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Drug-drug interactions between tyrosine kinase inhibitors and concomitance medications: Drug safety in cancer treatment

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ABSTRACT

Background: Tyrosine kinase inhibitors are increasingly used in the treatment of cancer. Drug interactions involving tyrosine kinase inhibitors are commonly encountered in clinical practice. Objectives: To analyze DDI between TKIs and the concomitant medication. Materials and Methods: Retrospective observational study carried out at Cho Ray hospital's oncology center. We evaluated the data of patients who were prescribed tyrosine kinase inhibitor from January 2023 to August 2023. Medication data were extracted from electronic medical records. Drug Interaction Checker (Drugs.com) and MicroMedex Drug Interaction (MM) were utilized to identify potential interactions between tyrosine kinase inhibitors and concomitant medications. Interactions were then assessed by the investigators for clinical significance. The main outcome was the frequency of significant drug interactions involving tyrosine kinase inhibitors and concomitant medications. Secondary outcomes included describing the nature and clinical impact of interactions and describing interactions by medication class. Results: A total of 250 patient files were included for analysis, in which 232 interactions were screened. 140 potential interactions were identified by Micromedex software, with 139 (49.1%) considered "major". Interaction Checker (Drugs.com) detected 73 (25.8%) potential interactions classified as "major" and 159 (74.1%) as "moderate" level of interaction. Potential clinical consequences included QTc prolongation, decreased tyrosine kinase inhibitor concentrations, and increased concentration of concurrently used drugs due to tyrosine kinase being inhibitors of CYP3A4. Conclusions: Drug interactions in prescriptions for TKIs are common in clinical practice. Therefore, physicians prescribing TKI should be careful of this phenomenon. Short-acting agents should be preferred for gastric acid suppression because PPIs alter the bioavailability of several TKIs. Prolongation of QT, which is also a major effect of TKIs drug interactions, is a life-threatening consequence. Oncology pharmacists should play a role in screening for tyrosine kinase inhibitor-linked interactions, recommending alternative drugs or dose timing strategies, and monitoring concurrently used drugs toxicity.

Keywords: *oncology, tyrosine kinase inhibitors, drug interactions*

1. INTRODUCTION

Tyrosine kinase inhibitors (TKIs) are molecularly targeted oral agents used increasingly in the treatment of cancer. The development of signal cascade directed small molecule inhibitors has created a paradigm shift in cancer pharmacotherapy, imparting specificity not previously achievable with cytotoxic agents. However, TKIs are associated with therapeutic challenges including unique adverse effects and susceptibility to drug–drug interactions. TKI-linked drug interactions occur most commonly when pH-dependent absorption of a TKI is impaired (coadministration with proton pump inhibitors or other acid suppressive agent), or when drug metabolism is altered by other interacting medications [1]. TKIs act as both substrates and

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inhibitors of enzyme systems involved in drug metabolism, most notably through the CYP3A4 enzyme [2]. Consequently, supportive care medications essential to maintaining patient comfort and functional capacity while receiving chemotherapy may be implicated in TKI-linked drug interactions [3]. Increased TKI concentrations can be reasonably anticipated in many oncology patients receiving TKIs and CYP3A4 inhibitors, such as ondansetron. Significant clinical consequences have been linked to both of these interaction mechanisms [4, 6]. Pharmacokinetic interactions that reduce TKI plasma concentrations (interacting medications which impair TKI absorption or induce TKI metabolism) may result in reduced TKI efficacy [6, 7]. Moreover, interactions that raise TKI plasma concentrations (interacting medications which inhibit TKI metabolism) increase the risk for various side effects associated with TKIs [8, 9]. Currently, very limited data are available to describe potentially harmful drug interactions associated with TKI therapy in hospitals in Viet Nam. Therefore, the main purpose of this study was to describe the frequency of TKI-linked drug interactions among cancer patients, with the aim to increase awareness of potentially harmful interactions to promote a more proactive approach to risk management. Collaboration between oncologists and pharmacists is likely to improve associated risks. Secondary goals include characterizing the identified interactions and potential clinical consequences.

2. MATERIALS AND METHODS

This was a retrospective study that analyzed the data of medication usage among outpatient prescribed TKIs at Chợ Rẫy hospital's oncology center. This study was approved by HIU Institutional Ethics Committee (decision date 07/03/2023, decision no. 95/PCT-HĐĐĐ), and was conducted according to the principles of Cho Ray hospital.

2.1. Patients

Adult patient's medical records in which TKIs were prescribed from January 2023 to August 2023 were included in this study.

Use of a tyrosine kinase inhibitor was identified by reviewing outpatient electronic medication health record. Any TKI listed in Table 1 and concurrent medications prescribed by oncology doctors, as well as any other health specialists, are included.

