İstanbul Journal of Pharmacy
Istanbul J Pharm, 54 (1): 32–39
DOI: 10.26650/IstanbulJPharm.2024.1207607

Original Article

Comparison of drug–drug interaction checking databases for interactions involving BCR-ABL tyrosine kinase inhibitors

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ABSTRACT

Background and Aims: BCR-ABL tyrosine kinase inhibitors (TKIs) are used for the treatment of chronic myeloid leukemia and are commonly involved in clinically significant drug–drug interactions (DDIs). In this study, we aimed to evaluate the consensus of DDI checking databases for interactions involving BCR-ABL TKIs.

Methods: We checked DDIs of 100 drugs with six BCR-ABL TKIs—dasatinib, imatinib, nilotinib, ponatinib, bosutinib, and asciminib—in two subscription-based databases (UpToDate and Micromedex) and two open-access databases (Drugs.com and Medscape). Databases were compared in terms of severity ratings, literature support ratings, and general interaction mechanism definitions using Fleiss' and Cohen's kappa statistics.

Results: A total of 410 interactions were found. Nilotinib was the most interacted TKI, with 88 interactions. Drugs.com detected the highest number of interactions (n = 355). The overall agreement levels of databases for the severity ratings and general mechanisms were calculated as 0.13 (p = 0) and 0.28 (p = 0), respectively. The Micromedex- UpToDate pair showed the highest agreement level in terms of severity ratings and general mechanism definitions, with kappa values of 0.23 and 0.45, respectively.

Conclusion: The differences among databases for DDIs involving BCR-ABL TKIs were statistically significant. Therefore, healthcare practitioners should check DDIs in multiple databases.

Keywords: Drug-drug interactions, chronic myeloid leukemia, tyrosine kinase inhibitors, TKIs, CML

INTRODUCTION

Chronic myeloid leukemia (CML) is a rare malignancy represented by BCR-ABL1 gene translocation. The Philadelphia chromosome is a cytogenetic feature of CML (Osman, & Deininger, 2021). Tyrosine kinase inhibitors (TKIs) are used to treat CML. Imatinib, dasatinib, and nilotinib are the first-line treatment options (Hsieh, Kirschner & Copland, 2021). Bosutinib, ponatinib, and asciminib are the newer TKI options for the treatment of this disease (Kennedy & Hobbs, 2018; Deeks, 2022).

Drug–drug interactions (DDIs) occur because of pharmacodynamic and pharmacokinetic mechanisms as well as pharmaceutical incompatibilities (Corrie & Hardman, 2011). TKIs are orally administered, target-specific weak bases with bioavailability problems (van Leeuwen, van Gelder, Mathijssen & Jansman, 2014). The increments in gastric pH by acid-suppressive drugs, such as proton pump inhibitors (PPIs), may result in poor therapy response due to the lack of bioavailability of TKIs (van Leeuwen et al., 2017). TKIs are metabolized by the cytochrome P450 enzyme system (CYP450), which puts them into the target of DDIs (van Leeuwen, van Gelder, Mathijssen & Jansman, 2014).

Patients with cancer often require complex treatment schemes, resulting in a higher prevalence of DDI, leading to DDI-related adverse events (Riechelmann & Del Giglio, 2009). A study on patients with cancer who used oral anticancer drug therapy found that 46% of them were exposed to potential DDIs. In this patient group, interactions that affect the nervous system, gastrointestinal tract, and QT interval were common (van Leeuwen et al., 2013).

DDI checking databases help health professionals identify potential DDIs; however, differences in detected DDIs and provided information were noted among DDI checking databases (Suriyapakorn et al., 2019). DDI checking databases show dif-

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Submitted: 21.11.2022 • **Revision Requested:** 18.11.2023 • **Last Revision Received:** 26.11.2023 • **Accepted:** 28.11.2023

ferent levels of scope, consistency, and completeness (Patel& Beckett, 2016). In a study that compared nine DDI checking databases for oral oncolytic-involving DDIs, Lexicomp and Drugs.com showed the highest performance (Marcath et al., 2018).

