Potentially hazardous drug–drug interactions in cancer patients treated with tyrosine kinase inhibitors: A multicenter retrospective study

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Abstract

Aims: Tyrosine kinase inhibitors (TKIs) improve patient outcomes, but the prevalence of clinically significant TKI-associated drug–drug interaction (DDI) is unknown. We aim to assess the risk prevalence between TKIs and other drugs in cancer patients.

Methods: This was a retrospective cross-sectional study conducted in three tertiary care hospitals. All medical data were collected in the computer-based medication prescription system from January 2020 to December 2020. The hazardous DDIs identification has been performed using US Food and Drug Administration-approved labels. Descriptive statistics and univariate and multivariate logistic regression analyses were applied to identify risk factors associated with potential hazardous interactions.

Results: A total of 2754 patients were included in our study. 413 hazardous DDIs were identified and 387 (14.1%) patients experienced at least one DDI. Proton pump inhibitor, dexamethasone and fluoroquinolones were most frequently implicated in clinically relevant DDIs with TKIs. In a multivariate analysis, younger age, the number of drugs and lung cancer had a higher risk for the occurrence of hazardous DDIs. Conclusions: The prevalence of hazardous DDIs is relatively high in the cancer patient population receiving TKIs treatment. The awareness of potential clinically relevant DDIs can help patients reduce the probability of adverse event of drugs.
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Keywords: Tyrosine kinase inhibitors; prevalence; cancer patients; hazardous drug–drug interaction; risk factors

Introduction

Tyrosine kinase inhibitors (TKIs) have emerged as an increasingly important group of drugs in oncology and have brought significant clinical benefit to patients with solid or hematologic malignancies[1]. All TKIs are administered orally, which makes administration more flexible, safer and convenient than parenteral treatment, while patients treated with TKIs for malignancies may increase the risk of drug–drug interactions (DDIs) [2]. Most TKIs are naturally weakly basic and the equilibrium of their ionized and nonionized form depends largely on the pH of the environment [3]. The absorption of these oral targeted drugs may be notably influenced when co-administered with acid-reducing agents, especially proton pump inhibitors (PPIs) [4]. In addition, most TKIs are also substrates of metabolizing CYPs, and exposure to these drugs may lead to significant alterations when strong CYP inhibitors or inducers are concomitantly used[5]. Furthermore, QT prolongation has been reported with the use of several TKIs, including dasatinib, osimertinib, and nilotinib.
The risk of developing proarrhythmic effects may markedly increase by the simultaneous use of another drug that can prolong the QTc interval [6].

Due to the narrow therapeutic index with most TKIs, DDIs involving TKIs can lead to reduced therapeutic effects of either drug or might be associated with serious or even fatal adverse events [2]. A multicenter retrospective study showed that 30.8% of cancer patients receiving TKIs were exposed to at least one major DDI (defined as a potentially severe or life-threatening interaction) [7]. It was estimated that death in 4% of cancer patients was caused by DDIs [8]. Therefore, recognition of these clinically relevant DDIs is one of the most important factors to be considered regarding efficacy and safety in prescribing decision making [6]. Although several studies have estimated the prevalence of TKI-associated drug interactions in cancer patients [7, 10], we located no studies that focused on the prevalence of clinically significant hazardous drug interactions with TKIs. The objectives of this study were to describe the prevalence and patterns of hazardous TKI-associated drug interactions in hospitalized Chinese cancer patients.

Materials and Methods

This was a retrospective cross-sectional study conducted in three tertiary care hospitals in Shanxi Province, China. All three hospitals do not have computerized drug interaction screening programs. The study protocol was approved by the ethics committees of the three hospitals. All medical institution data were collected in the computer-based medication prescription system of the selected hospitals from January 2020 to December 2020.

All patients with a diagnosis of solid tumor or hematological malignancy were treated with TKIs in the hospital setting. Patients who were treated with two or more drugs where at least one of the medicines was a TKI (Table 1) were considered eligible. Hazardous interacting combinations not involving the TKIs were not included in the study. The products that could not be identified in the electronic hospital data such as grapefruit juice, over the-counter and herbal preparations were not included in our study. A risky combination has been studied when the exposure periods of the two drugs overlap. Concurrent use of TKIs and other patient medications was confirmed for more than 1 day. If the drug was administrated in a different formulation (e.g., levofloxacin intravenously or orally), the drug was counted only once. Formulations containing two or more pharmacologically active ingredients were considered separately in the analysis. The experiment and clinical trials were carried out under the Basic & Clinical Pharmacology & Toxicology policyversion 2023 [11].

