

# QTc CHANGES ASSOCIATED WITH TYROSINE KINASE INHIBITORS IN CANCER PATIENTS

## 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:** This correlational study was conducted in Avicenna Medical College and Hospital Lahore with the collaboration of SKMH during November 2020 to May 2021. **Methodology:** One hundred and eighty patients with solid or hematological malignancies taking tyrosine kinase inhibitors for more than three months were included in the study. They underwent 12 lead ECG inside oncology department. QTc interval was calculated on ECG of all the patients and they were evaluated for presence of prolonged QT interval. Age, gender, duration of tyrosine kinase inhibitor use and presence of comorbid illness were correlated with 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 interval while 62 (34.5%) had prolonged QTc interval in our study participants. Binary logistic regression analysis revealed that advanced age of the patient and prolong 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 interval in our study. Special attention should be paid to the cancer patients with advancing age and prolonged use of tyrosine kinase inhibitors.

**Key words:** Cancer; QTc interval; Tyrosine kinase inhibitor

## Introduction

Recent Epidemiological statistics suggest that incidence and prevalence of almost all types of malignancies is on a rise in all parts of the world.<sup>1</sup> Limited data is available in this regard from our country but still situation is not different in terms of statistics regarding various types of cancers in Pakistan.<sup>2</sup> Surely, there has been new treatment options for malignant conditions which have revolutionized the treatment of these potentially fatal conditions.<sup>3</sup> Clinicians across the globe have been using these treatment options weighing the risks and benefits of these for individual patients.<sup>4</sup>

Surgery, chemotherapy, radiotherapy and immunotherapy have been the treatment options commonly used for the treatment of malignant diseases depending upon the type and stage of illness.<sup>5</sup> Tyrosine-kinase inhibitors have been in practice for quite some time now for management of various solid and hematological malignancies. Though they are considered as

effective options for advanced cancers but still associated with number of mild and serious adverse effects and require close monitoring from the treating clinician for prevention or early diagnosis of these adverse effects.<sup>6</sup>

Cardiac adverse effects have been reported with number of chemotherapeutic agents used for management of cancer including tyrosine kinase inhibitors. Kloth et al. published a study in 2015 to look for incidence of QTc abnormalities among patients of cancer using tyrosine kinase inhibitors. They concluded that almost all the tyrosine kinase inhibitors used in clinical practice have been associated with QTc prolongation but vemurafenib was found to be most strongly associated with cardiac arrhythmias.<sup>7</sup> Shah et al. published an interesting paper in 2013 highlighting that tyrosine kinase inhibitors used in oncology practice have been causing QT interval prolongation, left ventricular dysfunction and both systemic and pulmonary in significant number of patients. They recommended closed cardiac monitoring on cancer patients put on any tyrosine kinase inhibitor.<sup>8</sup> Qi et al. in 2013 published a meta-analysis regarding tyrosine kinase inhibitors causing hypertension. They concluded that most of the tyrosine kinase inhibitors have been related to new onset hypertension among the patients of cancer put on these medications.<sup>9</sup>

## **Objectives**

We therefore designed this study with the rationale to look for QTc changes associated with tyrosine kinase inhibitors and factors related to these changes among patients suffering from cancer.

## **Methodology of the study**

This correlational study was conducted in Avicenna Medical College and Hospital Lahore with the collaboration of SKMH during November 2020 to May 2021. Sample size was calculated by using the WHO sample size calculator by using population prevalence proportion of QTc prolongation with tyrosine kinase inhibitors as 28.8%<sup>11</sup> and keeping margin of error as 10%. Non-Probability purposive sampling technique was used to gather the sample. Patient from 18 to 70 years of age from both genders who were taking any Tyrosine Kinase inhibitors for any solid or hematological malignancy for more than three months were included in the study. 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 ethical review board of hospital, patients fulfilling above mentioned inclusion and exclusion criteria were included in the study. Tyrosine Kinase inhibitors is 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 set up are Imatinib, Nilotinib, Sorafenib, Pazopanib and Sunitinib.<sup>12</sup> 12 lead echocardiogram was performed by a trained cardiac technician on all the study participants and interpreted by consultant medical specialist or cardiologist. QTc interval >440 ms for males and > 460ms for females was taken as prolonged.<sup>13</sup>

### **Statistical analysis**

Data was entered and analyzed by using Statistical package for Social Sciences version 23.0. The qualitative data were presented as frequency distribution and quantitative data were presented as mean  $\pm$  SD..

