

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

DEHUA ZHAO, XIAOQING LONG and JISHENG WANG

Department of Clinical Pharmacy, The Third Hospital of Mianyang (Sichuan Mental Health Center),
Mianyang, Sichuan 621000, P.R. China

Received October 4, 2022; Accepted February 21, 2023

DOI: 10.3892/ol.2023.13747

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

1. Introduction
2. Expression and function of SLC transporters
3. Expression and function of ABC transporters
4. Transporter-mediated DDIs involving PARP inhibitors

5. Discussion
6. Conclusion

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

Correspondence to: Professor Dehua Zhao, Department of Clinical Pharmacy, The Third Hospital of Mianyang (Sichuan Mental Health Center), 190 Jiannan Dong Street, Mianyang, Sichuan 621000, P.R. China
Email: zhaoyaoshi0566@163.com

Key words: PARP inhibitors, breast-related cancer antigen, drug-drug interactions, transporters, pharmacokinetics

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

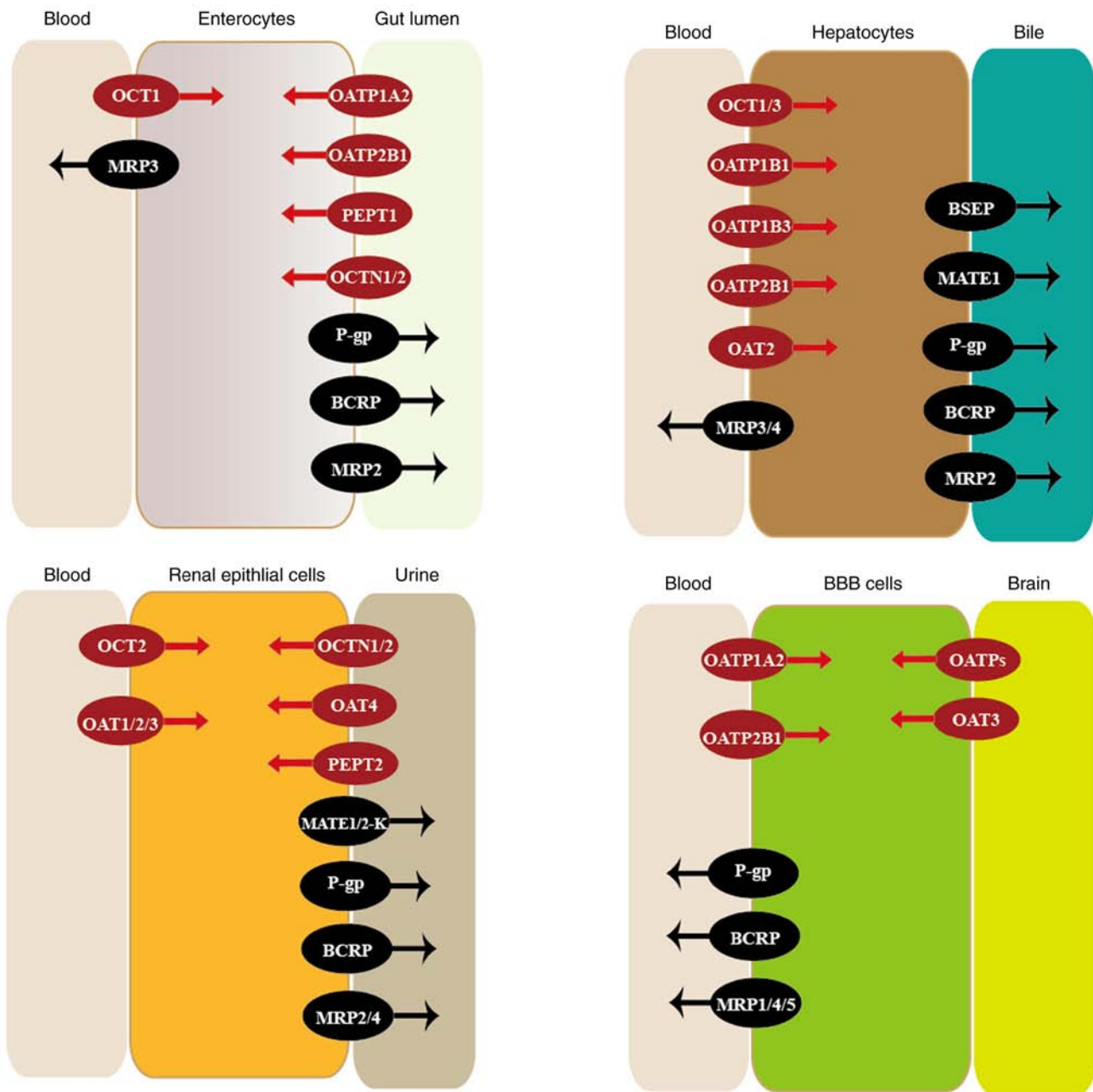


Figure 1. Location and function of transporters. Transporters are widely expressed in numerous tissues, where they have important roles in the membrane transport of various drugs. Influx transporters are colored in red, while efflux transporters are colored in black. BBB, blood-brain barrier; OCTs, organic 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 BCRP (33). The effects of P-gp and BCRP 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 BCRP) 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, BCRP	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 BCRP 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 may be overcome by inhibiting P-gp and BCRP (35). However, the combination of olaparib with P-gp and BCRP 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 BCRP substrate) (48). Therefore, dose adjustment is not recommended for P-gp and BCRP 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 μ M, 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 BCRP. In a DDI study, P-gp and BCRP 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 BCRP 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 BCRP 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 BCRP 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 BCRP 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 BCRP 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.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

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.

