Metabolism-related pharmacokinetic drug-drug interactions with poly (ADP-ribose) polymerase inhibitors (Review)

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Abstract. Poly (ADP-ribose) polymerase (PARP) inhibitors, including olaparib, niraparib, rucaparib, talazoparib and veliparib, have emerged as one of the most exciting new treatments for solid tumors, particularly in patients with breast-related cancer antigen 1/2 mutations. Oral administration is convenient and shows favorable compliance with the majority of patients, but it may be affected by numerous factors, including food, metabolic enzymes and transporters. These interactions may be associated with serious adverse drug reactions or may reduce the treatment efficacy of PARP inhibitors. In fact, numerous pharmacokinetic (PK)-based drug-drug interactions (DDIs) involve the metabolism of PARP inhibitors, particularly those metabolized via cytochrome P450 enzymes. The present review aims to characterize and summarize the metabolism-related PK-based DDIs of PARP inhibitors, and to provide specific recommendations for reducing the risk of clinically significant DDIs.

Contents

1. Introduction

In order to improve effectiveness and minimize the adverse effects of cancer treatment, more specific targeted agents have been identified (1). These novel agents have changed the course of cancer treatment and are capable of improving patient outcomes. One of the most promising classes of targeted antineoplastic agents is the poly (ADP-ribose) polymerase (PARP) inhibitors (2). PARP inhibitors may selectively eliminate those cells that have lost the homologous recombination repair pathway (3). The antitumor activity of PARP inhibitors involves inhibition of PARP enzymatic activity and an increase in the formation of PARP-DNA complexes, resulting in DNA damage, apoptosis and cell death, particularly in cancer cells (4). PARP inhibitors, including olaparib, niraparib, rucaparib, talazoparib and veliparib, are administered orally, which has an advantage in terms of flexibility, convenience and quality of life compared with traditional chemotherapy (5). However, as oral PARP inhibitors are extensively used, patients with cancer are at increased risk for drug-drug interactions (DDIs). As a consequence, the pharmacokinetics (PK) of PARP inhibitors may display high inter-individual variability in patients with cancer and a subsequently increased risk for serious toxicity or therapeutic failure (6-8).

DDIs are a major and growing clinical health problem, and could lead to unwanted toxicities or therapeutic failure. DDIs could be divided into pharmacodynamic (PD) and PK interactions (9). PD-based DDIs occur when medications cause additive, antagonistic or synergistic pharmacological effects, altering efficacy or producing adverse effects. PK-based DDIs are caused by changes in absorption, distribution, metabolism and excretion, leading to altered bioavailability of a drug and possible unfavorable outcomes. (e.g., increased toxicity and reduced treatment efficacy) (10). Metabolism-related DDIs are the most common PK-based DDIs. Due to the substantial potential for interaction between PARP inhibitors and other medications that modulate the activity of metabolic pathways, unwanted clinical consequences may occur from small changes in drug PK in patients with cancer (7,8). As such, this may result in an increased risk of non-compliance, dose reduction or therapy discontinuation, leading to suboptimal therapy.

The main objective of the present review is to characterize and summarize the PK parameters and metabolism-related PK-based DDIs for each PARP inhibitor. In addition, practical recommendations for managing DDIs during treatment with PARP inhibitors are provided.

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2. Mechanisms of action of PARP inhibitors

PARPs are a group of enzymes that play a key role in the DNA repair pathway. Among them, PARP-1, 2 and 3 are the most extensively studied (2). PARP-1, accounting for up to 90% of all PARP activity, promotes single-strand DNA break (SSB) repair via the base excision repair pathway (2,3). In addition, PARP-1 plays a central role in microhomology-mediated end joining repair, an error-prone pathway involved in double-strand DNA break (DSB) repair (4). Beyond DNA repair, PARPs are also involved in mitosis, transcriptional regulation, cell death, intracellular metabolism and telomere length (2).

Non-homologous end joining (NHEJ) and homologous recombination (HR) are two important pathways in the repair of DSBs. HR [for which breast-related cancer antigen 1/2 (BRCA1/2) are the first proteins to have been studied] is a high-fidelity repair pathway, while NHEJ is an error prone pathway that could lead to an accumulation of genetic aberrations, chromosomal instability, cell cycle arrest and apoptosis (1,2). If the HR pathway is altered, NHEJ is left as the only pathway able to repair the DNA. PARP inhibitors could bind to the nicotinamide adenine dinucleotide (NAD^+) binding pocket of PARP-1, producing conformational changes that stabilize the binding of PARP-1 and DNA (5). This process results in PARP-1 dysfunction, leading to the accumulation of unrepaired SSBs and inhibiting the progression of replication forks (RFs) (5). Ultimately, stalled RFs degrade into highly cytotoxic DSBs. HR proficient cells are able to repair the DSB and restart replication, while HR deficient cells (i.e., those with BRCA mutation) are unable to repair the accumulating DSBs, which may induce cell death. The mechanisms of action of PARP inhibitors are illustrated in Fig. 1.