This study focused on BCR-ABL TKI-involving DDIs and the compatibility of DDI checking databases in terms of severity ratings, literature support ratings, and general interaction mechanism definitions.

METHODS

Drug selection

The following BCR-ABL TKIs were used to treat CML: imatinib, dasatinib, nilotinib, bosutinib, ponatinib, and asciminib (Cancer.org, 2022). Four widely available DDI checking databases were included. According to the DDI sections of the drug information of these TKIs in these databases, 100 drugs were manually chosen. Except for transdermal fentanyl, all chosen drugs can be administered orally (Drugs.com, 2022; UpToDate Interactions, 2022; Medscape, 2022; IBM Micomedex, 2022). The selected drugs are classified according to the Anatomical Therapeutic Chemical Classification/Defined Daily Doses index system in Table 1 (WHO ATC/DDD Index, 2022). Orally administered drugs were chosen because they can be prescribed for acute or chronic diseases in outpatient settings, which could cause difficulties in identifying and monitoring interactions.

DDI Checking Databases

Two subscription-based (UpToDate and Micromedex) and two open-access (Drugs.com and Medscape) DDI checking databases were included. All databases provided information about the severity, mechanism, and management of the interactions. Only UpToDate and Micromedex provided information about the literature support of the interactions. Severity and literature support classifications of interactions are listed in Table 2.

Statistical analysis

The severity ratings, literature support ratings, and proposed mechanisms of these interactions assigned by databases were noted. Summary statistics were used to categorize DDIs according to severity ratings and general mechanisms. Severity ratings and general mechanisms were analyzed using Cohen's kappa and Fleiss' kappa statistics. The literature support ratings of UpToDate and Micromedex were compared using Cohen's kappa formula. The agreement levels of databases were evaluated using the Landis and Koch agreement classification (Landis & Koch, 1977).

RESULTS

After analyzing 100 drugs with six TKIs, 410 DDIs were found. Nilotinib was the most interacted TKI, with 88 (21%) interactions. Dasatinib constituted 20% of DDIs with 83 interactions. The least interacted TKI was asciminib, with 50 interactions (Figure 1).

None of the DDI checking databases detected all interactions. Drugs.com and Micromedex detected the highest and lowest number of interactions, with 355 and 164 interactions, respectively. The distribution of severity ratings differed among databases. The highest number of contraindicated interactions was detected by UpToDate, with 22 interactions. Moderate severity level was the most common severity rating among all databases (Figure 2).

The mechanisms of interactions were categorized according to the literature definitions (Cascorbi, 2012). The number of pharmacokinetic interactions was higher than other mechanism categories among databases. Of the 355 interactions detected by Drugs.com, 239 originated from pharmacokinetic mechanisms. The pharmacodynamic mechanism was the second most common DDI general mechanism. Drugs.com and UpToDate reported the highest pharmacodynamic DDIs, with 110 and 81 interactions, respectively. Some interactions were explained by the combination of pharmacodynamic and pharmacokinetic mechanisms. The highest number of this combination of mechanisms was detected by Medscape, with 30 interactions (Figure 3).

Some interactions with contraindicated severity warnings are listed in Table 3. The combinations of dasatinib and acid-suppressive drugs, such as PPIs and famotidine, were labeled as contraindicated by UpToDate. The proposed mechanism was gastric pH elevation with a result of a decrease in the dasatinib effect (UpToDate Interactions, 2022). Dasatinib, nilotinib, and bosutinib combinations with azole antifungals were listed as contraindicated DDIs. The CYP3A4 inhibition and additive QTc prolongation effects of azole antifungals cause increases in the TKI blood levels and arrhythmia. Additionally, the proposed mechanism for the nilotinib and posaconazole interaction in Medscape was described as CYP3A4 and p-glycoprotein inhibition, which differed from other databases. The combination of nilotinib and sotalol causes QTc prolongation, and this combination comes with a contraindicated warning in the UpToDate and Medscape DDI checking databases (Drugs.com, 2022; UpToDate Interactions, 2022; Medscape, 2022; IBM Solutions, 2022).

