Transporter-mediated drug-drug interactions involving poly (ADP-ribose) polymerase inhibitors (Review)

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Abstract. Poly (ADP ribose) polymerase (PARP) inhibitors are novel targeted anticancer agents that have been widely used in patients with cancer, particularly in patients with breast-related cancer antigen 1/2 mutations. PARP inhibitors are administered orally and have been associated with improved efficacy and toxicity profiles when compared to conventional chemotherapy agents; this improvement is convenient and results in good compliance among patients with cancer. However, as PARP inhibitors are administered long-term and frequently concomitantly with other therapeutic agents, the risk of drug-drug interactions (DDIs) is increasing. Transporters are widely expressed in numerous types of tissue, where they have crucial roles in the membrane transport of several drugs. An alteration in the activity and expression of transporters may change the drug pharmacokinetics (PKs) and cause DDIs. As the five PARP inhibitors (olaparib, niraparib, rucaparib, talazoparib and veliparib) are transporter substrates, inhibitors or inducers, the potential transporter-mediated DDIs with the use of PARP inhibitors should be taken into consideration when co-administered with other agents. The present review focused on recent findings on transporter-mediated DDIs with PARP inhibitors to provide specific recommendations for reducing the occurrence of undesired DDIs.

Contents

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1. Introduction

To date, the relationship between breast-related cancer antigen (BRCA1/2) and poly (ADP ribose) polymerase (PARP) enzymes has been well studied (1). Based on the genetic concept of synthetic lethality, several PARP inhibitors have been developed and approved for various clinical indications (1,2). PARP inhibitors are small-molecule targeted drugs that trap the PARP enzymes in DNA damage sites and prevent DNA repair, resulting in the accumulation of double-strand DNA breaks (DSBs) during the S phase of the cell cycle (3). Homologous recombination (HR)-proficient tumor cells are able to repair DSBs and restart (3), whereas HR-deficient tumor cells (i.e., those with BRCA mutation) that lost a functional HR pathway rely primarily on the nonhomologous end joining pathway to repair DSBs, resulting in the accumulation of genome instability and cell death (3). Olaparib, niraparib, rucaparib and talazoparib are currently approved for clinical use and veliparib is still under clinical investigation (2,4). PARP inhibitors are widely used in the treatment of numerous types of solid tumor, particularly in patients with BRCA1/2 mutations (2-4). PARP inhibitors are administered orally, which has the advantages of improved flexibility and convenience for the patients, but it may be affected by numerous factors, such as transporters (5).

Transporters are able to transport a wide range of endogenous and exogenous substrates and have an important role in their disposition (5). Transporters are generally divided into the solute carrier (SLC) family and the ATP-binding cassette (ABC) family. The SLC transporters are mainly involved in the uptake of small molecules into cells, whereas the ABC transporters harness energy from ATP hydrolysis and primarily function as efflux transporters. The SLC transporters mainly include organic anion transporters (OATs), organic anion-transporting polypeptides (OATPs), organic cation transporter (OCTs), organic cation and carnitine transporters (OCTNs) and peptide transporters (PEPTs) (6). Most SLC transporters are influx transporters and mediate the uptake of substrates into cells. The ABC transporters are classified into seven subfamilies designated ABCA to ABCG

based on their gene structure, amino acid sequence, domain organization and phylogenetic analysis (7). Among the ABC transporters, P-glycoprotein (P-gp), multi-drug resistance proteins (MRPs) and breast cancer resistance protein (BCRP) are the most extensively studied (7). Most ABC transporters are efflux transporters and export substrates out of cells using ATP as driving energy. Transporters are located throughout the body and they are involved in drug absorption, distribution, metabolism and excretion (8). An alteration in the activity and expression of a transporter may significantly change the PK profile of a drug and cause clinically relevant drug-drug interactions (DDIs) (9).

The five PARP inhibitors are the substrate of transporters and some of them are also transporter inhibitors (2-4). Therefore, it is essential to know the relationship between PARP inhibitors and transporter inhibitors, inducers or substrates. The purpose of the present review was to characterize and summarize the transporter-mediated DDIs for each PARP inhibitor. In addition, practical recommendations for managing DDIs involving PARP inhibitors were provided.