3. PK parameters of PARP inhibitors

The PARP inhibitors olaparib, niraparib, rucaparib, talazoparib and veliparib are administered orally. The oral absorption is rapid, with peak plasma concentration (C_{max}) achieved 0.5 to 3 h after dosing in healthy subjects and in patients with solid tumors (11-19). The oral bioavailability is quite different between the five PARP inhibitors. For instance, in niraparib it is ~73%, whereas in rucaparib it is 36% (13-15). Numerous factors may contribute to low oral bioavailability, such as the inability of a drug to cross cell membranes, poor water solubility and metabolic instability.

Among the five PARP inhibitors, niraparib has the highest volume of distribution (1,220 liters) (13,14), potentially indicating a higher tendency to concentrate in tumors and other tissues rather than in plasma. In terms of the plasma protein binding rate, >80% of olaparib and niraparib, ~70% of rucaparib and talazoparib, and only 51% of veliparib is bound to plasma proteins (11-20).

The five PARP inhibitors undergo slightly different metabolic pathways: Olaparib, rucaparib and veliparib are primarily metabolized by the cytochrome P450 (CYP) enzymatic pathway (11,15,19); talazoparib undergoes minimal hepatic metabolism, with identified metabolic pathways, including mono-oxidation, dehydrogenation, cysteine conjugation and glucuronide conjugation (17,18); and niraparib is metabolized primarily by carboxylesterases (CEs) amide hydrolysis to form a major inactive metabolite, and subsequently undergoes glucuronidation (13,14).

Excretion of the five drugs also varies. Talazoparib and niraparib both have a long elimination half-life ($T_{1/2}$) of 90 and 36 h, respectively (13,17), olaparib and rucaparib have a moderate $T_{1/2}$ of 11.9 and 19 h, respectively (11,15), whereas veliparib has a short $T_{1/2}$ (5.2 h) (19,20). This may explain why talazoparib and niraparib are recommended for administration once daily, while olaparib, rucaparib and veliparib are medications administered twice daily. Finally, talazoparib and veliparib are excreted primarily in the urine (17,19-21), whereas rucaparib is excreted primarily in the feces (15,16). For olaparib and niraparib, the average percent recovery of the administered dose is no different in the urine and feces (11,13). PK parameters for PARP inhibitors are demonstrated in Table I, and metabolic pathways related to PARP inhibitors are illustrated in Fig. 2.

4. Metabolism-related PK-based DDIs

Metabolism-related DDIs are the most common type of PK-based DDIs. Drug metabolizing enzymes are expressed throughout the body, including in the liver, intestines, kidneys, brain, heart, lungs and skin. In the small intestine, there are multiple CYP enzymes (22). An immunoblot study of microsomes indicated that CYP3A and CYP2C9 represent the major constituents of the intestinal CYP enzymes, accounting for 80 and 14% of total intestinal CYP enzymes, respectively (23). CYP3A4 was the main CYP3A enzyme, while CYP3A5 was only detected in certain individuals (24). The remaining detected CYP enzymes, in decreasing order of abundance, were CYP2C19, CYP2J2 and CYP2D6. Evidence indicated that a wide variety of orally administered drugs are metabolized by intestinal CYP enzymes, and that intestinal CYP enzyme-mediated metabolism could actually eliminate a large proportion of certain orally administered drugs before they enter the systemic circulation (24-26). Therefore, orally administered drugs that are subject to high intestinal metabolism not only suffer from low oral bioavailability, but they are also more likely to be susceptible to DDIs (27).

While certain oral drugs are metabolized by both the intestines and liver, the main site for drug metabolism is the liver, where both phase I and II metabolic enzymes are expressed in hepatocytes and the biliary epithelium. Phase I metabolic enzymes are primarily CYP enzymes, whereas phase II metabolic enzymes mainly include uridine diphosphate glucuronosyl transferases (UGTs) and sulfotransferases (SULTs). Unlike in the intestines, the major metabolic enzyme subfamilies are more evenly spread out across the liver (28). For phase I metabolism, CYP3A, CYP1A2, CYP2D6, CYP2C, CYP2B6, CYP2E1 and CYP4F are all major players (29). For phase II metabolism, UGT1A, UGT2B and SULT1A1 are the major metabolic enzymes (30). Inhibition or induction of any or all of these hepatic enzymes by co-administered medications or food may lead to increased toxicity or reduced treatment efficacy (31).