The main outcome was frequency of TKI-linked drug interactions. Secondary outcomes included classification of interactions by concurrent drugs and potential clinical consequence.

Sample size calculation: Based on the list of 710 patients prescribed to treat cancer with Tyrosine kinase inhibitors, the Yamane's formula for calculating sample size from a finite population is used.

$$n = \frac{\mathrm{N}}{1 + \mathrm{N}d^2}$$

Where:
N: population side
n = necessary sample size
d = margin of error, use d = 0.05 for 95% confidence interval.
The sample size was 250.

2.2. Potential TKI-Drug interactions

Potential interactions between TKIs and other drugs being used by patients were identified by querying drug interaction tools (Drugs.com, MicroMedex). The two database drug interaction classifications are listed in Table 2. Potential drug interactions excluded from the primary analysis include those with missing information, non-concomitant administration with a TKI, and non-systemic course of administration. After eliminating the interactions listed above, classification scheme of drug interactions was identified, and drug interactions considered to be “major” and “moderate” were included in the final analysis. A potential clinical consequence was defined as a drug interaction which may decrease TKI efficacy, increase TKI toxicity or increase concomitant drugs concentration. Focusing on these interactions offers a practical advantage in that such interactions are the most likely to result in interventions in clinical practice [10].

2.3. Statistics

Descriptive statistics were utilized to evaluate frequency of TKI-associated drug interactions. Interactions were then grouped by pharmacologic class, and class specific frequencies were identified.

Table 1. Tyrosine kinase inhibitors

Generic name	Trade name
Afatinib	Giotrif
Ceritinib	Spexib
Erlotinib	Tarceva
Gefitinib	Iressa
Imatinib	Glivec
Nilotinib	Tasigna
Osimertinib	Tagrisso
Pazopanib	Votrient
Lenvatinib	Lenvima
Ruxolitinib	Jakavi
Sorafenib	Nexavar

Table 2. Drug interaction classifications of the two databases

Micromedex Drug Interaction (MM)	
Classification	Description
Major	The interaction may be life threatening and/or require medical intervention to minimize or prevent serious adverse effects
Moderate	The interaction may result in an exacerbation of the patient's condition and/or require modification of therapy
Minor	The interaction would have limited clinical effects. Manifestations may include an increase in the frequency or severity of side effects but generally would not require major modification of therapy
Drug Interaction Checker (Drugs.com)	
Major	Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit
Moderate	Moderately clinically significant. Usually avoid combinations; use it only under special circumstances.
Minor	Minimally clinically significant. Minimize risk; assess risk and consider an alternative drug, take steps to circumvent the interaction risk and/or institute a monitoring plan.
Unknown	No interaction information available.

3. RESULTS

The study screened prescriptions in patient's medicational records of 250 patients. A total of 283 possible potential drug interactions were identified; 139 (49.1%) of which considered "major" by MicroMedex software, 73 (25.8%) and

202 (71.4%) considered “major” and “moderate” respectively by Drugs.com are included in the analysis. Drug interactions frequencies are listed in Table 3. Imatinib (n=96;41.38%), osimertinib (n=47; 20.26%), and pazopanib (n=42;18.10%) accounted for more than 70% of the identified interactions. Class specific interaction frequencies are listed in Table 3. The most frequently implicated pharmacologic classes interacting with TKIs were analgesic drug (n= 58; 25%), antiemetics (n=65; 28.01%), PPIs (n=43; 18.53%) and antineoplastic (others than TKIs) (n= 23; 9.91%). The pharmacologic class 'acid suppressive agents' included proton pump inhibitors and antacids. Because the acid-suppressing drugs were mainly PPIs, the latter were considered as a separate group. The pharmacologic class 'antiemetics' was Ondansetron (a serotonin 5-HT_3 receptor antagonist agent). The following potential clinical consequences characterized the identified interactions: QTc prolongation (n=73; 31.47%), decreased TKI concentration (n=53, 22.84%), and increased concomitant drugs concentration (n=106; 45.69%).