2. Expression and function of SLC transporters

The SLC transporters mainly include OATs, OATPs, OCTs, OCTNs, PEPTs and multi-drug and toxin extrusion proteins (MATEs). These transporters mediate the influx and efflux of various substrates across cellular membranes (6). The OATPs consist of 11 members grouped into 6 subfamilies. The OATPs transport large and fairly hydrophobic organic anions (10). Among the 11 OATPs, OATP1A2, OATP1B1, OATP1B3 and OATP2B1 have been identified as being critical for drug disposition (11,12). OATP1A2 and OATP2B1 are highly expressed in the intestinal epithelium, renal epithelium, retina, brain capillary endothelial cells, hepatocytes and red blood cells, where they have critical roles in the intestinal absorption, renal reabsorption and secretion, brain distribution and hepatic absorption (13). OATP1B1 and OATP1B3 are highly expressed in hepatocytes, where they are responsible for the hepatic uptake of substrates, such as conjugated bilirubin (13). In addition to their expression in normal tissues, several studies have indicated that certain OATPs are highly expressed in certain cancer cells.

The OCTs mainly include OCT1, OCT2 and OCT3, and they transport organic cations into cells (14). OCT1 is mainly expressed in the liver and at lower levels in certain other tissues; it is considered to be a liver-specific transporter, along with OATP1B1 and OATP1B3, having important roles in the uptake of substrates by hepatocytes (15). OCT2 is primarily expressed in the proximal kidney tubule cells and is generally considered to be a renal uptake transporter; it mediates the uptake of substrates into the kidneys and the excretion of substrates into urine (16). OCT3 is widely expressed in tissues, with moderate to high expression in the intestines, kidneys and liver; it is associated with intestinal absorption and hepatic and renal uptake (16).

There are two OCTN isomers in humans, namely OCTN1 and OCTN2 (17). OCTN1 is highly expressed in the kidneys and, to a lesser extent, in other tissues (17). OCTN2 is expressed in numerous tissues, such as the liver, kidneys, intestines, skeletal muscles, heart and placenta (17). OCTN1 and OCTN2 are involved in the intestinal absorption of carnitine and organic cations and their distribution to tissues (17).

The PEPTs mainly include PEPT1 and PEPT2; they are responsible for the uptake of peptides and peptide-like compounds (18). PEPT1 is primarily expressed in the small intestine; it mediates the absorption of substrates into the enterocyte (6,18). However, PEPT2 is primarily expressed in the kidneys and mediates the renal reabsorption of small peptides and peptide-like compounds (6,18).

The OATs mainly include OAT1, OAT2, OAT3 and OAT4; they transport organic anions (19). OAT1, OAT3 and OAT4 are highly expressed in the kidneys, where they are responsible for the uptake of substrates from the blood into the proximal tubule cells and the reabsorption of substrates from the ultrafiltrate (20). OAT2 is highly expressed in the liver and, to a lesser extent, in the kidneys and other tissues; it has a critical role in hepatic organic anion transport (21).

In contrast to other SLC transporters, the MATEs, including MATE1 and MATE2-K, are responsible for the efflux of organic cations (22). MATE1 is highly expressed in the kidneys and bile canaliculi, whereas MATE2-K exhibits a kidney-specific expression. These transporters mediate the export of substrates taken up by OCT1 and OCT2 (23).

3. Expression and function of ABC transporters

The ABC transporters are primary transporters that utilize energy derived from ATP hydrolysis to transport substrates across membranes (24). P-gp is the first described and identified ABC transporter; it is expressed in various tissues, including the intestine, kidneys, liver, brain and placenta (25). P-gp transports substrates from the intracellular to the extracellular space (25). In the intestine, P-gp inhibits the entrance of substrates from the intestinal lumen into the bloodstream, leading to reduced bioavailability of several orally administered drugs (26). In the liver and kidneys, P-gp mediates the transport of agents into bile and urine, respectively (25). In the brain, P-gp is crucial for the blood-brain barrier to limit the entrance of toxins and drugs into the central nervous system, protecting the brain from the toxic effects of exogenous compounds (27).

