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ORIGINAL ARTICLE

Drug-drug interactions in patients using tyrosine kinase inhibitors: A multicenter retrospective study

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Summary

Purpose: *Tyrosine kinase inhibitors (TKIs) are frequently used drugs in oncology practice. Although oral administration is an advantage, long-term use increases potential drug–drug interaction risk. The purpose of this study was to assess the prevalence of potential TKI–drug interaction (PTDI) in patients who used TKIs and increase awareness of this subject.*

Methods: *We retrospectively evaluated the data of 310 patients collected from four different oncology centers, where TKIs were administered for solid organ cancer, between January 2007 and December 2017. The potential interaction between TKI and any other prescribed drug was determined using ''Lexicomp® Drug Interactions, App Version 1.1'' software.*

Results: *Overall, 310 patients were included; among those, 301 (97.1%) were using another drug with TKI and 147 (47.4%) experienced PTDI at least once. The median number of additional drugs was 4 (range 1-12). We detected 250 PTDIs, of which 30.8% were major interactions. The most frequently interacting TKI was imatinib (29.6%), and the additional drug group was antibiotics (21.2%). We observed that PTDIs caused the following effects: TKI concentration was increased or decreased owing to 14.4% or 22.8% PTDIs, respectively, and electrocardiographic QT prolongation occurred in 22% of all PTDIs. Multivariate analysis demonstrated that use of higher number of additional drugs (odds ratio/OR=1.63), pre-existing lung cancer (OR=8.82), and use of pazopanib (OR=9.22) were potential risk factors.*

Conclusion: *The rate of PTDI is quite high in patients using TKIs. Effort must be made to increase awareness of this subject. Increasing awareness aids in lowering toxicity rates and providing efficient antitumor therapy.*

Key words: *tyrosine kinase inhibitors, drug-drug interactions, antibiotics, proton pump inhibitors, cancer*

Introduction

Tyrosine kinases take part in mostly all signaling pathways in a cell including proliferation, survival, apoptosis, metabolism, and differentiation [1]. There are two types of this enzyme: transmembrane receptor tyrosine kinase and cytoplasmic non-receptor tyrosine kinase. Mutation or overexpression of these proteins may cause uncontrolled cell proliferation [2]. Because many tumors express abnormal tyrosine kinase activity, therapies targeting these enzymes have reformed oncology practice in the recent years. Tyrosine kinase inhibitors (TKIs) are molecule-targeted oral anticancer agents

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that have been frequently used in oncologic and hematologic diseases since the last two decades. All TKIs are used orally, therefore their use is flexible and practical, thereby consequently improving the quality of life.

Drug interactions can be classified into pharmacokinetic and pharmacodynamic interactions. Pharmacodynamic interactions refer to an interaction in which one active compound alters the pharmacological effect of another. This effect can be synergistic, additive, or antagonistic. Pharmacokinetic interactions refer to an alteration in the absorption, distribution, metabolism, or elimination of drugs [3]. Use of TKIs with other drugs that decrease absorption or induce metabolism of TKI may result in sub-therapeutic levels of the drugs and bring about a decrease in TKI effect. On the contrary, drugs that inhibit the TKI metabolism may cause supra-therapeutic drug levels and toxicity. These interactions possibly lead to loss of therapeutic effects of TKIs or cause severe to fatal side effects.

Because TKIs are continuously used for a prolonged period and metabolized by cytochrome P450 (CYP) isozymes, patients who are administered these drugs are at a risk of experiencing drug-drug interactions [3]. The CYP enzyme family plays an essential role in drug metabolism. CYP3A4 is the main CYP enzyme and is responsible for the metabolism of more than half of all drugs [4]. It also takes part in the metabolism of almost all TKIs. For this reason, another drug concomitantly used with a TKI is likely to affect TKI metabolism over CYP3A4 isozyme. Another factor modifying the TKI effect is the gastrointestinal absorption of the drug. Although there are multiple factors, the main determinant of TKI absorption is its solubility depending on pH levels [5]. TKIs are weak basic drugs, and are thereby more soluble in an acidic environment. Elevated intragastric pH (acid-suppressing drugs) may cause a critical decrease in TKI bioavailability owing to decreased solubility [3,6,7]. Acid-suppressing drugs are widely used in cancer patients and are of great importance with regard to potential TKI-drug interaction (PTDI).