Fleiss' kappa statistic was used to evaluate the agreement level of DDI checking databases for categorizing the severity warnings of BCR-ABL TKI-involving interactions. The overall Fleiss kappa values of the four databases in terms of severity ratings and general mechanisms were 0.13 ($p = 0$; standard error [SE], 0.013; 95% confidence interval [CI], 0.10–0.15)

Table 1. Classifications of selected drugs according to the Anatomical Therapeutic Chemical Classification/Defined Daily Doses index system

Anatomical Therapeutic Chemical Classification/Defined Daily Doses drug classes of the selected drugs
N05, psycholeptics: alprazolam, aripiprazole, buspirone, chlorpromazine, clozapine, haloperidol, hydroxyzine, olanzapine, quetiapine, ramelteon, and risperidone
N06, psychoanaleptics: amitriptyline, donepezil, duloxetine, escitalopram, fluoxetine, imipramine, paroxetine, sertraline, and venlafaxine
A02, drugs for acid-related disorders: calcium carbonate, esomeprazole, famotidine, lansoprazole, magnesium carbonate, omeprazole, pantoprazole, rabeprazole, and sodium bicarbonate
J01, antibacterials for systemic use: azithromycin, ciprofloxacin, clarithromycin, doxycycline, levofloxacin, metronidazole, moxifloxacin, and sulfamethoxazole
B01, antithrombotic agents: apixaban, aspirin, clopidogrel, dabigatran, prasugrel, rivaroxaban, and warfarin
N02, analgesics: codeine, fentanyl, morphine, oxycodone, paracetamol, and tramadol
C08, calcium channel blockers: amlodipine, diltiazem, felodipine, nifedipine, and verapamil
C10, lipid-modifying agents: atorvastatin, fluvastatin, gemfibrozil, rosuvastatin, and simvastatin
C07, beta-blocking agents: carvedilol, metoprolol, nebivolol, and sotalol
M01, anti-inflammatory and antirheumatic products: diclofenac, ibuprofen, and naproxen
N03, antiepileptics: carbamazepine, phenobarbital, and phenytoin
A04, antiemetics and antinauseants: aprepitant, granisetron, and ondansetron
J02, antimycotics for systemic use: fluconazole, posaconazole, and voriconazole
G04, urologicals: alfuzosin, silodosine, and solifenacin
A10, drugs used in diabetes: metformin and repaglinide
R03, drugs for obstructive airway diseases: montelukast and theophylline
J04, antimycobacterials: isoniazid and rifampicin,
C01, cardiac therapy: amiodarone and ranolazine
C09, agents acting on the renin–angiotensin system: captopril and losartan
H02, corticosteroids for systemic use: dexamethasone and methylprednisolone
R05, cough and cold preparations: hydrocodone
A12, mineral supplements: potassium bicarbonate
C03, diuretics: spironolactone
M04, antigout preparations: colchicine
J05, antivirals for systemic use: tenofovir
H03, thyroid therapy: levothyroxine
R06, antihistamines for systemic use: cetirizine
A03, drugs for functional gastrointestınal disorders: metoclopramide
G03, sex hormones and modulators of the genital system: megestrol

Table 2. Severity and literature support classifications of databases

Databases	Classifications
	Severity classifications
UpToDate	No interaction between drugs (A), minor (B), moderate (C), major (D), and major (X)
Micromedex	Minor, moderate, major, and contraindicated
Drugs.com	Minor, moderate, major, and major-contraindicated
Medscape	Minor, monitor closely, serious, and contraindicated
	Literature support classifications
UpToDate	Poor, fair, good, and excellent
Micromedex	Fair, good, and excellent