Similar to P-gp, BCRP is an efflux pump located in numerous tissue types, such as the intestines, liver, kidneys, brain, testis and placenta (28). The bile salt export pump is predominantly expressed in the liver and functions to mediate the efflux of conjugated and unconjugated bile salts into bile (28).

The MRP family consists of nine MRP proteins. MRP2 is highly expressed in the liver, kidneys, small intestine, gall bladder and placenta (29). MRP1 is highly expressed in tumor cells, the lungs, brain, testis, kidneys, skeletal muscles and peripheral blood mononuclear cells, and to a lesser extent in the liver (29). Both MRP1 and MRP2 are associated with the excretion of numerous phase II metabolites and endogenous agents into bile, urine and the intestinal lumen (29,30). MRP3 is mainly expressed in hepatocytes and enterocytes. MRP4 is widely located in most tissues; both MRP3 and MRP4 are involved in the efflux of organic anions (31).

4. Transporter-mediated DDIs involving PARP inhibitors

Transporters have different tissue expression patterns; if they are expressed in the small intestine, liver, kidneys and

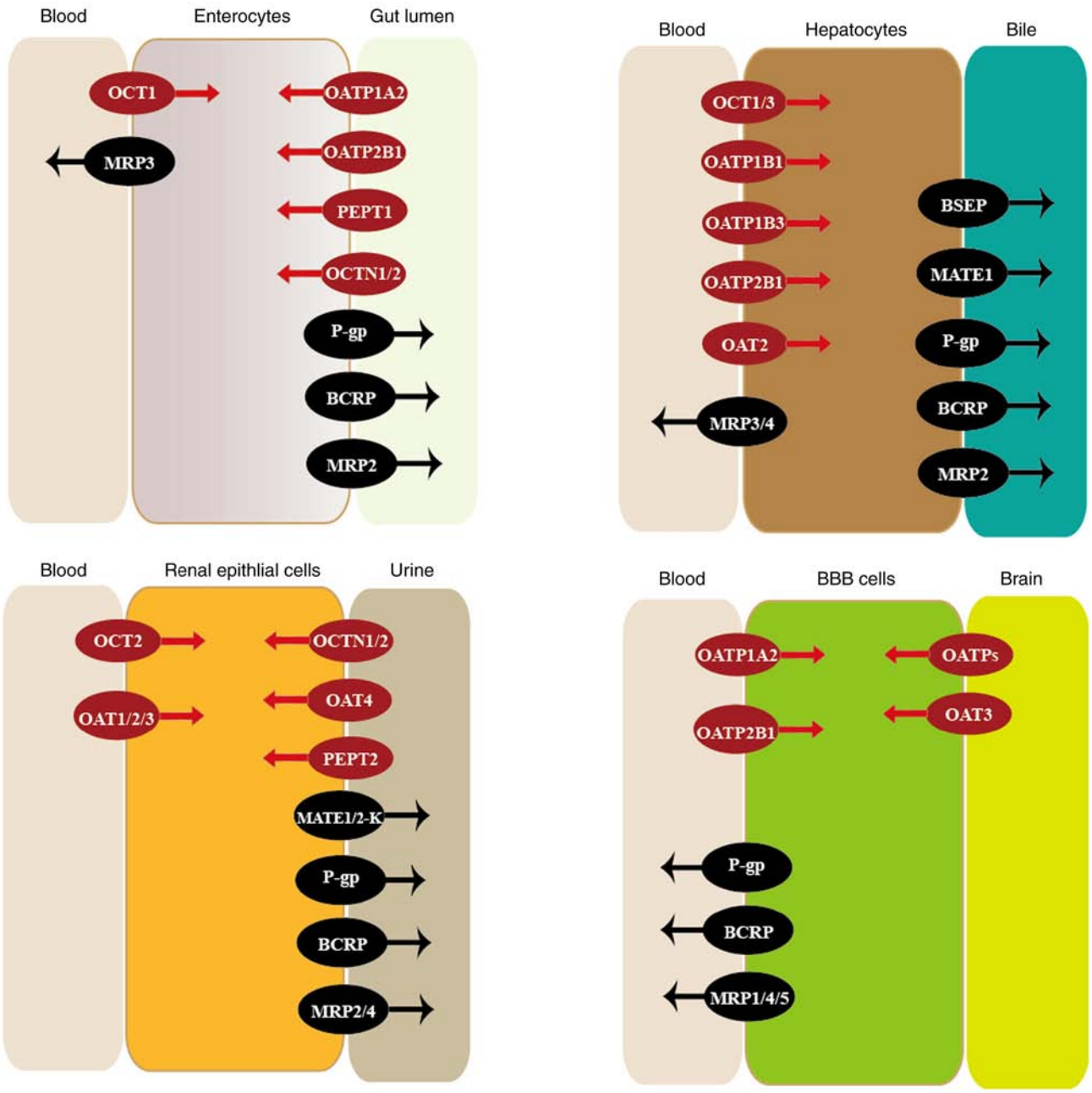

Figure 1. Location and function of transporters. Transporters are widely expressed in numerous tissues, where they have important roles in the membrane transport of various drugs. Influx transporters are colored in red, while efflux transporters are colored in black. BBB, blood-brain barrier; OCTs, organic cation transporters; MRPs, multi-drug resistance proteins; OATPs, organic anion-transporting polypeptides; PEPTs, peptide transporters; OCTNs, organic cation and carnitine transporters; P-gp, P-glycoprotein; BCRP, breast cancer resistance protein; OATs, organic anion transporters; BSEP, bile salt export pump; MATEs, multi-drug and toxin extrusion proteins.

blood-tissue barriers, they significantly affect the drug disposition, leading to clinically significant DDIs (32). The location and function of transporters are illustrated in Fig. 1. Most drugs are the substrates, inducers or inhibitors of transporters; thus, inhibition or induction of transporters may lead to alterations in the intestinal absorption, hepatic uptake, renal reabsorption, and biliary and renal excretion of drugs, causing clinically relevant DDIs, undesired toxicities or reduced therapeutic effects (9,32). The potential DDIs between PARP inhibitors and transporter inhibitors/inducers are listed in Table I. The potential DDIs between PARP inhibitors and transporter substrates are listed in Table II.