Advanced age not only increases cancer risk but also results in frequent occurrences of comorbid diseases. Increased frequency of such diseases compels patients to use higher number of drugs, which in turn increases the risk of PTDI. Another factor is that cancer patients often need symptomatic therapies which also increase the risk of PTDI [8].

In this multicenter study, we aimed to assess PTDI prevalence in patients with solid organ cancer who were taking TKIs as well as to raise awareness of physicians on this topic.

Methods

This study was approved by our Institutional Ethics Committee and was conducted according to the principles of the Declaration of Helsinki (decision date 07/06/2018, decision no.2016/2018).

Patients

The data of 310 patients collected from four oncology centers, where patients who were histologically diagnosed with solid organ malignancy between January 2007 and December 2017, prescribed with adjuvant/neoadjuvant TKIs for palliative purposes, aged >18 years, and regularly followed up and treated at the same center, were retrospectively evaluated. Data on oncological diagnosis, prescribed TKIs, age, sex, and comorbid diseases were collected from patient files. Comorbid diseases were identified as chronic diseases other than cancer. All drugs that were prescribed by oncologists or other physicians during TKI treatment period were recorded from patient files and electronic prescription systems.

Potential TKI–Drug interactions (PTDIs)

Potential interactions between TKIs and other drugs being used by patients were identified using "Lexicomp® Drug Interactions, App Version 1.1" [9]. The severity of interactions was staged as major, moderate, and minor (Table 1) [10]. Additional drugs were classified under acid-suppressants (proton pump inhibitors (PPIs), histamine-2 receptor antagonists), anti-emetics (serotonin-3 receptor antagonists and dopaminergic antagonists), non-steroid anti-inflammatory drugs (NSAIDs), acetaminophen, steroids, antihypertensive agents, narcotic analgesics, antibiotics (azole group antifungals, quinolones, macrolides, etc.), antidiabetic agents, and so on. Because the acid-suppressing drugs were mainly PPIs, the latter were considered as a separate group. For each patient, we investigated the total number of PTDIs, drug interaction severity, increase or decrease in TKI efficacy/level, and change in efficacy/therapeutic level of the additionally used drugs.

Statistics

The data obtained for this study were statistically analyzed using the Statistical Package for the Social Sciences Version 22.0 (SPSS Inc., Chicago, IL, USA) for Windows software. Descriptive statistics were used for analyzing the demographic characteristics of patients, cancer types, TKIs used, comorbidities, number of drugs

Table 1. Drug interactions severity definitions

Level of severity	*Description*
Major	Potentially severe or life-threatening interaction
Moderate	Interaction may cause deterioration in the patient's clinical status
Minor	Interaction is unlikely to be clinically relevant

used per patient, and drug interaction severity. To identify the risk factors related to PTDIs, multivariate logistic regression analysis was conducted. An occurrence of at least one PTDI (yes/no) was defined as a dependent variable, whereas age, sex, comorbidities (yes/no), cancer types, TKI used, other drug groups used (e.g., PPIs and NSAIDs), and the number of other drugs used were independent variables. The largest group was taken as the reference (ref.) for independent variables with more than two groups. A p value of<0.05 was considered to be statistically significant.

Table 2. Baseline characteristics

Characteristics	*n*	%
Study population	310	100
Median age, years (range)	56 (18-87)	
Sex		
Female	156	50.3
Male	154	49.7
Cancer type		
GIST	82	26.5
RCC	69	22.3
Breast	61	19.7
Lung	30	9.7
HCC	21	6.8
Sarcoma	21	6.8
Other	26	8.3
TKI used		
Imatinib	65	21.0
Lapatinib	61	19.7
Sunitinib	50	16.1
Pazopanib	48	15.5
Sorafenib	28	9.0
Erlotinib	21	6.8
Other	37	11.9
Concurrent supplementary drug with TKI		
Yes	301	97.1
No	9	2.9
Most commonly used additional drug		
PPI	181	58.4
NSAID /Acetaminophen	155	50.0
Antibiotic	100	32.3
Anti-hypertansive agent	81	26.1
Narcotic pain medications	63	20.3
Anti-emetic	60	19.4
No. of drugs used per patient, median (range)	4 (1-12)	
Comorbidities		
Yes	159	51.3
No	151	48.7