References

- Mittica G, Ghisoni E, Giannone G, Genta S, Aglietta M, Sapino A and Valabrega G: PARP inhibitors in ovarian cancer. *Recent Pat Anticancer Drug Discov* 13: 392-410, 2018.
- Tew WP, Lacchetti C, Ellis A, Maxian K, Banerjee S, Bookman M, Jones MB, Lee JM, Lheureux S, Liu JF, *et al*: PARP inhibitors in the management of ovarian cancer: ASCO Guideline. *J Clin Oncol* 38: 3468-3493, 2020.
- Rose M, Burgess JT, O'Byrne K, Richard DJ and Bolderson E: PARP inhibitors: Clinical relevance, mechanisms of action and tumor resistance. *Front Cell Dev Biol* 8: 564601, 2020.
- Hennes ER, Dow-Hillgartner EN, Bergsbaken JJ and Piccolo JK: PARP-inhibitor potpourri: A comparative review of class safety, efficacy, and cost. *J Oncol Pharm Pract* 26: 718-729, 2020.
- Nigam SK: What do drug transporters really do? *Nat Rev Drug Discov* 14: 29-44, 2015.
- Rives ML, Javitch JA and Wickenden AD: Potentiating SLC transporter activity: Emerging drug discovery opportunities. *Biochem Pharmacol* 135: 1-11, 2017.
- Beis K: Structural basis for the mechanism of ABC transporters. *Biochem Soc Trans* 43: 889-893, 2015.
- Zamek-Gliszczynski MJ, Sangha V, Shen H, Feng B, Wittwer MB, Varma MVS, Liang X, Sugiyama Y, Zhang L and Bendayan R; International Transporter Consortium: Transporters in drug development: International transporter consortium update on emerging transporters of clinical importance. *Clin Pharmacol Ther* 112: 485-500, 2022.
- König J, Müller F and Fromm MF: Transporters and drug-drug interactions: Important determinants of drug disposition and effects. *Pharmacol Rev* 65: 944-966, 2013.
- Thakkar N, Lockhart AC and Lee W: Role of organic anion-transporting polypeptides (OATPs) in cancer therapy. *AAPS J* 17: 535-545, 2015.
- Chen M, Hu S, Li Y, Gibson AA, Fu Q, Baker SD and Sparreboom A: Role of Oatp2b1 in drug absorption and drug-drug interactions. *Drug Metab Dispos* 48: 419-425, 2020.
- Zhou Y, Yuan J, Li Z, Wang Z, Cheng D, Du Y, Li W, Kan Q and Zhang W: Genetic polymorphisms and function of the organic anion-transporting polypeptide 1A2 and its clinical relevance in drug disposition. *Pharmacology* 95: 201-218, 2015.
- Alam K, Crowe A, Wang X, Zhang P, Ding K, Li L and Yue W: Regulation of organic anion transporting polypeptides (OATP) 1B1- and OATP1B3-Mediated Transport: An updated review in the context of OATP-Mediated drug-drug interactions. *Int J Mol Sci* 19: 855, 2018.
- Koepsell H: Role of organic cation transporters in drug-drug interaction. *Expert Opin Drug Metab Toxicol* 11: 1619-1633, 2015.
- Brosseau N and Ramotar D: The human organic cation transporter OCT1 and its role as a target for drug responses. *Drug Metab Rev* 51: 389-407, 2019.
- Samodelov SL, Kullak-Ublick GA, Gai Z and Visentin M: Organic cation transporters in human physiology, pharmacology, and toxicology. *Int J Mol Sci* 21: 7890, 2020.
- Pochini L, Galluccio M, Scalise M, Console L and Indiveri C: OCTN: A small transporter subfamily with great relevance to human pathophysiology, drug discovery, and diagnostics. *SLAS Discov* 24: 89-110, 2019.
- Brecht K, Schäfer AM and Meyer Zu Schwabedissen HE: Uptake transporters of the SLC21, SLC22A, and SLC15A families in anticancer therapy-modulators of cellular entry or pharmacokinetics? *Cancers (Basel)* 12: 2263, 2020.
- Nigam SK, Bush KT, Martovetsky G, Ahn SY, Liu HC, Richard E, Bhatnagar V and Wu W: The organic anion transporter (OAT) family: A systems biology perspective. *Physiol Rev* 95: 83-123, 2015.
- Ivanyuk A, Livio F, Biollaz J and Buclin T: Renal drug transporters and drug interactions. *Clin Pharmacokinet* 56: 825-892, 2017.
- Izat N and Sahin S: Hepatic transporter-mediated pharmacokinetic drug-drug interactions: Recent studies and regulatory recommendations. *Biopharm Drug Dispos* 42: 45-77, 2021.
- Nies AT, Damme K, Kruck S, Schaeffeler E and Schwab M: Structure and function of multidrug and toxin extrusion proteins (MATEs) and their relevance to drug therapy and personalized medicine. *Arch Toxicol* 90: 1555-1584, 2016.
- Motohashi H and Inui K: Organic cation transporter OCTs (SLC22) and MATEs (SLC47) in the human kidney. *AAPS J* 15: 581-588, 2013.