Olaparib is a substrate for P-gp and BRCP (33). The effects of P-gp and BRCP inhibitors or inducers on olaparib have not been evaluated in humans. In an *in vivo* study, the brain concentration and brain-to-plasma unbound concentration ratios of olaparib increased 10.7- and 5.3-fold, respectively, in mice treated with a combination of elacridar (a dual inhibitor of P-gp and BRCP) and olaparib relative to those that were not treated with elacridar (34). However, no significant differences in the plasma concentration of olaparib were observed between the two groups. A study revealed that olaparib resistance correlates with increased P-gp expression and the resistance is reversible following combination treatment with verapamil or elacridar (35). Therefore,

Table I. Potential drug-drug interactions between poly (ADP ribose) polymerase inhibitors and transporter inhibitors/inducers.

First author, year	Substrates	Transporters	Recommendations	(Refs.)
Song, 2022; Vaidyanathan, 2016	Olaparib	P-gp, BRCP	Adverse reactions monitoring is required	(34,35)
Martins, 2021; Sun, 2018; Morosi, 2020	Niraparib	P-gp, BCRP	Close monitoring of adverse reactions is needed when niraparib administered concomitantly with P-gp and BCRP inhibitors	(37-39)
Durmus, 2015; Liao, 2020; Chen, 2020	Rucaparib	P-gp, BCRP	Caution must be exercised when rucaparib is co-administered with P-gp and BCRP inhibitors	(42-44)
Elmeliegy, 2020; Yu, 2020; US Food and Drug Administration, 2020; European Medicines Agency, 2021	Talazoparib	P-gp, BCRP	Co-administration with strong P-gp inhibitors should be avoided. If co-administration is unavoidable, the talazoparib dose should be reduced to 0.75 mg once daily. Dose adjustment is not required for talazoparib when co-administered with rifampin. Concomitant use of strong BCRP inhibitors during treatment with talazoparib must be avoided; if co-administration cannot be avoided, the potential increased adverse reactions must be monitored	(51-54)
Lin, 2017	Veliparib	P-gp, BCRP, OCT2, MATE1, MATE2-K	Close clinical surveillance is required when veliparib is combined with P-gp and BCRP inhibitors	(57)

P-gp, P-glycoprotein; BCRP, breast cancer resistance protein; OCT, organic cation transporter; MATE, multi-drug and toxin extrusion protein.

