Chinese Expert Consensus on Drug-Drug Interactions Management of Poly ADP-ribose Polymerase Inhibitors

Branch of Oncology Pharmacists of Chinese Pharmacist Association, Committee of Clinical Pharmacy on Oncology of China Anticancer Association, Committee of Clinical Pharmacy on Oncology of Zhejiang Anticancer Association, Committee of Antineoplastic Drugs of Zhejiang Pharmaceutical Association, Committee of Zhejiang Evidence-based Pharmacy Association

Corresponding Authors: HUANG Ping, Department of Pharmacy, Zhejiang Provincial People's Hospital, Affiliated People's Hospital of Hangzhou Medical College, Key Laboratory of Endocrine Gland Diseases of Zhejiang Province and Clinical Research Center for Cancer of Zhejiang Province, Hangzhou 310014, China, Email: huangpwly@sina.com; ZHENG Xiaowei, Department of Education, Zhejiang Provincial People's Hospital, Affiliated People's Hospital of Hangzhou Medical College, Key Laboratory of Endocrine Gland Diseases of Zhejiang Province and Clinical Research Center for Cancer of Zhejiang Province, Hangzhou 310014, China, Email: zhengxw@zjcc.org.cn

Abstract: Poly ADP-ribose polymerase inhibitors (PARPi), which have been approved in recent years, are recommended by both National Comprehensive Cancer Network (NCCN) and Chinese Society of Clinical Oncology (CSCO) guidelines for the treatment of various cancers, including ovarian cancer, breast cancer, pancreatic cancer, prostate cancer, among others. Most PARPi are metabolized by cytochrome P450 enzyme system, leading to extensive interactions with other drugs commonly used in cancer patients. In this paper, a consensus expert group comprised of pharmacists, clinicians and methodological experts was established, and consensus opinions were formed based on clinical issue identification, data retrieval and evaluation and Delphi technique. Finally, the guiding expert opinions of PARPi drug-drug interactions (DDIs) management were formed to provide practical reference for health-care practitioners.

Key Words: Neoplasms; Poly ADP-ribose polymerase inhibitors (PARPi); Drug-drug interactions (DDI); Expert consensus

Practice Guideline Registration: Practice Guideline Registration for Transparency, PREPARE-2022CN596

Funds: National Natural Science Foundation of China (82003189); 10,000 Talents Plan of Zhejiang Province (2020R52029); New Heath Talents Program of Zhejiang Province (Office of Zhejiang Provincial Health Commission [2022] No.32, Office of Zhejiang Provincial Health Commission [2020] No.18)

Poly ADP-ribose polymerase inhibitors (PARPi) represent a novel class of anti-cancer targeted therapy. Since the first PARPi (olaparib) approved in China in 2018, four PARPi (olaparib, niraparib, fuzuloparib/fluzoparib and pamiparib) are currently available for Chinese patients with ovarian cancer, fallopian tube carcinoma (FTC), primary peritoneal carcinoma (PPC), and other types of tumor with positive breast cancer susceptibility gene (BRCA) mutations or homologous recombination repair (HRR) deficiency. Most PARPi (olaparib, fuzuloparib/fluzoparib and pamiparib), metabolized through the hepatic microsomal enzyme system, interact extensively with other drugs, which are often ignored in clinical practices, resulting in higher incidence of adverse reactions or compromised efficacy. This consensus summarizes drug-drug interactions (DDIs) data of PARPi listed in China, and provides reference for healthcare practitioners in the management of PARPi DDI. (registration number: PREPARE-2022CN596; registration platform: www.guidelines-registry.cn).

I. Statement of Consensus-making

This consensus focuses on DDIs between PARPi approved in China (olaparib, niraparib, fuzuloparib/fluzoparib and pamiparib) and drugs commonly used in cancer patients (analgesics, antiemetics, sedative hypnotics, anticoagulants and antimicrobials). The current document was

formulated based on the following steps: (1) Identify clinical issues, and clarify the existing DDIs between PARPi and target drugs; (2) Retrieve, process and evaluate data on DDIs; (3) Reach a consensus via Delphi technique based on the evaluated data.

1. Expert Group

The consensus expert group consists of 50 experts from various disciplines, including 33 pharmacists, 16 clinicians and 1 methodological expert. The data group composed of 4 graduate students was responsible for the collection and processing of research data.

2. Conflicts of Interest

All members in the consensus expert group were required to declare their conflicts of interest related to this project. After verification by the project steering committee, all members possess no conflicts of interest, and were allowed to participate in the entire research.