Intestinal drug-metabolizing enzymes affect drug absorption, while hepatic drug-metabolizing enzymes affect drug elimination (9,27). Drugs, food and herbal supplements that compete for metabolism by the same metabolic enzyme, or

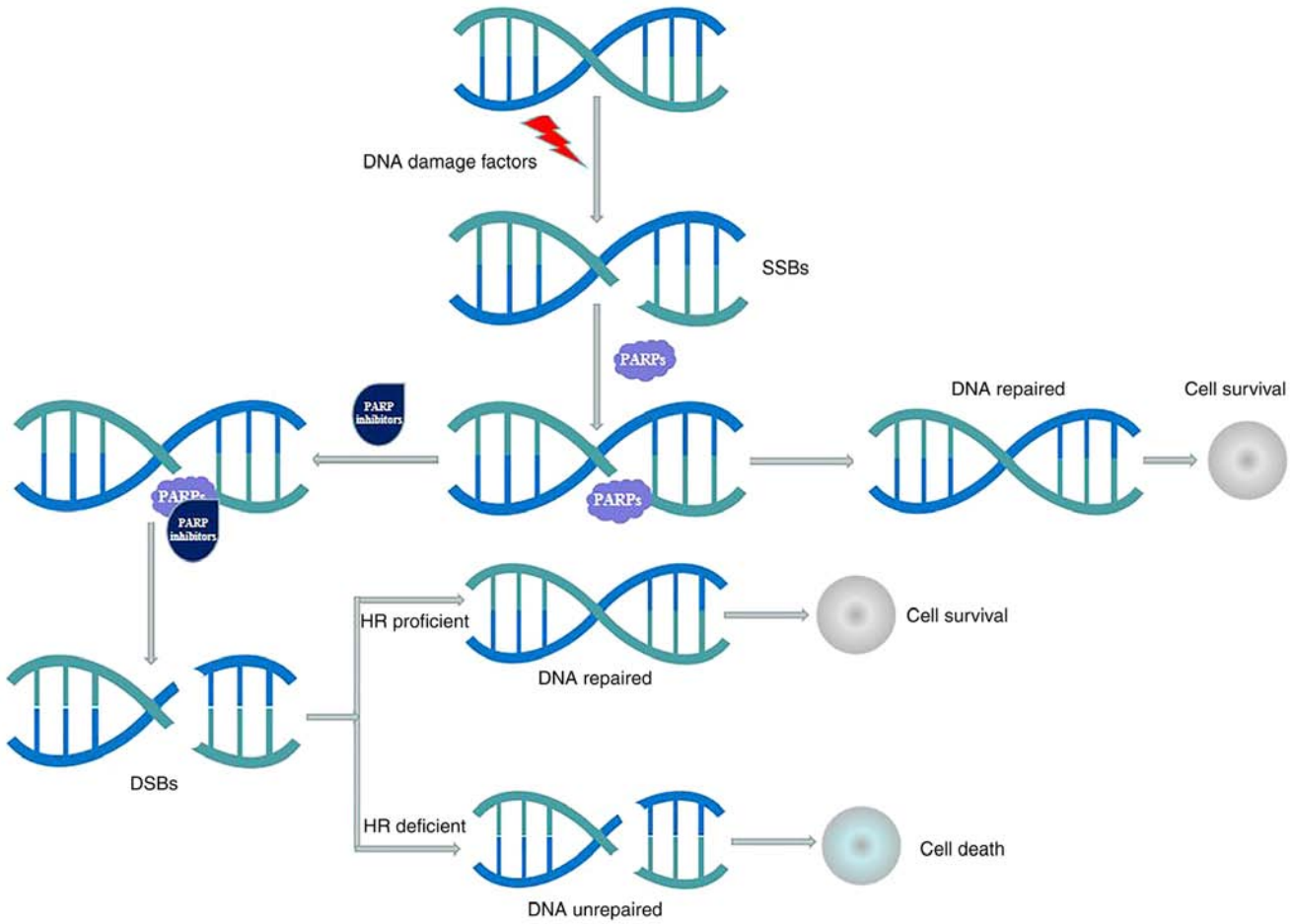

Figure 1. Mechanisms of action of PARP inhibitors. SSBs occur frequently in proliferating cells, and SSBs are repaired mostly by the PARP-dependent base excision repair pathway. PARP inhibitors may bind to the nicotinamide adenine dinucleotide binding pocket of PARP-1, producing conformational changes that stabilize the binding of PARP-1 and DNA. This process results in PARP-1 dysfunction, leading to the accumulation of unrepaired SSBs; ultimately, the unrepaired SSBs could be converted to DSBs. HR proficient cells are able to repair the DSBs and restart replication, while HR deficient cells are unable to repair the accumulating DSBs, which may induce cell death. PARP, poly (ADP-ribose) polymerase; SSB, single-strand DNA break; DSB, double-strand DNA break; HR, homologous recombination.

that inhibit or induce metabolic enzymes, may mediate DDIs, leading to an increase or decrease in the serum area under the curve (AUC) of the enzyme substrate (32). Increased or decreased exposure by alteration of metabolic enzyme activity may cause clinically relevant toxic effects or ineffectiveness of treatment with PARP inhibitors. In addition, as certain PARP inhibitors could inhibit or induce metabolic enzymes, they could also influence the exposure of other metabolic substrates (11,15). The DDIs between PARP inhibitors and enzyme inhibitors and inducers are listed in Table II. The DDIs between PARP inhibitors and other enzyme substrates are listed in Table III.