Table II. Potential drug-drug interactions between poly (ADP ribose) polymerase inhibitors and transporter substrates.

First author, year	Inhibitor drugs	Transporters	Recommendations	(Refs.)
McCormick, 2017	Olaparib	P-gp, BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2-K	Caution must be exercised when olaparib is combined with any statins	(36)
US Food and Drug Administration, 2021; European Medicines Agency, 2022	Niraparib	MATE1, MATE2-K, BCRP, OCT1	Caution is recommended when niraparib is combined with active substrates transported by MATE1, MATE2-K, BCRP and OCT1	(40,41)
Liao, 2020; US Food and Drug Administration, 2020; European Medicines Agency, 2022	Rucaparib	P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, MATE1, MATE2-K, OCT1, OCT2, MRP4	Dose adjustment is not required for P-gp and BRCP substrates when they are co-administered with rucaparib. Caution is advised when metformin is co-administered with rucaparib	(43,45,46)
Chang, 2020	Veliparib	OAT1, OAT3, OCT2, MATE1, MATE2-K	Appropriate clinical monitoring is required when veliparib is co-administered with P-gp substrates	(58)

NA, not applicable/not available; P-gp, P-glycoprotein; BCRP, breast cancer resistance protein; OCT, organic cation transporter; OAT, organic anion transporter; OATP, organic anion-transporting polypeptides; MATE2-K, multi-drug and toxin extrusion protein 2-K; MRP, multi-drug resistance protein.

olaparib resistance mayn be overcome by inhibiting P-gp and BRCP (35). However, the combination of olaparib with P-gp and BRCP inhibitors may lead to increased adverse reactions (e.g., anemia, gastrointestinal toxicities, fatigue, nasopharyngitis, arthralgia, myalgia, dysgeusia, headache and stomatitis); thus, adverse reaction monitoring is required.

Olaparib is an inhibitor of P-gp, BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2-K (36). Although it is unknown whether olaparib exhibits any clinically significant DDI when co-administered with substrates of these transporters, it cannot be ruled out (36). In particular, caution should be exercised when olaparib is combined with statins (36).

Niraparib is a substrate for P-gp and BCRP; its major primary metabolite M1 is a substrate for MATE1 and MATE2-K (37). *In vitro* studies have indicated that P-gp and BCRP do not have any significant impact on the bioavailability and liver disposition of niraparib (37). However, P-gp and BCRP may significantly increase the brain distribution of niraparib. In a study conducted in mice, co-administration of elacridar significantly increased the brain concentration of niraparib without significantly altering the plasma concentration (38). Therefore, P-gp and BCRP inhibitors may increase the brain concentration of niraparib, improving the treatment outcome in patients with brain tumors (37-39). However, close monitoring of adverse reactions [e.g., hematotoxicity, palpitations, gastrointestinal toxicities, mucositis, aspartate aminotransferase (AST) alanine aminotransferase (ALT) elevation, urinary tract infection and rash] is required when niraparib is administered concomitantly with P-gp and BCRP inhibitors.

Niraparib is an inhibitor of MATE1 and MATE2-K, as well as a weak inhibitor of BCRP and OCT1 (40,41). Clinically significant DDIs between niraparib and substrates of these transporters are unlikely to occur but cannot be ruled out (40,41). Thus, caution is needed when niraparib is combined with active substrates that are transported by these transporters, including metformin, irinotecan, rosuvastatin, simvastatin, atorvastatin and methotrexate.

Rucaparib is a substrate for P-gp and BCRP (42). An *in vitro* study revealed that P-gp and BCRP markedly reduce the oral bioavailability and brain accumulation of rucaparib (43). Similarly, an *in vitro* study revealed that verapamil reverses rucaparib resistance by inhibiting P-gp (44). Therefore, the effect of P-gp and BCRP inhibitors on the PK profile of rucaparib cannot be ruled out and there must be strict monitoring for toxicities (e.g., gastrointestinal toxicities, fatigue, hematotoxicities, dysgeusia, AST/ALT elevation, stomatitis and rash) when rucaparib is co-administered with P-gp and BCRP inhibitors.