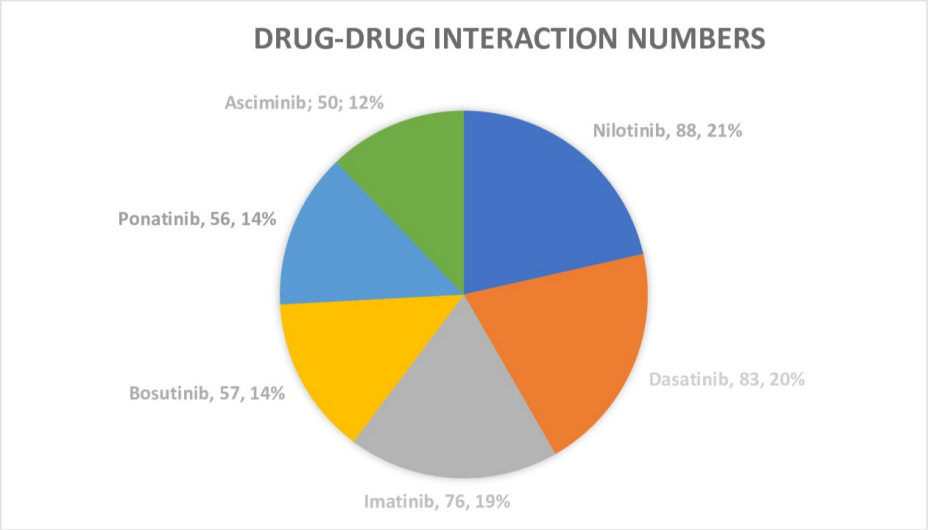

Figure 1. Distribution of drug–drug interactions according to the tyrosine kinase inhibitor type.

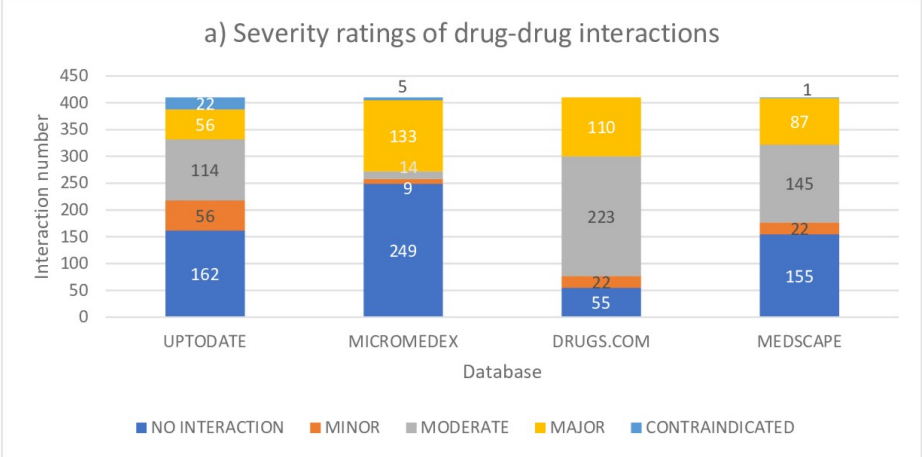

Figure 2. Distribution of the severity ratings and general mechanisms of drug–drug interactions according to the databases.

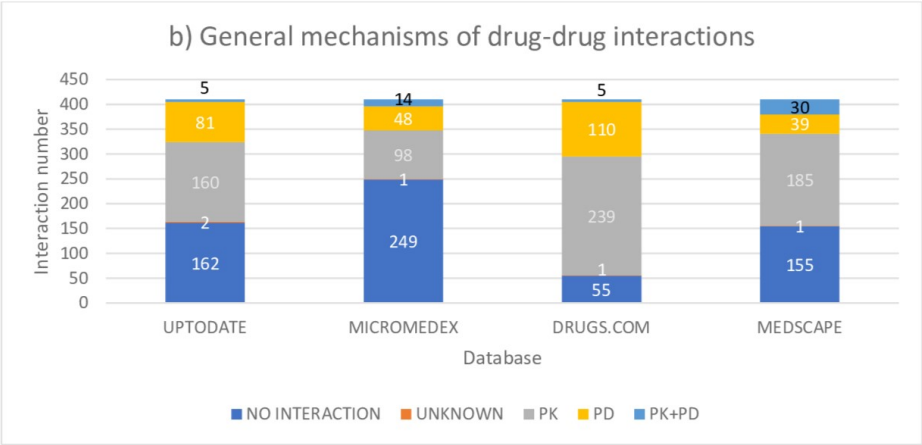

Figure 3. Distribution of the severity ratings and general mechanisms of drug–drug interactions according to the databases.