- Locher KP: Mechanistic diversity in ATP-binding cassette (ABC) transporters. *Nat Struct Mol Biol* 23: 487-493, 2016.
- Elmeliegy M, Vourvahis M, Guo C and Wang DD: Effect of P-glycoprotein (P-gp) inducers on exposure of P-gp substrates: Review of clinical drug-drug interaction studies. *Clin Pharmacokinet* 59: 699-714, 2020.
- Suzuki K, Taniyama K, Aoyama T and Watanabe Y: Evaluation of the role of P-glycoprotein (P-gp)-Mediated efflux in the intestinal absorption of common substrates with elacridar, a P-gp inhibitor, in rats. *Eur J Drug Metab Pharmacokinet* 45: 385-392, 2020.
- Storelli F, Anoshchenko O and Unadkat JD: Successful prediction of human steady-state unbound brain-to-plasma concentration ratio of P-gp substrates using the proteomics-informed relative expression factor approach. *Clin Pharmacol Ther* 110: 432-442, 2021.
- Mao Q and Unadkat JD: Role of the breast cancer resistance protein (BCRP/ABCG2) in drug transport-an update. *AAPS J* 17: 65-82, 2015.
- Amawi H, Sim HM, Tiwari AK, Ambudkar SV and Shukla S: ABC Transporter-mediated multidrug-resistant cancer. *Adv Exp Med Biol* 1141: 549-580, 2019.
- Cole SP: Targeting multidrug resistance protein 1 (MRP1, ABCB1): Past, present, and future. *Annu Rev Pharmacol Toxicol* 54: 95-117, 2014.
- Järvinen E, Deng F, Kidron H, Finel M: Efflux transport of estrogen glucuronides by human MRP2, MRP3, MRP4 and BCRP. *J Steroid Biochem Mol Biol* 178: 99-107, 2018.
- Liu X: Transporter-Mediated drug-drug interactions and their significance. *Adv Exp Med Biol* 1141: 241-291, 2019.
- Dufour R, Daumar P, Mounetou E, Aubel C, Kwiatkowski F, Abrial C, Vatoux C, Penault-Llorca F and Bamdad M: BCRP and P-gp relay overexpression in triple negative basal-like breast cancer cell line: A prospective role in resistance to Olaparib. *Sci Rep* 5: 12670, 2015.
- Song YK, Kim MJ, Kim MS, Lee JH, Chung SJ, Song JS, Chae YJ and Lee KR: Role of the efflux transporters Abcb1 and Abcg2 in the brain distribution of olaparib in mice. *Eur J Pharm Sci* 173: 106177, 2022.
- Vaidyanathan A, Sawers L, Gannon AL, Chakravarty P, Scott AL, Bray SE, Ferguson MJ and Smith G: ABCB1 (MDR1) induction defines a common resistance mechanism in paclitaxel- and olaparib-resistant ovarian cancer cells. *Br J Cancer* 115: 431-441, 2016.
- McCormick A and Swaisland H: In vitro assessment of the roles of drug transporters in the disposition and drug-drug interaction potential of olaparib. *Xenobiotica* 47: 903-915, 2017.
- Martins MLF, Loos NHC, Mucuk S, de Jong D, Lebre MC, Rosing H, Tibben M, Beijnen JH and Schinkel AH: P-Glycoprotein (ABCB1/MDR1) controls brain penetration and intestinal disposition of the PARP1/2 inhibitor niraparib. *Mol Pharm* 18: 4371-4384, 2021.
- Sun K, Mikule K, Wang Z, Poon G, Vaidyanathan A, Smith G, Zhang ZY, Hanke J, Ramaswamy S and Wang J: A comparative pharmacokinetic study of PARP inhibitors demonstrates favorable properties for niraparib efficacy in preclinical tumor models. *Oncotarget* 9: 37080-37096, 2018.
- Morosi L, Matteo C, Ceruti T, Giordano S, Ponzo M, Frapolli R, Zucchetti M, Davoli E, D'Incalci M and Ubezio P: Quantitative determination of niraparib and olaparib tumor distribution by mass spectrometry imaging. *Int J Biol Sci* 16: 1363-1375, 2020.
- US Food and Drug Administration. Label. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208447s02s024tbl.pdf. Accessed June 20, 2022.
- European Medicines Agency. Product information. Available from: https://www.ema.europa.eu/en/documents/product-information/zejula-epar-product-information_en.pdf. Accessed June 20, 2022.
- Durmus S, Sparidans RW, van Esch A, Wagenaar E, Beijnen JH and Schinkel AH: Breast cancer resistance protein (BCRP/ABCG2) and P-glycoprotein (P-GP/ABCB1) restrict oral availability and brain accumulation of the PARP inhibitor rucaparib (AG-014699). *Pharm Res* 32: 37-46, 2015.
- Liao M, Jaw-Tsai S, Beltman J, Simmons AD, Harding TC and Xiao JJ: Evaluation of in vitro absorption, distribution, metabolism, and excretion and assessment of drug-drug interaction of rucaparib, an orally potent poly(ADP-ribose) polymerase inhibitor. *Xenobiotica* 50: 1032-1042, 2020.