Rucaparib was found to be an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, MATE1, MATE2-K, OCT1, OCT2 and MRP4 (45,46). A phase I study revealed that co-administration of rucaparib and digoxin increased the digoxin area under the curve (AUC) by 20% (47). Another phase I study conducted in patients with advanced solid tumors demonstrated that rucaparib slightly increased the plasma concentration of rosuvastatin (a BRCP substrate) (48). Therefore, dose adjustment is not recommended for P-gp and BRCP substrates when they are co-administered with rucaparib (45,46). As the inhibition of MATE1, MATE2-K, OCT1 and OCT2 may decrease the renal elimination and hepatic uptake of metformin, caution is advised when metformin is co-administered with rucaparib (43,45,46).

Talazoparib is a substrate for P-gp and BCRP (49). An *in vivo* study revealed that overexpression of P-gp decreases the brain accumulation of talazoparib (50). In patients with advanced solid tumors, concomitant administration of itraconazole (a P-gp inhibitor) with talazoparib increased the AUC and maximum concentration (C_{max}) of talazoparib by 56 and 40%, respectively (51). In addition, PK analysis revealed that strong P-gp inhibitors, including amiodarone, carvedilol, clarithromycin, itraconazole and verapamil, increased talazoparib exposure by 45% (52). Therefore, the concomitant use of strong P-gp inhibitors must be avoided. If co-administration is unavoidable, the talazoparib dose must be reduced to 0.75 mg once daily (52-54). Co-administration of P-gp inhibitors, including azithromycin, atorvastatin, diltiazem, felodipine, fluvoxamine and quercetin, increased talazoparib exposure by 8% (52-54). It is recommended to monitor for potential adverse reactions when these P-gp inhibitors are co-administered with talazoparib and dose adjustment is based on tolerability (54). Co-administration of rifampin (a P-gp inducer) with talazoparib increased the talazoparib C_{max} by 37% with no effect on the AUC. These results suggest that dose adjustment for talazoparib is not required when co-administered with rifampin (51,53,54). However, the effect of other P-gp inducers on talazoparib exposure remains elusive (53,54). Thus, caution is advised when rucaparib is co-administered with other P-gp inducers. Co-administration with BCRP inhibitors may increase talazoparib exposure. Therefore, the concomitant use of strong BCRP inhibitors during treatment with talazoparib must be avoided. If co-administration cannot be avoided, the potential adverse reactions must be monitored (54). *In vitro* studies have revealed that talazoparib is not a transporter inhibitor or inducer (53,54).

Veliparib is a substrate for P-gp, BCRP, OCT2, MATE1 and MATE2-K (55). Population PK analysis has revealed that P-gp, MATE1, MATE2-K and OCT2 did not significantly impact the plasma AUC of veliparib (56). A study conducted in mice and cells revealed that P-gp and BCRP did not have any critical role in the systemic clearance of veliparib but an essential role in the brain accumulation of veliparib (57). The results indicated that elacridar slightly increased the plasma AUC of veliparib but significantly increased the brain accumulation of veliparib (57). Therefore, inhibition of P-gp and BCRP may improve the efficacy of veliparib in patients with brain tumors, but close clinical surveillance is required when veliparib is combined with P-gp and BCRP inhibitors (57).

In a DDI study, veliparib inhibited OAT1, OAT3, OCT2, MATE1 and MATE2-K with half-maximal inhibitory concentration (IC_{50}) values of 1,371, 505, 3,913, 69.9 and 69.5 μM, respectively (55). The maximum unbound plasma concentration of veliparib after a single oral dose of 50 mg was lower than the IC_{50} values for these transporters (55). These results indicated that veliparib has a minimal potential for DDIs with these transporters (55). However, in an *in vitro* study, veliparib significantly increased the accumulation of doxorubicin in liver cancer cells with P-gp overexpression by inhibiting the expression of P-gp (58). Therefore, veliparib may reverse P-gp-mediated multidrug resistance (MDR) in liver cancer cells and this may benefit patients with liver cancer, particular those who are not sensitive to chemotherapy due to the overexpression of P-gp (58). However, appropriate clinical monitoring is required when veliparib is co-administered with P-gp substrates.