Table 3. Examples of the contraindicated drug–drug interactions with BCR-ABL tyrosine kinase inhibitors (Drugs.com, 2022; UpToDate Interactions, 2022; Medscape, 2022; IBM Solutions, 2022)

TKI + interacting drug	Databases (severity and LS)	Mechanism	Clinical effect
Dasatinib + PPIs*/famotidine	**U:** Major (X) *LS: Good* **Mi:** Major *LS: Fair* **D:** Major **Me:** Major	(Consensus) Gastric pH ↑	(Consensus) Dasatinib effect ↓
Dasatinib + fluconazole	**U:** Moderate (C) *LS:Fair* **Mi:** Contraind. *LS: Fair* **D:** Moderate **Me:** Monitor closely	CYP3A4 inhibition and QTc prolongation CYP3A4 inhibition CYP3A4 inhibition CYP3A4 inhibition and QTc prolongation	Dasatinib level ↑ and QTTc ↑ Dasatinib level ↑ Dasatinib level ↑ Dasatinib level ↑
Dasatinib + posaconazole	**U:** Major (X) *LS:Fair* **Mi:** Contraind. *LS: Fair* **D:** Major **Me:** Monitor closely	CYP3A4 inhibition and QTc prolongation CYP3A4 inhibition CYP3A4 inhibition CYP3A4 inhibition	Dasatinib level ↑ and QTc ↑ Dasatinib level ↑ Dasatinib level ↑ Dasatinib level ↑
Nilotinib + fluconazole	**U:**Moderate (C) *LS: Fair* **Mi**:Contraind. *LS: Fair* **D:** Major **Me:** Serious	QTc prolongation by a QT-prolonging moderate CYP3A4 inhibitor drug CYP3A4 inhibition and QTc prolongation QTc prolongation CYP3A4 inhibition and QTc prolongation	QTc ↑ Nilotinib level ↑ and QTc ↑ QTc ↑ Nilotinib level ↑ and QTc ↑
Nilotinib + posaconazole	**U:** Major (X) *LS: Fair* **Mi:** Contraind. *LS :Fair* **D:** Major **Me:** Monitor closely	CYP3A4 inhibition CYP3A4 inhibition QTc prolongation CYP3A4 and p-glycoprotein inhibition	Nilotinib level ↑ Nilotinib level ↑ QTc ↑ Nilotinib level ↑
Bosutinib + posaconazole/voriconazole	**U:** Major (X) *LS: Good* **Mi:** Major *LS: Fair* **D:** Major **Me:** Serious	(Consensus) CYP3A4 inhibition	(Consensus) Bosutinib level↑
Bosutinib + clarithromycin	**U:** Major (X) *LS: Good* **Mi:** Major *LS: Fair* **D:** Major **Me:** Serious	CYP3A4 inhibition and QTc prolongation CYP3A4 inhibition CYP3A4 inhibition CYP3A4 inhibition	Bosutinib level ↑ and QTc ↑ Bosutinib level ↑ Bosutinib level ↑ Bosutinib level ↑
Nilotinib + sotalol	**U:** Major (X) *LS: Fair* **Mi:** Major *LS: Fair* **D:** Major **Me:** Contraind.	(Consensus) QTc prolongation	(Consensus) QTc ↑
Nilotinib + colchicine	**U:** Major (D) *LS: Good* **Mi:** Contraind. *LS: Fair* **D:** Major	CYP3A4 and p-glycoprotein inhibition CYP3A4 and p-glycoprotein inhibition P-glycoprotein inhibition	Colchicine level ↑ Colchicine level ↑ Colchicine level ↑
Nilotinib + Amiodarone	**U:** Major (X) *LS: Fair* **Mi:** Major *LS: Fair* **D:** Major **Me:** Serious	QTc prolongation QTc prolongation and CYP3A, CYP2C8, and p-glycoprotein inhibition QTc prolongation QTc prolongation and CYP3A4 and p-glycoprotein inhibition	QTc ↑ QTc ↑ and ↑ levels of both drugs QTc ↑ QTc ↑ and ↑ levels of both drugs

Abbreviations: TKI, tyrosine kinase inhibitor; LS, literature support ratings; U, UpToDate; Mi, Micromedex; D, Drugs.com; Me, Medscape; CYP3A4, cytochrome P450 3A4 enzyme; PPI, proton pump inhibitors; Contraind, contraindicated.
*Lansoprazole, pantoprazole, omeprazole, esomeprazole, and rabeprazole.