GIST: gastrointestinal stromal tumors, RCC: renal cell carcinoma, HCC: hepatocellular carcinoma, PPI: proton-pump inhibitor, NSAIDs: nonsteroidal anti-inflammatory drugs

Results

Patient characteristics

In total, 310 patients were included in the study. Their median age was 56 years (range 18-87), and of the total patients, 50.3% were female. There were 9 different cancer types and 12 different TKIs (sunitinib, sorafenib, lapatinib, erlotinib, axitinib, imatinib, crizotinib, regorafenib, pazopanib, vemurafenib, dabrafenib, vandetanib), and 51.3% (n=159) of the patients had at least one comorbid disease. Moreover, 301 patients (97.1%) were using another drug along with TKI. Among them, the most frequently prescribed group was PPIs (58.4%). The median number of additional drugs used was 4 (range 1-12). Table 2 lists the baseline characteristics of the study patients.

Potential TKI–drug interactions

Of the 310 patients, 147 (47.4%) had at least one PTDI, i.e., 98 of these patients had only one PTDI and 49 had more than one. There were a total of 250 PTDI of which 30.8% were major, 46.8% were moderate, and 22.4% were minor. Ten patients had concomitant drug usage which was contraindicative (7 patients experienced erlotinib–PPI interaction and 3 experienced pazopanib–atorvastatin interaction). The most frequently interacting TKIs were imatinib (29.6%) and pazopanib (25.6%) and the most frequently interacting additional drugs were antibiotics (21.2%) and PPIs (16.4%) (Figure 1). We observed that 22.8% of all PTDIs caused a potential decrease in TKI concentration,

Table 3. Characteristics of interactions

Characteristics	*n*	%
Total interaction event	250	100
Level of severity		
Major	77	30.8
Moderate	117	46.8
Minor	56	22.4
Adverse consequences		
Increased toxicity of TKI	36	14.4
Decreased effectiveness of TKI	57	22.8
Increased toxicity of co-medication	38	15.2
Decreased effectiveness of co-medication	23	9.2
QT interval prolongation	55	22.0

