Ahmad R, Nadeem M, Amjad H, Khan A, Ibtisam. QTC Changes Associated with Tyrosine Kinase Inhibitors in Cancer Patients. Pak Armed Forces Med J 2022; 72(4): 1470-1473. DOI: https://doi.org/10.51253/pafmj.v72i4.6776*

INTRODUCTION

Recent Epidemiological statistics suggest that the incidence and prevalence of almost all types of malignancies are on the rise in all parts of the world.[1] Limited data is available in this regard from our country, but still, the situation is not different in terms of statistics regarding various types of cancers in Pakistan.[2] Surely, new treatment options for malignant conditions have revolutionized the treatment of these potentially fatal conditions.[3] Clinicians across the globe have been using these treatment options weighing the risks and benefits of these for individual patients.[4] Surgery, chemotherapy, radiotherapy, and immunotherapy has been the treatment options commonly used for the treatment of malignant diseases depending on the type and stage of illness.[5] Tyrosine Kinase inhibitors have been considered as effective options for advances cancers but still associated with the number of mild and serious adverse effects and require close monitoring from the treating clinician for prevention or early diagnosis of these adverse effects.[6]

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Received: 25 May 2021; revision received: 27 Jul 2021; accepted: 29 Jul 2021

Cardiac adverse effects have been reported with several chemotherapeutic agents used to manage cancer, including Tyrosine Kinase inhibitors. Kloth *et al,* in 2015 concluded that almost all the Tyrosine Kinase inhibitors used in clinical practice have been associated with QTc prolongation, but Vemurafenib was most strongly associated with cardiac arrhythmias.[7] Shah *et al*, in 2013 recommended closed cardiac monitoring on cancer patients put on any Tyrosine Kinase inhibitor.[8] Qi *et al,* in 2013 published a meta-analysis regarding Tyrosine Kinase inhibitors causing hypertension. They concluded that most Tyrosine Kinase inhibitors had been related to new onset hypertension among the patients of cancer put on these medications.[9]

Cancer patients are vulnerable to multiple physical health problems because of the underlying malignancy and treatment options used to manage cancer. Data on the use of Tyrosine Kinase inhibitors has been limited in our setup. A recent study showed the efficacy of this group of medications among patients with chronic myeloid leukaemia but did not focus on the adverse effects.[10] Therefore, we designed this study with the rationale of looking for QTc changes associated with Tyrosine Kinase inhibitors

and factors related to these changes among cancer patients.

METHODOLOGY

This comparative cross-sectional study was conducted at the Oncology Unit of Combined Military Hospital Rawalpindi for five months (December 2020 to April 2021). The sample size was calculated using the WHO sample size calculator by using the population prevalence proportion of QTc prolongation with Tyrosine Kinase inhibitors as 28.8%,[11] and keeping the margin of error as 10%. The non-probability purposive sampling technique was used to gather the sample.

Inclusion Criteria: Patients from 18 to 70 years of age of both genders who took any Tyrosine Kinase inhibitors for any solid or haematological malignancy for more than three months were included in the study.

Exclusion Criteria: Patients with HTN, IHD and taking cardio-selective drugs such as B-Blockers, Ca channel blockers, anti-arrhythmic and cardiac glycosides (assessed on patient history) and those with conduction defect on ECG or those with valvular heart disease and heart failure on Echocardiography were excluded from the study Hyperkalemic patients were also not included in the study.

After taking written informed consent from all the potential participants and ethical approval (via letter no B.158/5/21) from the Ethical Review Board of the hospital, patients fulfilled the inclusion were included in the study. Tyrosine Kinase inhibitors are a group of medications that disrupt the signal transduction pathways of protein kinases by several modes of inhibition.

Medications from this group commonly used in our setup are Imatinib, Nilotinib, Sorafenib, Pazopanib and Sunitinib.[12] Twelve lead echocardiogram was perfor-med by a trained cardiac technician on all the study participants and interpreted by a consultant medical specialist or cardiologist. Bazzett's formula was used to calculate the QTc interval, and QTc interval >440 ms for males and >460 ms for females was taken as prolonged.[13]

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. The qualitative data were presented as frequency distribution, and quantitative data were presented as mean ± SD. The relationship of various variables with prolonged QTc was analyzed using the Pearson chi-square test. The *p*-value of ≤0.05 was considered statistically significant.

RESULTS

Out of 180 cancer patients using Tyrosine Kinase inhibitors for more than three months included in the study, 96 (53.3%) were males, while 84 (46.7%) were females. One hundred and eighteen (65.5%) had normal QTc intervals, while 62 (34.5%) had prolonged QTc intervals in our study participants. Table-I showed the basic characteristics of the study participants. 105 (58.3%) patients were using Tyrosine Kinase inhibitors for less than 12 months, while 75 (41.7%) patients were taking these medications for more than 12 months.