Olaparib. Olaparib is primarily metabolized by CYP3A (11,12). It was previously shown that following administration of a single radiolabeled dose, unmetabolized olaparib was the major circulating component (70%) in plasma (11), and accounted for 15 and 6% of radioactivity in urine and feces, respectively (11,12). Most of its metabolism is attributable to oxidation reactions, and subsequently, a number of metabolites that are produced go under glucuronide or sulfate conjugation (11,12).

The co-administration of olaparib with itraconazole was noted to increase the AUC and C_{max} of olaparib by 170 and 42%, respectively (7). Similarly, fluconazole, a moderate CYP3A inhibitor, was predicted to increase the AUC and C_{max} of olaparib by 121 and 14%, respectively (11). As such, the concurrent use of strong and moderate CYP3A inhibitors should be avoided. If a CYP3A inhibitor must be co-administered, the olaparib dose should be reduced to 150 mg (capsule) or 100 mg (tablet) administered twice daily for a strong CYP3A inhibitor, or to 200 mg (capsule) or 150 mg (tablet) received twice daily for a moderate CYP3A inhibitor (7,11,12). In addition, grapefruit, grapefruit juice and seville orange juice should be avoided during olaparib treatment, since they are CYP3A inhibitors (11,12).

When co-administered with rifampicin, the AUC and C_{max} of olaparib were noted to decrease by 87 and 71%, respectively (7). Efavirenz, a moderate CYP3A inducer, was predicted to decrease the AUC and C_{max} of olaparib by ~60 and 31%, respectively (11). Thus, the concurrent use of strong or moderate CYP3A inducers should also be avoided. If use of a moderate CYP3A inducer cannot be avoided, there exists a potential for decreased efficacy of olaparib (7,11,12).

Table I. PK parameters for poly (ADP-ribose) polymerase inhibitors.

PK	Recommended dose	T_{max}, h	Bioavailability, %	Volume of distribution, liters	Plasma protein binding, %	Metabolism enzymes	$T_{1/2}$, h	Clearance, l/h	Excretion	
									Urine, %	Feces, %
Olaparib (tablet)	300 mg twice daily	1.5	NA	158±136	82	CYP3A4, CYP3A5, UGTs, SULTs,	14.9±8.2	7.4±3.9	44	42
Olaparib (capsules)	400 mg twice daily	1-3	NA	167±196	82	CYP3A4, CYP3A5, UGTs, SULTs	11.9±4.8	8.6±7.1	44	42
Niraparib	300 mg once daily	3	73	1220±1114	83	CEs (major), CYP1A2, CYP3A4, UGTs	36	16.2	47.5	38.8
Rucaparib	600 mg twice daily	1.9	36	113-262	70	CYP2D6 (major), CYP1A2, CYP3A4, UGTs, SULTs	17-19	15.3-79.2	17.4	71.9
Talazoparib	1 mg once daily	1-2	40	420	74	Minimal hepatic metabolism (<10%)	90±58	6.45	68.7	19.7
Veliparib	400 mg twice daily	0.5-1.5	73	173	51	CYP2D6 (major), CYP1A2, CYP2C19, CYP3A4, UGTs	5.2	20.9	79.4	5

PK, pharmacokinetic; CYP, cytochrome P450; UGTs, uridine diphosphate glucuronosyl transferases; SULTs, sulfotransferases; CEs, carboxylesterases.

In an *in vitro* study, olaparib acted as both an inhibitor and inducer of CYP3A, an inhibitor of UGT1A1 and an inducer of CYP2B6 (33). Physiologically based PK (PBPK) modeling predicted that olaparib could increase the AUC of midazolam (a CYP3A substrate) by 61% and the C_{max} by 18%, and increase the AUC of raltegravir (a UGT1A1 substrate) by 7% and the C_{max} by 4% (34). As a result, caution should be taken when sensitive CYP3A substrates or agents with a narrow therapeutic index are combined with olaparib, but restricting the simultaneous use of olaparib and UGT1A1 substrate is not recommended (11,12,34).

Niraparib. Niraparib is primarily metabolized by CEs to form a major inactive metabolite (M1) that is subsequently metabolized by UGTs into minor inactive metabolites (M10) (13,14,35). The minor pathway of the oxidative metabolism of niraparib is primarily metabolized by CYP1A2 and CYP3A4, with minor contributions from CYP2D6 (13,14). In a PK study, M1 and M10, the subsequently formed M1 glucuronides, were the major circulating components (36). The influence of CEs or UGT polymorphisms on niraparib PK was not evaluated, and co-administration of CYP enzyme inhibitors or inducers is not expected to cause clinically significant DDIs (13,14).