### **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 interval while 62 (34.5%) had prolonged QTc interval in our study participants. Table I showed the basic characteristics of study participants and application of Pearson chi-square test. 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. Binary logistic regression analysis revealed that advanced age of the patient and prolong use of tyrosine kinase inhibitors was statistically significantly associated with QTc prolongation in our study (p-value<0.001) while gender of patient and presence of comorbidities had no such association found in our study.

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

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

**Table II: The correlated factors relating to QTc prolongation in cancer patients using tyrosine kinase inhibitors: the binary logistic regression**

	<b>p-value</b>	<b>OR (95% CI)</b>
Gender(ref. is male)	0.820	0.918 (0.440-1.914)

Age (ref. is <40 years)	<0.001	4.301 (2.059-8.984)
Duration of TKI use (ref. is <12 months)	<0.001	7.594 (3.632-15.877)
Presence of comorbidities (ref. is no comorbidities)	0.876	1.064 (0.486-2.331)

## Discussion

Cancer patients usually undergo aggressive treatment strategies involving use of surgical options, chemotherapeutic agents and radiotherapy. Underlying malignant disease and use of various treatment options prone the patients towards various health related problems. Different classes of chemotherapeutic agents used for management of cancer have different spectrum of adverse effects.<sup>14</sup> Treating team needs to be watchful of the relevant adverse effects of medication used to manage the patient so that they could be recognized early and addressed appropriately. Use of Tyrosine kinase inhibitors have been on a rise in oncology practice in last decade. We therefore planned this study with the objective to look for QTc changes associated with tyrosine kinase inhibitors and factors related to these changes among patients suffering from cancer.

Ghatalia et al.<sup>15</sup> in 2015 published a study with the objective to look for QTc changes associated with the use tyrosine kinase inhibitors among patients suffering from various types of cancers. They concluded that though most cases were of low clinical significance but still QTc prolongation was associated with use of tyrosine kinase inhibitors. Our study supported the findings generated by Ghatalia et al. as more than 35% of patients included in our study had prolonged QTc interval.

Menna et al.<sup>16</sup> in 2017 published an interesting paper on various types of chemotherapeutic agents used to manage cancer and risk of QTc prolongation. They discussed extensively the risk associated with various options and coined that tyrosine kinase inhibitors are not free from the risk of QTc prolongation and clinicians should be carrying out regular ECG in such patients. Our study findings were not different from Menna et al. and tyrosine kinase inhibitors emerged as chemotherapeutic agents causing QTc prolongation in significant number of patients. QTc prolongation in most cases could be a finding of low clinical significance but in some patients this may lead to serious consequences. Case report published by Kondo et al.<sup>17</sup> in

2021 is very important in this regard which highlighted that this finding could be very dangerous in high risk patients. In the case they reported, 85-year-old female who was on tyrosine kinase inhibitors had sudden death followed by QTc prolongation. Our results though preliminary in this regard but clearly depict the magnitude of problem in high risk population.

Our study had few limitations as well. Cross-sectional study design is not the best to establish cause and effect relationship therefore we cannot conclude that QTc prolongation was a result of tyrosine kinase inhibitor use. Small sample size and limited study duration was also an issue in generalizability of results. Long term follow-up was not done in the patients so long term effects of these agents could not be assessed.

### **Conclusion**

Significant number of cancer patients using tyrosine kinase inhibitors had prolonged QTc interval in our study. Special attention should be paid to the cancer patients with advancing age and prolonged use of tyrosine kinase inhibitors.

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