5. Discussion

Transporters are membrane-bound proteins that mediate the movement of substrates across biological membranes. In addition, these proteins mediate the transport of drug molecules (5). Transporters are located throughout the body, suggesting their crucial roles in drug disposition (5-7). By altering the expression and activity of transporters, a perpetrator agent may change the PK parameters for an affected drug, leading to clinically significant DDIs (9,32). In addition, when two agents are able to be carried by the same transporter, there may be competition for the same transporter site, producing a competitive inhibition and leading to clinically significant DDIs (32).

Transporters have a broad substrate spectrum and facilitate the transport of several drugs. The five PARP inhibitors are substrates for P-gp and BRCP. In a DDI study, P-gp and BRCP inhibitors did not have any significant impact on the systemic exposure of olaparib, niraparib and veliparib, but significantly increased their brain accumulation, indicating that P-gp and BRCP inhibitors may improve treatment outcomes when co-administered with olaparib, niraparib or veliparib in patients with brain tumors (34,37,57). For rucaparib and talazoparib, P-gp and BRCP have critical roles in their systemic exposure and brain accumulation, indicating that dose adjustment or caution is required when rucaparib and talazoparib are co-administered with strong P-gp and BRCP inhibitors or inducers (43,51,52). PARP inhibitors are also transporter inhibitors. *In vitro* and *in vivo* studies have demonstrated that, apart from talazoparib, the other four PARP inhibitors inhibit several transporters (36,40,41,47,48,55). As it cannot be ruled out that the four PARP inhibitors may cause clinically relevant DDIs with certain transporter substrates, it is recommended that close monitoring of adverse reactions is ensured when olaparib, niraparib, rucaparib and veliparib are administered concomitantly with these substrates.

Metabolism- and transporter-mediated DDIs are the most common DDIs that affect the PK profile of a drug (59,60). Metabolic enzymes are primarily localized in the liver and small intestine, whereas transporters are widely distributed throughout the body (5,59). As a result, the effects of transporters on the PK profile of drugs are more complex (5,32). Metabolic enzymes significantly contribute to drug absorption and metabolism, leading to alterations in the systemic exposure of drugs (61). Similarly, transporters have crucial roles in drug absorption, distribution and elimination, leading to alterations in the distribution and systemic exposure of drugs (5). Furthermore, because numerous transporters and metabolic enzymes share common locations, substrates, inhibitors and inducers, they may exert coordinated effects on drug absorption and metabolism (59,62).

Increased expression of ABC drug transporters in cancer cells is one of the mechanisms leading to cancer MDR; these transporters may export drugs from cells, leading to reduced intracellular drug concentrations (63,64). P-gp and BRCP are two of the most extensively studied ABC multidrug transporters; these transporters are highly expressed in numerous solid tumors and have broad substrate specificity. *In vitro* studies have indicated that P-gp and BRCP inhibitors, such as elacridar, partially reverse the resistance to olaparib and rucaparib (35,65,66).

Based on the available studies, the present review comprehensively summarized the expression and function of transporters and the DDIs between transporters and PARP inhibitors. In addition, specific recommendations for managing the potential DDIs were also provided. However, studies on the DDIs between transporters and PARP inhibitors are limited and further clinical studies are needed to evaluate the efficacy and safety of PARP inhibitors when they are combined with transporter inhibitors, inducers or substrates.

6. Conclusion

Transporters have critical roles in drug disposition and DDIs. The five PARP inhibitors are substrates for transporters. Alterations in the activity and expression of these transporters may influence the oral bioavailability, tissue distribution and elimination of PARP inhibitors and consequently cause clinically relevant DDIs. Furthermore, apart from talazoparib, the other four PARP inhibitors may inhibit certain transporters; thus, they may have a significant impact on the PK profile of substrates for transporters. In summary, PARP inhibitors may exhibit transporter-mediated DDIs and various DDIs may lead to reduced efficacy and increased toxicity. However, certain DDIs may contribute to increasing the tissue distribution and intracellular concentrations of certain drugs, which may enhance the drug efficacy and overcome MDR.

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Authors' contributions

DZ and XL conceived the study and performed the literature search. DZ drafted the manuscript. DZ and JW revised the manuscript. All 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

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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