Neither niraparib nor M1 inhibits CYP or UGT isoforms, although niraparib is a weak CYP1A2 inducer at high concentrations (13,14,35). Therefore, the clinical relevance of a DDI could not be completely ruled out, and caution should be used when niraparib is combined with CYP1A2-sensitive substrates, particularly those having a narrow therapeutic range (14).

Rucaparib. *In vitro*, rucaparib is primarily metabolized by CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4, although with a low metabolic turnover rate; subsequently, the metabolites undergo sulfation and glucuronidation (15,16). It was reported that following administration of a single radiolabeled dose of rucaparib, unmetabolized rucaparib was the major component and accounted for 64% of the radioactivity in plasma (37). The major metabolic pathways for rucaparib are oxidation, N-demethylation, N-methylation and glucuronidation (15).

In a population PK study, the steady-state concentrations of rucaparib did not differ significantly across CYP2D6 or CYP1A2 genotype subgroups (15,16,38). Concurrent use of a strong CYP1A2 or CYP2D6 inhibitor did not show significant impact on rucaparib PK. As such, concurrent administration of CYP inhibitors or inducers with rucaparib is not restricted (15,16). *In vitro*, rucaparib has been revealed to be a moderate inhibitor of CYP1A2, and a weak inhibitor of CYP2C9, CYP2C19, CYP3A, CYP2C8, CYP2D6 and UGT1A1 (8,15). Rucaparib has been shown to induce CYP1A2 and downregulate CYP2B6 and CYP3A4 at clinically relevant concentrations (15,16,39).

In a DDI study in patients with cancer, the effects of a steady dose of rucaparib at 600 mg twice daily on caffeine (a CYP1A2 substrate), S-warfarin (a CYP2C9 substrate), omeprazole (a CYP2C19 substrate) and midazolam (a CYP3A substrate) were evaluated (8). Rucaparib exhibited no effect on the C_{max} of caffeine, although it moderately increased the AUC by 1.55% (8). Rucaparib increased the AUC of S-warfarin by