Table 3. Drug specific interaction frequencies

Concomitance drugs		**TKIs**	
Drug	n=232 (%)	TKI	n= 232 (%)
Ondansetron	65 (28.01%)	Ceritinib	7 (3.02%)
Celecoxib	2 (0.86%)	Erlotinib	6 (2.59%)
Diclofenac	2 (0.86%)	Gefitinib	12 (5.17%)
Itraconazole	2 (0.86%)	Imatinib	96 (41.38)
Ciprofloxacin	2 (0.86%)	Lenvatinib	12 (5.17%)
Levofloxacin	2 (0.86%)	Nilotinib	6 (2.59%)
Amoxicillin	1 (0.43%)	Osimertinib	47 (20.26%)
Doxycycline	1 (0.43%)	Pazopanib	42 18.10%)
Phosphalugel	6 (2.57)	Ruxolitinib	3 (1.29%)
Methylprednisolone	10 (4.31%)	Sorafenib	1 (0.43%)
Dexamethasone	1 (0.43%)		
Gabapentin	2 (0.86%)		
Pregabalin	2 (0.86%)		
Tramadol/acetaminophen	58 (25%)		
Promethazine	6 (2.57)		
Olanzapine	2 (0.86%)		
Hydroxyurea	16 (6.89%)		
Mercaptopurine	2 (0.86%)		
Vincristine	3 (1.29%)		
Vinorelbine	1 (0.43%)		

Concomitance drugs		TKIs	
Tamoxifen	1 (0.43%)		
Ritonavir	2 (0.86%)		
PPI	43 (18.53)		

All data are expressed as frequency (percentage); Concomitance: drugs interacting with tyrosine kinase inhibitors; TKI: tyrosine kinase inhibitors interacting with other drugs

Table 4. Group specific interaction frequencies

Group	n = 232 (%)
Antiemetic	65 (28.01)
NSAID	4 (1.72)
Antifungal	2 (0.86)
Antibiotic	6 (2.59)
Antacid	6 (2.59)
Steroid	11 (4.74)
Anticonvulsant	4 (1.72)
Analgesic (narcotic/acetaminophen)	58 (25)
Antihistamine	6 (2.59)
Antipsychotic	2 (0.86)
Antineoplastic	23 (9.91)
Antiviral	2 (0.86)
PPI	43 (18.53)

4. DISCUSSIONS

In this study the researcher reviewed medication files of 250 patients prescribed tyrosine kinase inhibitors (TKIs) for potentially clinically significant drug interactions. As expected, most of these patients had potential drug interactions, and consistent with clinical practice, a large portion of these interactions were likely to have significant consequences. We demonstrated the importance of recognizing drug interactions in oncology patients prescribed TKIs, particularly when coadministered with PPIs agents, tramadol/acetaminophen or agents that may increase the risk for drug-induced prolongation of the QT interval, such as antiemetics.

To the best of researcher's knowledge, this is the first study to describe the frequency of potentially harmful TKI-linked drug interactions solely focusing on oncology patients prescribed tyrosine kinase inhibitors in a hospital of Viet Nam. International studies such as Keller et al [7] retrospectively reviewed the prescription records of 356 patients prescribed TKIs finding 109 interactions (44.7%) of which were considered severe. This analysis included 20 TKIs. In a similar study, van Leeuwen et al [12]. described the prevalence of various drug interactions among oncology patients receiving any oral anticancer agent, 16% in whom a major drug interaction was identified. While the study included six TKIs, prevalence was reported for only two TKI-associated interactions (dastinib/nilotinibproton pump inhibitor, 24% of dastinib/nilotinib patients). Seven of the ten TKI agents evaluated in this study contain cautionary or black box warnings regarding potential QT prolongation and Torsades de pointes (TdP) in their package labeling. In a comprehensive analysis of regulatory data on the QT liability of TKIs, Shah et al [10] report larger QT interval aberration with vandetinib, sunitinib, and nilotinib when compared to other TKIs. QT prolongation

greater than 500 ms is generally accepted as a significant risk factor for ventricular arrhythmias [16]. TKIs are unlikely to cause this degree of QT prolongation alone [14, 15], making drug interactions particularly important in oncology; as many agents coprescribed with TKIs may increase the risk for larger magnitude QT prolongation and by extension, arrhythmic events [1]. The most frequently occurring interactions identified in our analysis (ondansetron, tramadol/acetaminophen and TKI) which may result in additive QT prolongation demonstrate the need for careful assessment of torsadogenic risk in oncology patients being initiated on TKIs. The risk for additive QT prolongation posed by TKI-linked drug interactions may be reduced by careful assessment of risk factors for TdP (female sex, electrolyte abnormalities, baseline QT prolongation, heart failure, bradycardia), and periodic monitoring of the electrocardiogram [15]. The use of proton pump inhibitors for conditions such as gastroesophageal reflux disease, peptic ulcer disease, or dyspeptic symptoms is extremely common and highly frequent among cancer patients. Many TKIs exhibit pH-dependent solubility; that is, enhanced solubility in acidic conditions and diminished solubility in basic conditions. In patients receiving TKIs, the routine use of acid suppressive agents for palliation of gastrointestinal symptoms related or unrelated to their primary malignancy may result in impaired TKI absorption [2]. TKI and acid suppressive drug interactions accounted for approximately 30% of the interactions identified in this analysis and should be anticipated in clinical practice.