Table 4. Kappa values of databases for the severity ratings, literature support ratings, and general mechanisms of drug–drug interactions in binary combinations

Database pairs	Kappa value	Agreement level	Standard error	95% CI
Severity rating agreements				
Micromedex–UpToDate	0.23	Fair	0.025	0.179–0.278
Micromedex–Medscape	0.22	Fair	0.027	0.170–0.277
Micromedex–Drugs.com	0.19	Slight	0.022	0.142–0.227
UpToDate–Drugs.com	0.11	Slight	0.027	0.066–0.172
Drugs.com–Medscape	0.1	Slight	0.031	0.038–0.158
UpToDate–Medscape	0.09	Slight	0.031	0.030–0.115
Literature support rating agreements				
Micromedex–UpToDate	0.25	Fair	0.032	0.183–0.307
General mechanism agreements				
Micromedex–UpToDate	0.45	Moderate	0.035	0.382–0.519
Micromedex–Medscape	0.37	Fair	0.036	0.302–0.423
UpToDate–Drugs.com	0.36	Fair	0.033	0.291–0.421
Micromedex–Drugs.com	0.25	Fair	0.026	0.198–0.301
UpToDate–Medscape	0.22	Fair	0.038	0.143–0.292
Drugs.com–Medscape	0.16	Slight	0.031	0.096–0.218

Abbreviation: CI, confidence interval.

and 0.28 (p = 0; SE, 0.014; 95% CI, 0.25–0.30). According to the agreement level classification, the kappa level of severity ratings indicated that the databases showed a slight agreement level. The kappa value for the general mechanisms of interactions, that is, 0.28, indicated a fair agreement level among databases.

Databases were compared in binary combinations to identify the severity and literature support agreement levels of database pairs. UpToDate and Micromedex showed a fair agreement level in terms of severity and literature support ratings, with kappa values of 0.23 and 0.25, respectively. The other database pairs showed slight agreement in terms of severity classifications. The lowest agreement level among database pairs was identified in the UpToDate–Medscape databases, with a kappa value of 0.09. The Micromedex–UpToDate database pair showed the highest agreement level among database pairs, with a kappa value of 0.45 in terms of general mechanism agreements. The Drugs.com–Medscape database pair showed the lowest agreement level, with a kappa value of 0.16, and the other database pairs showed fair agreement levels (Table 4).

DISCUSSION

This study demonstrated that databases had a slight agreement level regarding BCR-ABL TKI-involving DDIs in terms of severity ratings. Only two database pairs—Micromedex–UpToDate and Micromedex–Medscape—showed a fair agreement level, and the other database pairs slightly agreed on the severity ratings of interactions. Micromedex and UpToDate showed a fair agreement level in terms of literature support ratings.

The proposed mechanisms attracted to DDIs were also commonly different among databases. The overall kappa value for the general mechanism compatibility of the databases was 0.28, with a fair agreement level. The highest agreement level was observed between Micromedex and UpToDate, with a kappa value of 0.45, which indicated a moderate agreement level. Drugs.com and Medscape, two open-access databases, were slightly compatible in terms of the general mechanism explanation of DDIs, which was the lowest agreement level among database pairs.

In a study that compared DDI checking databases for bipolar medication-involving DDIs, databases showed a slight agreement level in terms of severity ratings (Monteith, Glenn, Gitlin M & Bauer, 2020). In another study that evaluated the sensitivity of five databases on oral oncolytic-involving DDIs, the databases showed a significant difference, and Lexi-Interact and Drugs.com had the highest sensitivity (95%) (Bossaer & Thomas, 2017).