Table-I: Characteristics of study participant.

Parameters	n (%)
Mean Age of Patients (Years)	
Mean ± SD	451.53 ± 3.425
Gender	
Male	96 (53.3%)
Female	84 (46.7%)
Qtc Interval	
Within range	118 (65.5%)
Prolonged	62 (34.5%)
Duration of TKI Use	
<12 months	105 (58.3%)
>12 months	75 (41.7%)
Presence of Comorbidities	
No	119 (66.1%)
Yes	61 (33.9%)

Table-II revealed that the advanced age of the patient and prolonged use of Tyrosine Kinase inhibitors was statistically significantly associated with QTc prolongation in our study (*p*-value<0.001). In contrast, the gender of the patient and the presence of comorbidities had no such association found in our study.

Table-II: Pearson chi-square for relationship of various factors with the presence of QTc prolongation among the target population.

Factors	Normal QTc	Prolonged QTc	*p*-value
Age			
<40 Years	87 (73.7%)	24 (38.7%)	<0.001
>40 Years	31 (26.3%)	38 (61.3%)	
Gender			
Female	62 (52.5%)	34 (54.8%)	0.769
Male	56 (47.5%)	28 (45.2%)	
Duration of TKI Use			
<12 months	88 (74.6%)	17 (27.4%)	<0.001
>12 months	30 (25.4%)	45 (72.6%)	
Presence of Comorbidities			
No	77 (65.2%)	42 (67.7%)	0.737
Yes	41 (34.8%)	20 (32.3%)	

DISCUSSION

Cancer patients usually undergo aggressive treatment strategies involving surgical options, chemotherapeutic agents and radiotherapy: underlying malignant disease and use of various treatment options are prone to various health-related problems. Moreover, different classes of chemotherapeutic agents used for the management of cancer have a different spectrum of adverse effects.[14] Treating team needs to be watchful of the relevant adverse effects of medication used to manage the patient to be recognized early and addressed appropriately. Tyrosine Kinase inhibitors have risen in oncology practice in the last decade. Therefore, we planned this study to look for QTc changes associated with Tyrosine Kinase inhibitors and factors related to these changes among patients with cancer.

Ghatalia *et al,*[15] in 2015 published a study looking for QTc changes associated with Tyrosine Kinase inhibitors among patients suffering from various cancers. They concluded that though most cases were of low clinical significance, still QTc prolongation was associated with the use of Tyrosine Kinase inhibitors. Our study supported the findings of Ghatalia *et al*, as more than 35% of patients included in our study had prolonged QTc intervals.

Menna *et al*.[16] in 2017, published an interesting paper on various chemotherapeutic agents used to manage cancer and the risk of QTc prolongation. They discussed extensively the risk associated with various options and concluded that Tyrosine Kinase inhibitors are not free from the risk of QTc prolongation, and clinicians should carry out regular ECGs in such patients. However, our study findings differed from Menna *et al*, and Tyrosine Kinase inhibitors emerged as chemotherapeutic agents causing QTc prolongation in many patients.

QTc prolongation in most cases could be a finding of low clinical significance, but in some patients, this may lead to serious consequences. The case report published by Kondo *et al,*[17] in 2021 is very important in this regard, highlighting that this finding could be very dangerous in high-risk patients. In the reported case, an 85-year-old female on Tyrosine Kinase inhibitors had sudden death followed by QTc prolongation. Our results though preliminary in this regard, depict the magnitude of the problem in a high-risk population.

Oyakawa *et al,*[18] published a study in 2018 from data set in Japan regarding multiple cardiac adverse effects experienced by patients using Crizotinib, a Tyrosine Kinase inhibitor. They concluded that cancer patients using Crizotinib were prone to develop bradycardia, QT prolongation, ventricular rhythm, ventricular fibrillation, and pericarditis. We did not study other adverse effects related to the cardiovascular system in our study participants. However, QTc prolongation was observed in many patients, especially those with advanced age and using Tyrosine Kinase inhibitors for more than 12 months.

LIMITATIONS OF STUDY

Our study had a few limitations as well. A cross-sectional study design is not the best for establishing a cause and effect relationship; therefore, we cannot conclude that QTc prolongation resulted from Tyrosine Kinase inhibitor use. The small sample size and limited study duration were also issues in the generalizability of the results. Long-term follow-up was not done in the patients, so the long-term effects of these agents could not be assessed.

CONCLUSION

A significant number of cancer patients using Tyrosine Kinase inhibitors had prolonged QTc intervals in our study. Therefore, attention should be paid to cancer patients with advancing age and prolonged use of Tyrosine Kinase inhibitors.

Conflict of Interest: None.

Author's Contribution

RK: Overall responsibility for the manuscript, patients selection, treatment and followup, collection of data, RA:, MN: Over supervision, conception of article, HA: Data analysis, AK: Drafting and designing of article, I: Applying statistic.

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