44. Chen Z, Ling K, Zhu Y, Deng L, Li Y and Liang Z: Rucaparib antagonize multidrug resistance in cervical cancer cells through blocking the function of ABC transporters. *Gene* 759: 145000, 2020.
45. US Food and Drug Administration. Label. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209115s0081bl.pdf. Accessed June 20, 2022.
46. European Medicines Agency. Product information. Available from: https://www.ema.europa.eu/en/documents/product-information/rubraca-epar-product-information_en.pdf. Accessed June 20, 2022.
47. Xiao JJ, Nowak D, Ramlau R, Tomaszewska-Kiecana M, Wysocki PJ, Isaacson J, Beltman J, Nash E, Kaczanowski R, Arold G and Watkins S: Evaluation of drug-drug interactions of rucaparib and CYP1A2, CYP2C9, CYP2C19, CYP3A, and P-gp substrates in patients with an advanced solid tumor. *Clin Transl Sci* 12: 58-65, 2019.
48. Liao M, Jeziorski KG, Tomaszewska-Kiecana M, Láng I, Jasiówska M, Skarbová V, Centkowski P, Ramlau R, Górnaś M, Lee J, *et al*: A phase I, open-label, drug-drug interaction study of rucaparib with rosuvastatin and oral contraceptives in patients with advanced solid tumors. *Cancer Chemother Pharmacol* 88: 887-897, 2021.
49. Guney Eskiler G, Cecener G, Egeli U and Tunca B: Talazoparib nanoparticles for overcoming multidrug resistance in triple-negative breast cancer. *J Cell Physiol* 235: 6230-6245, 2020.
50. Kizilbash SH, Gupta SK, Chang K, Kawashima R, Parrish KE, Carlson BL, Bakken KK, Mladek AC, Schroeder MA, Decker PA, *et al*: Restricted delivery of talazoparib across the blood-brain barrier limits the sensitizing effects of PARP inhibition on temozolomide therapy in glioblastoma. *Mol Cancer Ther* 16: 2735-2746, 2017.
51. Elmeliegy M, Láng I, Smolyarchuk EA, Chung CH, Plotka A, Shi H and Wang D: Evaluation of the effect of P-glycoprotein inhibition and induction on talazoparib disposition in patients with advanced solid tumours. *Br J Clin Pharmacol* 86: 771-778, 2020.
52. Yu Y, Durairaj C, Shi H and Wang DD: Population pharmacokinetics of talazoparib in patients with advanced cancer. *J Clin Pharmacol* 60: 218-228, 2020.
53. US Food and Drug Administration. Label. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211651s0061bl.pdf. Accessed June 20, 2022.
54. European Medicines Agency. Product information. Available from: https://www.ema.europa.eu/en/documents/product-information/talzenna-epar-product-information_en.pdf. Accessed June 20, 2022.