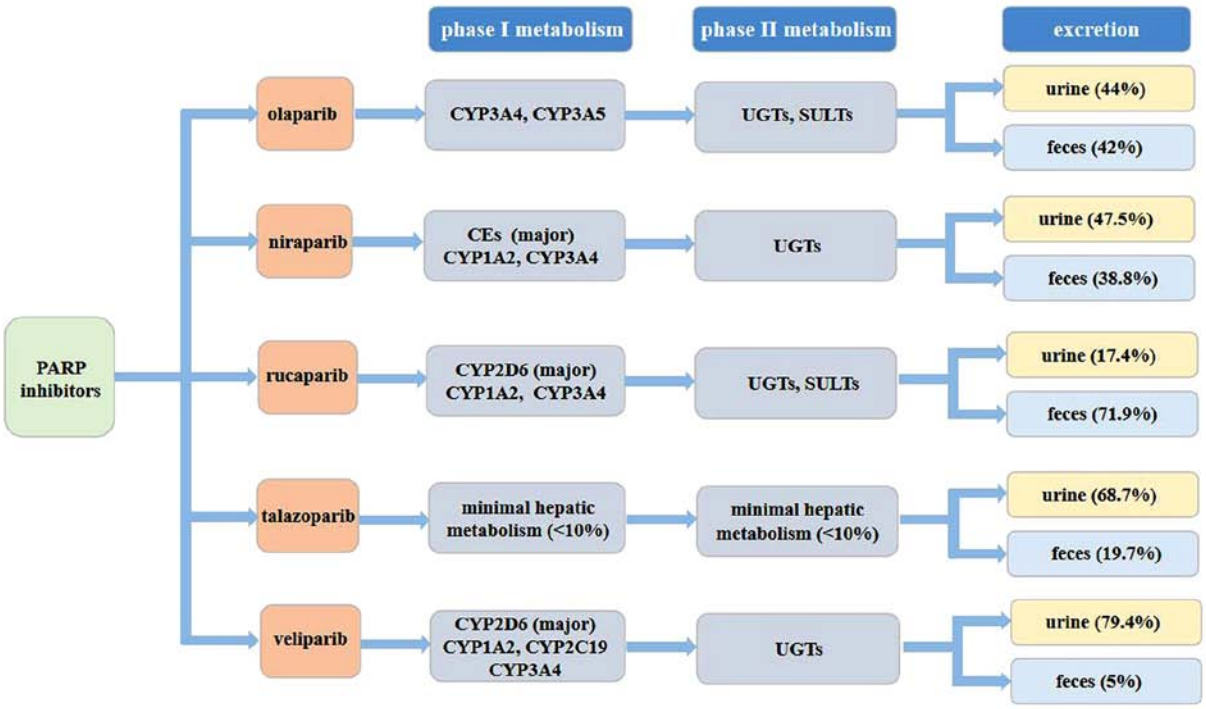

Figure 2. Metabolic pathways related to PARP inhibitors. Olaparib, rucaparib and veliparib are primarily metabolized by the CYP enzymatic pathway, and subsequently, the metabolites that are produced go under glucuronide or sulfate conjugation. Talazoparib undergoes minimal hepatic metabolism, and niraparib is metabolized primarily by carboxylesterases to form a major inactive metabolite, and subsequently undergoes glucuronidation. Talazoparib and veliparib are excreted primarily in the urine, whereas rucaparib is excreted primarily in the feces. For olaparib and niraparib, the average percent recovery of the administered dose presents no difference in urine and feces. PARP, poly (ADP-ribose) polymerase; UGTs, uridine diphosphate glucuronosyl transferases; SULT, sulfotransferases; CYP, cytochrome P450.

0.49% and the C_{max} by 0.05%, increased the AUC of omeprazole by 0.55% and the C_{max} by 0.09%, and increased the AUC of midazolam by 0.38% and the C_{max} by 0.13% (8). According to the study, co-administration of rucaparib could increase the systemic exposure of CYP1A2, CYP3A, CYP2C9 or CYP2C19 substrates, which may increase the risk of toxicities of these drugs (8). Hence, patients should be appropriately monitored, and dose adjustments should be considered for CYP1A2, CYP3A, CYP2C9 and CYP2C19 substrates, particularly for those with a narrow therapeutic index, if clinically indicated (8,15,16).

DDI studies to evaluate the effect of rucaparib on the PK of UGT1A1 substrates have not been established, but a statement is included in the summary of the product characteristics (SmPC) to indicate that special caution should be paid when rucaparib is combined with UGT1A1 substrates (i.e. irinotecan) in patients with cancer and UGT1A1*28 (15,16).

Talazoparib. Talazoparib undergoes minimal hepatic metabolism (<10%) (17,18). The identified metabolic pathways instead include mono-oxidation, dehydrogenation, cysteine conjugation of mono-desfluoro-talazoparib and glucuronide conjugation (17,18,40). Following oral administration of a single radiolabeled dose, no major circulating metabolites were identified in plasma, and talazoparib was the only circulating drug-derived entity identified (17). Therefore, inhibition or induction of metabolism is unlikely to affect the talazoparib exposure (17,18).

In vitro, talazoparib has not been revealed to be an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5, or an inducer of CYP1A2, CYP2B6 or CYP3A4 at clinically relevant concentrations (17,18). Furthermore, talazoparib is not an inhibitor of UGT isoforms (UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7 and UGT2B15) (17). As such, clinically significant DDIs are unlikely to occur when talazoparib is combined with other CYP or UGT substrates (17,18).

Veliparib. Based on a PK study conducted in patients with cancer, veliparib is metabolized by multiple CYP enzymes, including CYP1A2, CYP2D6, CYP2C19 and CYP3A4, with CYP2D6 playing a key role in the formation of M8, the primary active metabolite in humans (19). It was reported that 79.4% of the veliparib dose was excreted in the urine as the unmetabolized drug, indicating that metabolism contributes to at most 30% of total clearance (19,21). Veliparib is metabolized by multiple pathways, including oxidation catalyzed by CYP enzymes and UGT-mediated N-carbamoyl glucuronidation (21,41). The contribution of CYP enzymes to total veliparib clearance remains unclear, but may not be significant. Based on these findings, CYP enzyme polymorphisms or co-administration of veliparib with CYP enzymes inhibitors or inducers likely would not cause any clinically relevant metabolism-related DDIs (19,21,41).

Veliparib has not been demonstrated to inhibit activities of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP2B6, CYP2C8 and CYP3A4, or to induce the activities of CYP1A2, CYP2B6, CYP2C9 and CYP3A4 at clinically relevant concentrations (21). Therefore, veliparib is not likely to cause any clinically relevant CYP enzyme-related DDIs (21).

Table II. DDIs between poly (ADP-ribose) polymerase inhibitors and enzyme inhibitors and inducers.

Drugs	Inhibitors	Inducers	AUCR	$C_{max}R$	Recommendations	(Refs.)
Olaparib	Itraconazole		2.70	1.42	Avoid co-administration with strong and moderate CYP3A inhibitors and consider alternative medicines with less CYP3A inhibition. If co-administration is unavoidable, reduce the olaparib dose to 150 mg (capsule) or 100 mg (tablet) received twice daily for a strong CYP3A inhibitor, and 200 mg (capsule) or 150 mg (tablet) received twice daily for a moderate CYP3A inhibitor.	(7,11,12,33)
	Fluconazole		2.21	1.14		
		Rifampin	0.13	0.29	Co-administration with strong and moderate CYP3A inducers should be avoided.	
		Efavirenz	0.40	0.69	If a moderate CYP3A inducer cannot be avoided, pay attention to the potential decreased efficacy.	
Niraparib	NA	NA	NA	NA	Co-administration of CYP enzyme inhibitors or inducers would not cause clinically significant DDIs.	(13,14)
Rucaparib	CYP1A2 inhibitor		1.16	1.16	Concomitant administration of CYP inhibitors or inducers with rucaparib is not restricted.	(15,16,37)
	CYP2D6 inhibitor		1.00	1.01		
Talazoparib	NA	NA	NA	NA	Co-administration of enzyme inhibitors or inducers would not cause clinically significant DDIs.	(17,18)
Veliparib	NA	NA	NA	NA	Co-administration of CYP2D6 inhibitors or inducers would not cause clinically significant DDIs.	(19,21,41)