The interaction of the drug contained in the study was determined by product labeling approved by food and drug administration (FDA). Hazardous interacting combinations were identified using the words ‘contraindicated,’ ‘avoid’ or ‘do not be coadministered’ within the labeling [12]. Due to the same interaction mechanism, the hazardous DDIs were counted only once when the same type of drugs was successively used for a patient, such as lansoprazole and omeprazole. Hazardous combinations were classified by the mechanism into two major groups: pharmacokinetic DDIs and pharmacodynamic DDIs [13]. The DDIs were also subdivided into (i) drug absorption interactions, defined as combinations of drugs that may influence the process of TKI absorption; (ii) metabolism-related interactions, defined as TKI given concomitantly with a CYP inducer or inhibitor that has the potential to increase the toxic effects or decrease the effectiveness of TKI; and (iii) QTc interactions, defined as drug combinations with potential QTc interval prolongation and/or torsades de pointes inducing properties [14].

Descriptive statistics were applied to characterize the whole study sample with regard to age, sex, length of hospital stay, cancer type, number of drugs per patient, comorbidities, and interaction characteristics. Univariate and multivariate logistic regression analyses were used to identify risk factors associated with potential hazardous interactions. The dependent variable was the occurrence of at least one potential hazardous interaction per patient. The explanatory variables were age, number of drugs, number of comorbidities, length of hospital stay and tumor type (hemato-oncology/oncology). Because certain cancer types only occur in men or women, much of the information that gender would contribute to the regression analysis is implicit in cancer type, and gender was not included as a potential risk factor.

RESULTS Patient Characteristics
A total of 2754 patients were investigated in this study, with a mean age of 57.6 years (range 7-96 years), of whom 1129 (41%) were female. The number of prescriptions per patient was 8.1 and the average length of hospital stay was 6.5 days. Table 2 presents the summary results of demographic characteristics. Of the 2754 patients, 15 TKI drugs were ultimately included, as shown in Table 1. The median comorbidity per patient was 1.1, with 58.2% of patients presenting with at least one comorbidity.

**Study of hazardous drug–drug interactions**

A total of 413 harmful DDIs were detected in 387 (14.1%) patients (Table 2), taking into account only TKI interactions. Pharmacokinetic harmful DDI was found in 89.8% of all cases. In most cases, drug absorption interactions (n=324), metabolism-related interactions (n= 47), and interactions with QT intervals (n=42) were involved. Potentially harmful DDIs associated with TKIs and other drugs are listed in Table 3. PPI, dexamethasone, and fluoroquinolones were most commonly associated with clinically relevant DDIs with TKIs. The most common hazardous combination was coadministration of gefitinib with PPIs. The second most common combination was dasatinib or erlotinib with a PPI.

**Analysis of potential risk factors**

In the univariate analysis, the incidence of hazardous DDIs was significantly associated age, the number of prescribed medications, length of hospital stays, types of tumors, and types of cancer. Age [odds ratio (OR) 0.97 (95% confidence interval (CI) 0.96–0.98)], the number of drugs [odds ratio (OR) 1.12 (95% confidence interval (CI) 1.09–1.14)] and lung cancer [OR 2.75 (95% CI 1.17–6.47)] showed a higher risk for occurrence of hazardous DDIs in the analysis results of multivariate binary logistic regression (Table 4).

**Discussion**

Our study demonstrated that the frequency of hazardous TKI-associated drug interactions was relatively high in cancer patients, with 14.3 instances per 100 patients being developed at least one harmful DDI. In this study, we found that the number of concomitant drug use was identified as a risk factor for the incidence of potential drug interactions. Previous studies have also confirmed that the number of concomitantly used drugs is positively correlated with the risk of DDIs[15, 16]. Hazardous DDIs are more likely to occur in patients with lung cancer. PPI use might contribute to this higher risk in lung cancer patients treated with gefitinib. There is an interesting finding that younger age is associated with the development of hazardous DDIs, possibly due to the drug interaction profile of dasatinib. Our study population used dasatinib mainly for oral treatment of childhood leukemia, and it can interact with strong CYP inhibitors and inducers, as well as PPIs.