Polypharmacy has increased among elderly patients in recent decades (Haider, Johnell, Thorslund & Fastbom, 2007). Comorbidities and polypharmacy are related to the number of DDIs among these patients (Hohl, Dankoff, Colacone & Afilalo, 2001). DDIs are related to hospital visits and hospitalizations. DDI checking databases help health practitioners to check interactions between multiple drugs (Vonbach, Dubied, Krähenbühl & Beer, 2008). However, the information provided by these databases about interactions and their ability to detect interactions is variable (Reis & Cassiani, 2010). In our study, none of the databases detected all interactions, and the information provided by the databases differed. Drugs.com detected

355 interactions, which made it the most detecting database in our study.

CML is a hematological disorder with a median age of 55 years that presents with a mutation resulting in an active BCR-ABL1 tyrosine kinase. Before the discovery of BCR-ABL TKIs, the treatment options for CML were busulfan and hydroxyurea, with major cytotoxic complications (An et al., 2010). After the introduction of TKIs for the treatment of CML, patients' life expectancies reached near the normal range (Luskin & DeAngelo, 2018). TKIs are often involved in DDIs with different mechanisms (van Leeuwen et al., 2014).

Because of the older age of patients with CML, comorbidities are common, with an incidence of 55.5% (Saydam et al., 2022). Drugs used to treat comorbidities and TKIs may interact and change the TKI efficacy (Luskin & DeAngelo, 2018). Gastric pH-changing drugs, CYP3A4 inhibition or induction, drugs with a changing effect on p-glycoprotein and other transport activities, and combination with QTc prolongations change the effect of TKIs (van Leeuwen et al., 2014). In a study that evaluated the TKI-related DDIs in 105 patients with CML, 159 DDIs were detected (Osorio et al., 2018).

Some interactions in our study with contraindicated warnings were listed. All databases listed interactions with dasatinib and acid-suppressive drugs. There was a consensus on the proposed mechanism for this interaction, which was explained by the decrease in the dasatinib effect due to the gastric pH elevation. UpToDate rated this group of interactions with a good documentation level, whereas Micromedex considered the literature support level as fair (Drugs.com, 2022; UpToDate Interactions, 2022; Medscape, 2022; IBM Micromedex, 2022).

The nilotinib–posaconazole interaction was found in all databases. UpToDate and Micromedex showed a contraindicated warning with a CYP3A4 inhibition-related mechanism (UpToDate Interactions, 2022; IBM Micromedex, 2022). Medscape also reported an increase in the nilotinib blood levels due to p-glycoprotein inhibition (Medscape, 2022). On the other hand, the proposed mechanism of this interaction was shown as QTc prolongation due to the combining of two drugs with a QTc prolongation effect in Drugs.com with a major severity warning (Drugs.com, 2022).

CONCLUSION

CML is a hematological malignancy treated with BCR-ABL TKIs. These drugs are often involved in DDIs because of their chemical structures and metabolic pathways. Databases are important tools for detecting and understanding DDIs; however, significant differences in severity ratings, literature support levels, and the proposed mechanisms are noted among databases. In our study, databases, at most, showed slight agreement in terms of severity ratings and fair agreement in terms of general mechanisms. The significant differences among databases are concerning, and these disparities should be resolved in the future to provide better healthcare to patients with CML. We recommend using multiple DDI databases to evaluate BCR-ABL TKI-involving DDIs.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- A.G., E.D., M.B.Y., A.Ü.; Data Acquisition- A.G.; Data Analysis/Interpretation- A.G.; Drafting Manuscript- A.G.; Critical Revision of Manuscript- A.G., E.D., M.B.Y., A.Ü.; Final Approval and Accountability- A.G., E.D., M.B.Y., A.Ü.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared no financial support.

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How cite this article

Günay, A., Demirpolat, E., Yerer, M.B., & Ünal, A. (2024). Comparison of drug–drug interaction checking databases for interactions involving BCR-ABL tyrosine kinase inhibitors. *İstanbul Journal of Pharmacy, 54*(1), 32–39. DOI: 10.26650/IstanbulJPharm.2024.1207607