55. Kikuchi R, Lao Y, Bow DA, Chiou WJ, Andracki ME, Carr RA, Voorman RL and De Morais SM: Prediction of clinical drug-drug interactions of veliparib (ABT-888) with human renal transporters (OAT1, OAT3, OCT2, MATE1, and MATE2K). *J Pharm Sci* 102: 4426-4432, 2013.
56. Stodtmann S, Nuthalapati S, Eckert D, Kasichayanula S, Joshi R, Bach BA, Mensing S, Menon R and Xiong H: A population pharmacokinetic meta-analysis of veliparib, a PARP Inhibitor, Across Phase 1/2/3 trials in cancer patients. *J Clin Pharmacol* 61: 1195-1205, 2021.
57. Lin F, de Gooijer MC, Roig EM, Buil LC, Christner SM, Beumer JH, Würdinger T, Beijnen JH, van Tellingen O: ABCB1, ABCG2, and PTEN determine the response of glioblastoma to temozolomide and ABT-888 therapy. *Clin Cancer Res* 20: 2703-2713, 2014.
58. Chang L, Hou Y, Zhu L, Wang Z, Chen G, Shu C and Liu Y: Veliparib overcomes multidrug resistance in liver cancer cells. *Biochem Biophys Res Commun* 521: 596-602, 2020.
59. van Leeuwen RW, van Gelder T, Mathijssen RH and Jansman FG: Drug-drug interactions with tyrosine-kinase inhibitors: A clinical perspective. *Lancet Oncol* 15: e315-e326, 2014.
60. Zhao D, Long X and Wang J: Dose adjustment of poly (ADP-Ribose) Polymerase inhibitors in patients with hepatic or renal impairment. *Drug Des Devel Ther* 16: 3947-3955, 2022.
61. Koinuma K, Tsuchitani T, Imaoka A, Akiyoshi T and Ohtani H: Relative contributions of metabolic enzymes to systemic elimination can be estimated from clinical DD_I studies: Validation using an *in silico* approach. *Int J Clin Pharmacol Ther* 59: 231-238, 2021.
62. Yu J, Petrie ID, Levy RH and Ragueneau-Majlessi I: Mechanisms and clinical significance of pharmacokinetic-based drug-drug interactions with drugs approved by the U.S. Food and Drug Administration in 2017. *Drug Metab Dispos* 47: 135-144, 2019.
63. Choi YH and Yu AM: ABC transporters in multidrug resistance and pharmacokinetics, and strategies for drug development. *Curr Pharm Des* 20: 793-807, 2014.
64. Chen Z, Shi T, Zhang L, Zhu P, Deng M, Huang C, Hu T, Jiang L and Li J: Mammalian drug efflux transporters of the ATP binding cassette (ABC) family in multidrug resistance: A review of the past decade. *Cancer Lett* 370: 153-164, 2016.
65. Lombard AP, Liu C, Armstrong CM, D'Abronzio LS, Lou W, Chen H, Dall'Era M, Ghosh PM, Evans CP and Gao AC: Overexpressed ABCB1 induces olaparib-taxane cross-resistance in advanced prostate cancer. *Transl Oncol* 12: 871-878, 2019.
66. Lawlor D, Martin P, Busschots S, Thery J, O'Leary JJ, Hennessy BT and Stordal B: PARP Inhibitors as P-glycoprotein Substrates. *J Pharm Sci* 103: 1913-1920, 2014.