The interacting drugs in the TKI-involved hazardous interactions were mostly PPI. The total prevalence proportion of PPI use among all cancer patients was 16% and 21% in two large and representative healthcare databases, respectively[17]. Among cancer patients, PPI are often recommended to treat conditions related to gastrointestinal disease such as gastroesophageal reflux disease, dyspepsia, or gastritis[4]. While elevated gastric pH can result in clinically significant reductions in dissolution, absorption, and pharmacokinetics of some TKIs that exhibit pH-dependent solubility when used with PPI [17]. In a study in patients with non-small-cell lung cancer, maximum concentration of gefitinib decreased by 61% and plasma exposure by 46% when co-administered with lansoprazole, esomeprazole, or omeprazole daily for 15 days [18]. Similarly, the bioavailability of dasatinib was reduced by approximately 40% by concomitant administration of a daily dose of 40 mg omeprazole for 4 days [19]. In addition, a recent clinical retrospective study showed that the risk of death increased by 16% in cancer patients receiving various TKIs with concurrent PPI therapy[20]. In another retrospective study, shorter progression-free survival and overall survival were observed in patients with advanced non-small-cell lung cancer treated with erlotinib and acid suppression compared with a group without acid suppression[21]. Although using H2Ras instead of PPIs and a time-staggering mitigation strategy are sometimes recommended for management of the DDI between TKIs and PPIs [1, 17], these strategies may not be effective for every TKI. In clinical practice, the clinically relevant drug absorption interactions with certain TKIs often exists, and it will be important to understand when and to what extent such interactions may reduce the drug efficacy[4].
The use of potentially QTc-prolonging TKIs is contraindicated with fluoroquinolones or domperidone because both can cause QTc prolongation. These TKIs are known to prolong the QT interval through their effects on intracellular signaling, mainly by inhibiting the phosphoinositide 3-kinase pathway \[6\]. Drug combinations that could lead to QT interval prolongation are a known risk for life-threatening cardiac arrhythmias and sudden cardiac death. Fluoroquinolones are commonly used antibiotic agents that are effective for a variety of infections among the patients being treated for cancer. Nevertheless, cardiac side effects such as an amplified risk of QT interval prolongation and TdP have also been observed in patients using fluoroquinolones \[22, 23\]. Among reported cases with antibiotic-induced QT prolongation, drug interactions are the most common acquired risk factor for TdP \[24\]. Additionally, domperidone used drug for the prevention of cancer chemotherapy-induced postprandial dyspepsia is known property to prolong the QT interval \[25\]; it is uncommon to induce clinically significant arrhythmias without coadministering other QT-prolonging drugs\[26\]. So the concomitant usage of potential QT-prolonging TKIs may markedly increase the risk of developing proarrhythmic effects. Therefore, certain TKI administration in such patients with simultaneous use of other drugs (e.g., fluoroquinolones and domperidone) that can prolong the QT should be monitored closely, and if possible, an alternative medicine that can not affect the QT interval should be chosen \[27\].

A major limitation of this study is that we did not assess the clinical impact of these hazardous drug interactions due to the restricted information available in the medication prescription system. Although there was a significant association between ADRs or mortality and DDIs in other published studies \[20, 28\], insights into the clinical consequences of other hazardous combinations in cancer patients remain largely unknown. Furthermore, we only studied the drug combinations during the period of hospitalization, and it is unknown whether the relatively short time overlapping therapies will influence the overall effect of cancer treatment.

Another limitation is the reliance on FDA-approved TKI product label to identify all of the harmful drug combinations. However, the alerts and recommendations of potentially hazardous drug pairs in different databases are not entirely consistent \[29\]. The drug combination information of labeling is mostly based on information obtained from healthy volunteer studies, drug–drug interaction studies, and in vitro experiments. However, drug labeling is the primary source of information for prescribers and health care systems, and for consistency, we also used the label for information to identify hazardous combinations. In addition, we did not study hazardous drug combinations involving herbal medicines, and OTC drugs used in hospital DDIs.

The high prevalence of potentially clinically relevant drug interactions with TKIs in hospital settings is of particular concern, since adverse drug reactions (ADRs) caused by these harmful DDIs may have a major impact on public health\[16\]. Computerized drug interaction screening programs may help identify, prevent/reduce, and manage these DDIs. However, even if screening software has been used in some hospitals, the prevalence of DDIs in cancer patients is still high \[30\]. It is not clear to what extent the prescribing physicians were aware of the potential clinical impact of these contraindications and whether they have taken effective measures to prevent potentially hazardous drug interactions \[16\]. A potentially harmful combination may be knowingly prescribed because the patient has tolerated the combination in the past or because the potential benefits to the patient outweigh the risks \[15\]. However, when patients struggle with the affordability of expensive targeted drugs, reducing the efficacy or increasing the severe toxicity of these expensive drugs owing to overlooked DDIs is simply unacceptable\[15\]. As an integral part of the healthcare system, clinical pharmacists can play an important role in the management of the clinical significance of DDIs, which has been confirmed in several studies \[31-33\]. To better address this issue, collaborations with clinical pharmacists have been conducted to develop a screening method to avoid these hazardous drug combinations \[34\].

**Conclusion**

The current findings shows that cancer patients treated with these oral targeted drugs are at considerable risk for DDIs. It was found that patients with lung cancer, increasing number of drugs used concomitantly and younger age were more likely to be exposed to harmful drug combinations, highlighting the need for active surveillance to prevent adverse events caused by DDIs. Collaborations with a clinical pharmacist may
effectively manage the risks associated with DDIs.

**Data availability statement**

The data used to support the findings of this study are available from the corresponding author upon request.

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**Conflict of interest disclosure**

The authors declare no competing interests.

**Author Contributions**

Haitao Wang conceived the study and participated in its design and coordination and helped draft the manuscript. Kanghuai Zhang, Qianting Yang and Haitao Shi carried out the acquisition of data and performed the statistical analysis. Na Wang, Siping Feng and Youjia Li participated in the acquisition, analysis and interpretation of data. Jiao Xie, Yan Wang and Li Zhang participated in the design of the study, acquisition of data and drafting of the manuscript. Yao Zheng participated in the conception, design and coordination of the study.

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