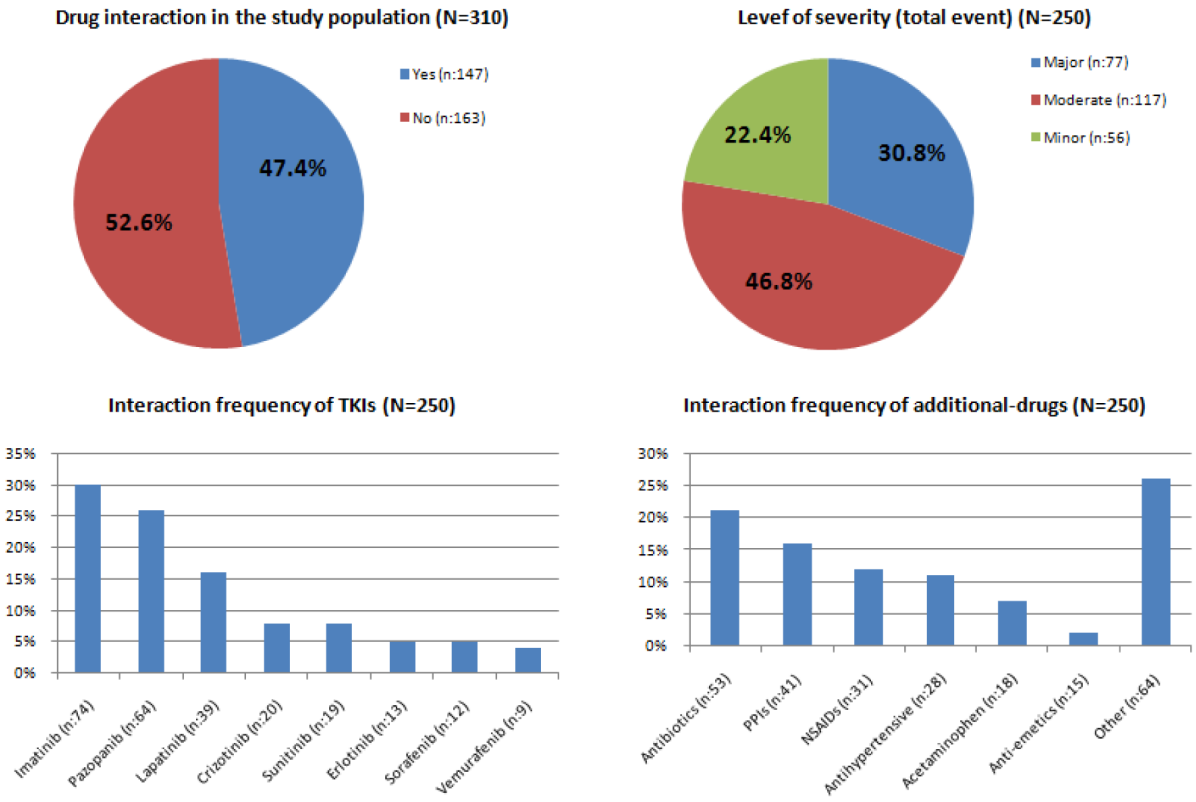

Figure 1. Interaction frequency and types.

Table 4. Multivariate logistic regression analysis of factors associated with potential drug-drug interactions

Variable	*OR*	*95% CI*	*p value*
Age	1	0.98-1.03	0.20
Male sex	1.55	0.69-3.45	0.28
Comorbidities (ref: Yes)	1.48	0.75-2.90	0.24
Cancer type (Ref: GIST)			0.13
Lung	8.82	1.04-74.9	0.04
RCC	0.36	0.14-0.88	0.02
Breast	0.31	0.08-1.13	0.07
HCC	0.26	0.03-2.01	0.20
Colorectal	0.17	0.01-2.77	0.21
Used TKI (ref: Imatinib)			0.001
Pazopanib	9.22	3.61-25.2	<0.001
Sunitinib	4.62	1.29-16.5	0.01
Erlotinib	0.09	0.01-0.89	0.03
Sorafenib	2.63	0.43-15.8	0.29
Additional drug class (ref: Yes)			
Antibiotic	4.62	2.23-9.57	<0.001
PPI	1.62	0.83-3.17	0.15
Anti-emetic	1.39	0.63-3.05	0.40
Narcotic Pain Medications	1.28	0.57-2.89	0.53
NSAID /Acetaminophen	0.83	0.42-1.63	0.60
No. of additional drugs used	1.63	1.30-2.07	<0.001

OR: odds radio, CI: confidence interval, GIST: gastrointestinal stromal tumors, RCC: renal cell carcinoma, HCC: hepatocellular carcinoma, PPI: proton-pump inhibitor, NSAIDs: nonsteroidal anti-inflammatory drugs.

whereas 14.4% showed a potential increase in TKI levels which led to toxicity. When TKI types were analyzed separately, crizotinib (33%) and sunitinib (16%) were found to most frequently cause a potential decrease in TKI effect, whereas pazopanib (52%) and erlotinib (43%) predominantly caused a potential increase in TKI toxicity; 22% of all PTDIs resulted in potential QT prolongation. Table 3 lists the characteristics of interactions.

Potential risk factors

All patients were included in the multivariate logistic regression analysis. Age, sex, and pre-existing comorbid diseases were not statistically significant risk factors ($p<0.05$). Cancer type, TKI used, additional drugs used, and increased drug quantities were potential risk factors. When gastrointestinal stromal tumors were considered as the reference group, the risk of drug interaction was 8.8-fold higher in patients with lung cancer (OR=8.82 [95% CI, 1.04–74.9], p=0.04), whereas patients with renal cell carcinoma (RCC) had 2.7-fold lower risk. When imatinib group was considered as the reference group, pazopanib group had 9.2-fold higher risk for PTDI (OR=9.22 [95% CI, 3.6–25.2], $p<0.001$), whereas erlotinib group had 11.1-fold lower risk. Patients using antibiotics had a 4.6-fold higher risk, and a higher number of additional drugs were related to 1.6-fold higher PTDI risk. Our

logistic regression analysis results with regard to PTDI risk factors are presented in Table 4.