3. Collection of Evidence

Evidence supported the consensus including drug labels, research papers and DDI databases, including Medscape (https://reference.medscape.com/), Ddinter (http://ddinter.scbdd.com/) and Drug Bank (https://go.drugbank.com/). A total of 42 interactions from drug labels, 9 from literature and 1,947 from drug databases were obtained, and relevant data of target drugs was included. In instances where data were absent in drug labels, literature or databases,, the deduction of interaction existence was performed through mechanism analyses based on the pharmacokinetic/pharmacodynamic characteristics of drugs and their impact on metabolic enzymes and transporters.

According to the *Guiding Principles of Drug-Drug Interactions Research* issued by China State Food and Drug Administration in 2012, the *New Draft of Guiding Principles of Drug-Drug Interactions Test* issued by US Food and Drug Administration in 2006, and *Drug-Drug Interactions: the Effect of Study Design and Data Analysis on Dosage and Instructions* issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in 2006, before the approve of new drugs, it is necessary to carry out *in vivo* research according to their impact on metabolic enzymes and transporters *in vitro*, and it is only necessary to select representative drugs such as the most potent inhibitor/inducer, and the most sensitive or specific substrate recommended. Therefore, literature and product instructions usually merely contain interactions of commonly used and representative drugs. Even though databases contain more information of DDI, they are not all-inclusive. Thus, it is necessary to fully understand DDI through mechanism analyses and deduction.

4. Consensus-making

The consensus was reached by the members of the expert group through public discussion of existing evidence (accepted by 80% or more). In case of disagreement, the recommendation was modified and voted again via Delphi technique. Literature data was all obtained from unconventional clinical research, which could not be evaluated according to the mainstream evidence quality evaluation system. Therefore, all members of the expert group divided the evidence into three categories (see Table 1).

Table 1 Categories of Consensus Evidence

Category	Level of Evidence	Source of Evidence
I	High	Interactions included in drug labels
II	Medium	Interactions included in databases or research papers
III	Low	Interactions deducted from mechanism

5. Users and Target Population of Application

This consensus is applicable to healthcare practitioners in medical institutions at all levels, including clinicians, clinical pharmacists and other professional and technical personnel in oncology and

related departments. The target population of application is cancer patients treated with PARPi.

6. Promotion, Implementation and Updates of Consensus
After the release of this consensus, the consensus expert group will promote it through academic journals, conferences and social media. This consensus is to be updated according to the list of new drugs, the release of latest research data and clinical needs of PARPi, and the update frequency will depend on the actual situation.

II. DDI Mechanisms of PARPi
Drug-drug interactions mechanisms of PARPi are as follows: (1) The combination with other drugs/food affects the metabolism/excretion enzymes of PARPi, leading to changed concentrations of PARPi in the body; (2) PARPi affect metabolism/excretion enzymes of other drugs, causing concentrations changes of other drug; (3) Adverse reactions increase with such combinations. Metabolic enzymes of PARPi and their effects on related enzymes are shown in Table 2.

Table 2 Metabolic Enzymes of PARPi and Their Effects on Related Enzymes

Medicine	Metabolic Enzymes	Substrates	Effects on Related Enzymes[1-3]
Olaparib	CYP3A4/5	P-gp substrate	CYP3A inhibitor and inducer; CYP2B6 inducer; UGT1A1, BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K inhibitors; P-gp inhibitor
Niraparib	CarE	P-gp and BCRP substrates	CYP1A weak inducer; BCRP weak inhibitor; MATE1 and MATE2 inhibitors
Fuzuloparib/fluzoparib	CYP3A4	-	-
Pamiparib	CYP2C8, CYP3A	-	-

Note: PARPi: Poly ADP-ribose polymerase inhibitors; P-gp: P-glycoprotein; UGT1A1: Uridine diphosphate glucuronosyltransferase 1A1; BCRP: Breast cancer resistance protein; OATP1B1: Organic anion transporting polypeptide 1B1; OCT1: Organic cation transporter 1; OCT2: Organic cation transporter 2; OAT3: Organic anion transporter 3; MATE1: Multidrug and toxin extrusion transporter 1; MATE2K: Multidrug and toxin extrusion transporter 2K; MATE2: Multidrug and toxin extrusion transporter 2; -: No data available.

III. Consensus on PARPi DDI Management
Consensus 1: Avoid the combination of olaparib and CYP3A strong/moderate inhibitors. The dosage of olaparib should be reduced appropriately if such combination is inevitable (Level I evidence).