This study is primarily limited by the small number of patients included, as well as its retrospective nature and inherent selection and misclassification bias. Being geographically limited implies that our findings may not be applicable in other hospitals. In addition, the study was conducted at a large academic medical center where clinicians may have comparatively greater familiarity with TKIs for unestablished indications or palliation, which may over represent TKI use and by extension, interaction frequency. The use of electronic medication documentation may be considered a limitation. Importantly, this study identified the frequency with which TKI-linked interactions occurred but did not capture pharmacist interventions aimed at reducing associated risk, or the effect such interventions may have on clinical outcomes. Prospective studies are needed to quantify benefits associated with pharmacist interventions in this context. The oncology pharmacist must be well positioned to anticipate TKI-linked drug interactions prior to initiation of therapy, as well as conduct drug interaction screening in outpatient oncology so that risk reducing, and administration strategies may be deployed. Several interventions have demonstrated the benefits associated with pharmacist involvement in the care of patients receiving oral chemotherapy. Given the frequency of major potential drug interactions identified in this analysis, patients can benefit significantly from pharmacist interventions focused on the prevention and management of TKI related drug interactions.

5. CONCLUSIONS

The frequent introduction of novel tyrosine kinase inhibitors as well as the increased use of these agents in oncology makes knowledge of common TKI-associated drug interactions important to oncologists and pharmacists. We demonstrate that drug interactions in patients receiving TKIs are frequent, and primarily impart risk for additive QT prolongation and decreased TKI exposure. With increased awareness, doctors can use drug-drug interactions checker software more frequently to avoid potential harm. Also, an improvement of health policies and hospital systems can be useful, for example, displaying a warning on electronic prescription systems in cases where any of the patient's existing medicines interact with the newly prescribed drug. Patients should especially be informed about the potential risks of over-the-counter drugs and alternative therapies. We believe that increasing awareness of this subject will help reduce the prevalence of drug-drug interactions and therefore will lower drug toxicity as well as facilitate the establishment of an effective anticancer treatment.

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Tương tác thuốc-thuốc giữa nhóm thuốc ức chế tyrosine kinase và các thuốc dùng đồng thời: An toàn trong điều trị ung thư

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TÓM TẮT

Đặt vấn đề: hiện nay nhóm thuốc Tyrosine kinase được sử dụng ngày càng nhiều trong chữa trị bệnh ung thư. Tương tác giữa nhóm thuốc này và các thuốc sử dụng đồng thời đang xảy ra ngày càng nhiều trong thực hành lâm sàng. Mục đích nghiên cứu: phân tích các tương tác thuốc-thuốc giữa các thuốc nhóm TKI và những thuốc dùng đồng thời trong điều trị ung thư. Đối tượng và Phương pháp nghiên cứu: Nghiên cứu mô

tả cắt ngang được thực hiện tại Trung tâm Ung bướu Chợ Rẫy. Hồi cứu bệnh án của những bệnh nhân được kê đơn thuốc ức chế tyrosine kinase từ tháng 1 năm 2023 đến tháng 8 năm 2023. Công cụ kiểm tra tương tác Interactions checker (Drugs.com) và Micromedex drug interactions (MM), được sử dụng để xác định các tương tác tiềm ẩn giữa thuốc ức chế tyrosine kinase và các thuốc dùng đồng thời. Kết quả: Tổng cộng 250 hồ sơ bệnh án được đưa vào phân tích, 232 tương tác được sàng lọc, trong đó 140 tương tác tiềm ẩn được xác định bằng phần mềm Micromedex, với 139 (49.1%) trong số đó ở mức độ "nặng". Công cụ kiểm tra tương tác IC (Drugs.com) đã phát hiện 73 (25.8%) tương tác tiềm ẩn được phân loại là tương tác mức độ "nặng" và 159 (74.1%) là tương tác ở mức độ "trung bình". Kết luận: TKI đang được sử dụng ngày càng nhiều trong thực hành ung thư. Vì vậy, bác sĩ kê đơn TKI nên cẩn thận với các tương tác thuốc của nhóm thuốc này. Dược sĩ đóng vai trò quan trọng trong việc sàng lọc các tương tác liên quan đến thuốc ức chế tyrosine kinase, đề xuất các loại thuốc thay thế hoặc chiến lược điều chỉnh liều lượng và theo dõi độc tính của các thuốc đồng sử dụng.

Từ khóa: *ung bướu, thuốc ức chế tyrosine kinase, tương tác thuốc*

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