DDIs, drug-drug interactions; CYP, cytochrome P450; AUCR, ratio of the AUC; $C_{max}R$, ratio of the C_{max}; NA, not applicable/not available.

Table III. DDIs between poly (ADP-ribose) polymerase inhibitors and other enzyme substrates.

Drugs	Metabolic substrates	AUCR	C_{max}R	Recommendations	(Refs.)
Olaparib	Midazolam	1.61	1.18	Caution should be used when olaparib is combined with sensitive CYP3A substrates or agents with a narrow therapeutic index	(33,34)
	Raltegravir	1.07	1.04	Restricting the concomitant use of olaparib with UGT1A1 substrates is not recommended.	
Niraparib	NA	NA	NA	Caution should be used when niraparib is combined with CYP1A2 substrates with a narrow therapeutic index.	(13,14)
Rucaparib	Caffeine	2.55	1.00	Dose adjustments should be considered for CYP1A2, CYP3A, CYP2C9 and CYP2C19 substrates, particularly for those with a narrow therapeutic index.	(8,15,16)
	S-warfarin	1.49	1.05		
	Omeprazole	1.55	1.09		
	Midazolam	1.38	1.13		
Talazoparib	NA	NA	NA	Clinically significant DDIs appear unlikely to occur between talazoparib and other CYP or UGT substrates.	(17,18)
Veliparib	NA	NA	NA	Veliparib is not likely to cause any clinically relevant metabolism-related DDIs.	(19,21)

DDIs, drug-drug interactions; CYP, cytochrome P450; UGTs, uridine diphosphate glucuronosyl transferases; AUCR, ratio of the AUC; C_{max}R, ratio of the C_{max}; NA, not applicable/not available.

5. Conclusions

PK-based DDIs occur when one agent influences the absorption, distribution, metabolism or excretion of another agent. Altered metabolism is among the most complex of these processes (42). Of the five aforementioned PARP inhibitors, olaparib is primarily metabolized by CYP3A (11), rucaparib has a low metabolic turnover rate and is metabolized primarily by CYP2D6, and to a lesser extent by CYP1A2 and CYP3A4 (15), and talazoparib undergoes minimal hepatic metabolism (17). Veliparib is metabolized by multiple metabolic enzymes, with CYP2D6 as the major enzyme and nearly 13% of veliparib undergoing hepatic metabolism by the activity of CYP2D6 (19). Niraparib is primarily metabolized by CEs, with subsequent metabolism by UGT into inactive metabolites (13). As the metabolism of these five PARP inhibitors involves CYP enzymes to varying degrees, each has a unique set of DDIs. For example, for olaparib, the concurrent use with strong or moderate CYP3A inhibitors and inducers should be avoided, or if unavoidable, the dose of olaparib must be adjusted (7,11,12,33). Conversely, the co-administration of CYP inhibitors or inducers with niraparib, rucaparib, talazoparib or veliparib would likely not cause clinically significant DDIs (13-19,27,37,41). In addition, PARP inhibitors themselves may cause the inhibition or induction of CYP enzymes. With the use of olaparib, niraparib or rucaparib, caution should be exercised when used with sensitive CYP substrates, particularly those with a narrow therapeutic margin (11-16,33,34). As talazoparib and veliparib are neither inhibitors nor inducers of CYP enzymes at clinically relevant concentrations, clinically significant DDIs appear unlikely to occur in combination with other CYP substrates (17-19,21).

CYP enzymes are primarily localized in the liver and small intestines, and as such they could make a major contribution to the first-pass elimination of substrate drugs after oral administration (43). There are both similarities and differences between the hepatic and intestinal CYP enzymes (44). For example, while the drug rifampin could induce both hepatic and intestinal CYP3A, grapefruit juice appears to be selective for intestinal CYP3A (45). For certain orally administered drugs, intestinal metabolism could eliminate a large proportion of the drugs before they are able to enter the systemic circulation. Orally administered drugs that are intestinal CYP substrates not only suffer from low oral bioavailability, but they are also more likely to be susceptible to DDIs with other CYP substrates, inhibitors or inducers. However, the hepatic CYP metabolism, intestinal CYP metabolism and transporters are both involved in the first-pass elimination; thus, distinguishing the intestinal CYP metabolism related DDIs from the others could be difficult, and clinical studies regarding DDIs mediated by intestinal CYP enzymes are at present lacking.