Discussion

Drug-drug interaction has been a well-known problem in oncology for several years, and is significant owing to its importance with regard to efficiency, safety, and cost of treatment. This interaction, better defined in conventional treatments, is a lesser known important problem for TKIs, which are being used as a treatment option since the last few years. There have been numerous reviews and studies regarding drug-drug interactions involving conventional chemotherapeutics, but TKI-specific drug interaction studies remain limited [3,8,11,12]. In our study, we assessed the prevalence of potential TKI-drug interactions (PTDI) for 12 different TKIs.

Herein, we found that almost all of the patients (97.1%) were using at least one additional drug, and 47.4% of these patients were exposed to at least one PTDI from a total of 250 PTDIs. Of these, 30.8% were major interactions which may have potentially serious consequences. Keller et al. [11] retrospectively detected 244 PTDIs in their cohort of 356 patients and reported that 44.7% of those were major interactions. In a retrospective study involving 898 patients, Van Leeuwen et al. [13] reported that the prevalence of drug-drug interaction was 46% in patients administered with any oral anticancer agent; 16% of these PTDIs were major interactions. There were 6 TKIs in their study, and the prevalence of interaction was reported for 2 TKIs. Because this study included all oral anticancer drugs, it may not be suitable to compare the results of this study with ours. Owing to only few studies on TKI-specific drug interactions, there is insufficient data for making effective comparisons. Hence, we think that our study will be a significant addition to the literature.

Bowlin et al. [8] detected PTDIs which could cause a decrease in TKI efficiency in 23% of patients using sunitinib and 57% of patients using erlotinib. Keller et al. [11] reported a decrease in TKI plasma concentration in 48.6% and increase in 2.8% in their study cohort. These potential changes were determined using Lexicomp® Drug Interactions software. In our study we detected PTDIs after including all TKIs, of which 22.8% caused a potential decrease in TKI efficacy and 14.4% led to a potential increase in TKI toxicity. When we analyzed TKI types separately, crizotinib (33%) and sunitinib (16%) had the most frequent potential decrease in TKI effect, whereas pazopanib (52%) and erlotinib (43%) had the most frequent potential increase in TKI toxicity. The most probable reason for the difference between our results and those of Bowlin's and Keller's study is that our study represents recent trends in oncology practice. Because new TKIs have become available for use in the last 5 years, patients as well as interaction rates were divided into more groups. Another factor is the increasing awareness of TKI-drug interactions as well as a consequent decrease in the prevalence of interaction.

Acid-suppressing drugs are commonly used in both cancer patients and non-cancer population [14,15]. Because the solubility of most TKIs depends on pH levels, routine use of acid-suppressing agents for the palliation of primary malignancy-related or unrelated gastrointestinal symptoms may lead to impaired TKI absorption [16-19]. In our study, the drug most frequently used along with TKI was proton pump inhibitors (PPIs) at a rate of 58.4%. Pazopanib and erlotinib are known to interact with PPI, and these were concomitantly used with a TKI by 45% and 33% of our patients, respectively. We need to effectively reduce such a high usage frequency. Although there have been many studies on the pharmacokinetics of TKI-PPI interaction, there is no clear recommendation on the management of this interaction. Acid-suppressing agents and TKI interaction are especially important for crizotinib, dasatinib, erlotinib, gefitinib, lapatinib, and pazopanib [16,17,20-22]. It is not possible for a physician to know about all the TKI-drug interactions; therefore, drug-drug interaction checker software can be used before prescribing any drug to a patient who is undergoing treatment with TKI. Unless an absolute indication exists, such as Zollinger–Ellison syndrome or peptic ulcer, short-acting antacid drugs should be preferred. If acid-suppressing drug use is absolutely necessary, TKI should be given 2 h before the administrant of acid suppressant [11]. In patients using PPI for acid suppression, the choice of drug is also important. Pantoprazole may alter TKI pharmacokinetics by inhibiting drug carriers including breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) [23]. Because many TKIs are substrates for BCRP and/or P-gp, pantoprazole should be carefully prescribed or replaced with other PPIs during TKI therapy [6]. Increasing TKI dose to increase TKI absorption in patients who use PPI is not an effective strategy and thus not recommended (i.e., PTDI risk increases with an off-target effect) [11]. In a study investigating TKI bioavailability in patients using PPI by administering TKI together with an acidic drink (cola) [24], erlotinib bioavailability was found to be increased by 40%. Considering these results, it may be a practical solution to give acidic drinks

to patients who use PPI or to those who need to use histamine-2 receptor antagonists twice a day.