In the liver, drugs are metabolized by phase I and II drug metabolizing enzymes. Given the predominant role of CYP enzymes in the metabolism of drugs, the majority of studies investigating drugs as either culprits or casualties of DDIs arising from enzyme inhibition or induction have focused on CYP inhibitors, inducers or substrates (33,38,43,44). However, for certain drugs, phase II metabolism through UGTs or SULTs is dominant in their metabolism, and may

also be implicated in DDIs, in particular glucuronidation (46). UGT enzymes catalyze the conjugation of various endogenous (e.g., bilirubin) and exogenous (e.g., drugs) compounds, thereby inhibition or induction of UGT enzymes may significantly alter the elimination of UGT substrates and lead to clinically significant DDIs (47,48). While UGT enzymes are involved in the phase II metabolism of the five aforementioned PARP inhibitors (11-19), the effect of UGT inhibitors and inducers on the PK of PARP inhibitors has not been established.

For screening of new drugs for the inhibition of UGT enzymes, the Food and Drug Administration and European Medicines Agency DDI guidelines recommend study of the inhibition of UGT enzymes known to be involved in DDIs, including UGT1A1 and UGT2B7, if one of the major elimination pathways of the investigational drug is direct glucuronidation (49,50). Previous studies have demonstrated that human liver microsomes and recombinant proteins as the enzyme sources, together with *in vitro-in vivo* extrapolation approaches, could predict the likelihood of interactions arising from UGT enzyme inhibition *in vivo* (51-53). Based on *in vitro* data, olaparib is an inhibitor of UGT1A1 and rucaparib is a weak inhibitor of UGT1A1, whereas neither niraparib nor talazoparib are inhibitors of UGT isoforms (11-18). Clinical studies regarding the effects of PARP inhibitors on the PK of UGT substrates have not yet been established, but PBPK modeling predicts that olaparib may increase the AUC of raltegravir (a UGT1A1 substrate) by 7% and the C_{max} by 4%, which is not considered to be clinically meaningful (11,12,33). In addition, a statement is included in the SmPC to reflect that special caution should be paid when rucaparib is co-administered with UGT1A1 substrates (15,16). As niraparib and talazoparib are not inhibitors of UGT isoforms, clinically significant DDIs appear unlikely to occur when niraparib and talazoparib are combined with other UGT substrates.

The clinical significance of DDIs depends on several factors including the PK/PD relationship, the genetic polymorphisms, the therapeutic index of the victim drug, the potency and concentration of the inhibitor or inducer, the bioavailability of the victim drug, whether the victim drug is a prodrug or an active drug, and the effects of disease on PK and PD parameters (10). An interaction should be considered clinically significant if it leads to unfavorable outcomes such as reduced treatment efficacy or increased adverse drug reactions (ADRs). However, few DDI studies are conducted in patient populations to evaluate therapeutic outcomes, nor are they long enough to completely assess the development of ADRs.

PK-based DDI studies often use a no effect boundary of 80-125% to determine whether an interaction is clinically significant. With this approach, if the AUC is contained completely between 80 and 125%, the interaction is considered not clinically significant. However, this default no effect boundary may occasionally be inappropriate, particularly for medications with a narrower therapeutic index (10). For example, for certain medications, a 20% increase in AUC may lead to severe side effects. Thus, the no effect boundary should be individualized for a given drug whenever possible with the exposure-response data.

In order to detect patients at risk from harmful DDIs, any potential DDIs must be identified. Several methods are available for reducing the risk of clinically significant interactions, such as PBPK models and population PK studies (33,54,55). Furthermore, to make DDI information more accessible, several DDI screening software programs and databases have been developed and are being implemented as clinical decision support tools (56,57). However, understanding DDIs remains an ongoing challenge and significant gaps in our knowledge remain. In addition, numerous studies have concentrated on representative DDIs between two medicines, but it is quite common for patients to be receiving more than two medicines at one time. As such, the DDIs could be very complex and exceedingly difficult to predict. Thus, therapeutic drug monitoring (TDM) may be a favorable option in managing DDIs (58,59). For numerous drugs there is a clear relationship between plasma concentrations, ADRs and treatment efficacy, and dose adjustments could be made if plasma concentrations are outside of the therapeutic range (60). Furthermore, TDM has the advantage of monitoring drug treatment continuously over long periods of time, which may bring about improved treatment outcomes (61). Further research is required to confirm the clinical relevance of TDM as a tool in DDI management.

Ultimately, in order to achieve the improved management of DDIs, clinicians and clinical pharmacists should be consulted to perform a complete assessment of the DDI risk for a given patient, to give recommendations to reduce these risks and to arrange subsequent patient monitoring measures.

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Authors' contributions

DZ and JW designed the study. DZ and XL performed the literature search. DZ drafted and revised the manuscript. All the authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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