In our study, the most frequently interacting drug group was antibiotics (azole group antifungals, quinolones, macrolides, etc.). There are various interaction mechanisms with respect to antibiotics. Azole group antifungals, such as ketoconazole, and macrolide group antibiotics, such as clarithromycin, are potent inhibitors of CYP3A4, and therefore may decrease TKI metabolism and increase toxicity [25-27]. Another interaction with antibiotics is the risk of QT prolongation, especially for quinolone antibiotics [28-30]. Another group of drugs that can lead to QT prolongation is the commonly used anti-emetic drugs. Anti-emetic drugs (selective 5-HT3 antagonists, dopamine receptor antagonists) are another group of drugs that are commonly used in oncology practice and can lead to QT prolongation. The majority of TKIs [31,32] have a risk of causing QT prolongation; hence, concomitant use of these agents may cause life-threatening arrhythmias. Keller et al. [11] reported that 48.6% of patients receiving TKI are exposed to interactions that potentially prolong QT interval. In our study, there was a potential risk of QT prolongation for 22% of PTDIs. All physicians should be cautious of QT prolongation. These medications should not be used together unnecessarily. If an absolute indication is present, ECG should be performed before and 1 week after the concomitant therapy [3].

Here, the number of drugs used concurrently during the risk assessment of PTDI was defined as a risk factor (risk increased by 1.6-fold). It is not surprising that as the number of medications used increases, increase in PTDI risk noted in our study was consistent with that reported in other studies [8,13,33]. Age, sex, and the presence of comorbidities were not significant risk factors for PTDI. Some previous studies have revealed that old age is also a risk factor [34,35], whereas in other studies, no relationship between age and PTDI frequency has been reported [33,36,37]. Again, in these studies, different conclusions have been attained regarding sex, comorbid disease status, and type of cancer as potential risk factors. However, because these studies are not specific to TKI-drug interactions, they are found unsuitable for making comparisons.

Our study has a few limitations. First, it was a retrospective analysis. All drug interactions identified by us are theoretical and have been determined using the drug interaction checker software. We presented potential interaction rates which may not completely represent clinical results because clinical toxicity data were unavailable. Another limitation was that patient data regarding the use of over-the-counter medicines and herbal remedies could not be obtained. This suggests the possibility of a much higher prevalence of PTDIs than what has been detected in our study.

Conclusion and suggestions

TKIs are frequently used in oncology practice. Oral drug administration may seem advantageous but prolonged use increases potential drug-drug interaction risk. Therefore, physicians prescribing TKI should be careful of this phenomenon.

No additional medication should be given without a definite indication for the patient using TKI. In particular, 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 PTDI, is a life-threatening consequence. Awareness of this subject should be increased, and when potential QT-prolonging agents need to be used together, patients should be monitored using ECG.

When these drug interactions are inevitable, physicians should be well-trained to perform appropriate intervention (dose adjustment, monitoring, etc.). Prospective studies on this subject are insufficient and more studies are required. Awareness seminars on drug-drug interactions should be given to physicians. Despite all educational efforts, it may not be possible for a physician to memorize all the potential interactions. With increased awareness, physicians 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 when any of the patient's existing medicines interact with the newly prescribed drug. Health professionals as well as patients should be aware of this subject. Patients should especially be informed about the potential risks of over-the-counter drugs and alternative therapies.

We believe that increasing the 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 antitumor therapy.

Previous presentation

Part of our work was presented as a poster at the 2017 ESMO congress, 08 Sep 2017, Madrid, Spain.

Conflict of interests

The authors declare no conflict of interests.

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