Combining with itraconazole, a strong CYP3A inhibitor, or fluconazole, a moderate CYP3A inhibitor, can increase the area under curve (AUC) of olaparib by 170% and 121%, respectively[2,4]. The incidence of grade 3 and above adverse reactions associated with itraconazole in combination with olaparib (8.5%) is higher than that with olaparib alone (3.4%)[5]. Therefore, the combination of olaparib and CYP3A strong/moderate inhibitors is not recommended. It is suggested that olaparib be reduced from the standard dose of 300 mg bid to 150 mg bid (in combination with a CYP3A moderate inhibitor) and 100 mg bid (in combination with a CYP3A strong inhibitor) if such combination is inevitable[4,5].

Consensus 2: Avoid the combination of olaparib and CYP3A strong/moderate inducers (Level I evidence).

The combination of olaparib and rifampicin, a strong CYP3A inducer, can shorten the time to peak (t_{max}) of olaparib from 1.49 h to 0.78 h, decrease the peak concentration (C_{max}) by 71%, and the AUC by 87%[4]. The combination of olaparib and efavirenz, a moderate CYP3A inducer, is expected

to reduce the AUC of olaparib by approximately 60%[2]. Therefore, the combination of olaparib and CYP3A strong/moderate inducers is not recommended to avoid negative effects on efficacy[2].

Consensus 3: Avoid the combination of fuzuloparib/fluzoparib and CYP3A4 strong inhibitors. Discontinuing fuzuloparib/fluzoparib is recommended if the use of a CYP3A4 strong inhibitor is inevitable (Level I evidence).

Combining with itraconazole, a strong CYP3A4 inhibitor, the C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of fuzuloparib/fluzoparib increased by 51%, 325% and 381%, respectively[6]. Therefore, it is suggested in the label that fuzuloparib/fluzoparib be suspended if the use of a CYP3A4 strong inhibitor is inevitable; After the CYP3A4 strong inhibitor is cleared for 5-7 half lives, the initial dosage and frequency of fuzuloparib/fluzoparib can be restored[7]. For patients who have been using CYP3A4 inhibitors for a long time, niraparib or pamiparib is preferred.

Consensus 4: Avoid the combination of fuzuloparib/fluzoparib and CYP3A4 moderate inhibitors. The dose of fuzuloparib/fluzoparib should be reduced appropriately if the combination is inevitable (Level I evidence).

Fluconazole, a moderate CYP3A4 inhibitor, can increase the C_{max} of fuzuloparib/fluzoparib to 1.32 times, and the AUC_{0-t} and $AUC_{0-\infty}$ to 2.05 times and 2.10 times, respectively[8]. Therefore, the combination of fuzuloparib/fluzoparib and CYP3A4 moderate inhibitors is not recommended. It is suggested that the standard dose of fuzuloparib/fluzoparib be lowered from 150 mg bid to 50 mg bid if such combination is inevitable[8].

Consensus 5: Avoid the combination of fuzuloparib/fluzoparib and CYP3A4 strong inducers (Level I evidence).

Rifampicin, a strong CYP3A4 inducer, can reduce the C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of fuzuloparib/fluzoparib to 32.0%, 10.4% and 10.4%, respectively[9]. Therefore, the combination of fuzuloparib/fluzoparib and CYP3A4 strong inducers should be avoided as indicated in the instructions[7].

Consensus 6: Pamiparib can be used with CYP3A strong/moderate/weak inhibitors without adjusting the dosage; Caution should be exercised when used with CYP3A strong inducers and CYP2C8 strong inhibitors (Level I evidence).

Pamiparib is metabolized by CYP2C8 and CYP3A. Rifampicin, a strong CYP3A inducer, has little effect on the C_{max} of pamiparib, but it can reduce its AUC_{0-t} and $AUC_{0-\infty}$ by 38% and 43%, respectively[10]. Therefore, the combination of pamiparib and CYP3A strong inducers should be cautious, since it can compromise the efficacy of this PARPi. Itraconazole, a strong CYP3A inhibitor, does not affect the AUC of pamiparib, so it is unnecessary to adjust the dosage of pamiparib when given in combination with strong/moderate/weak CYP3A inhibitors. Since DDI data between pamiparib and CYP2C8 strong inhibitors/inducers are not available, caution should be exercised in case of such combinations[11].

Consensus 7: When combining Olaparib or niraparib and P-gp strong inhibitors/inducers, more attention should be paid to adverse reactions and efficacy monitoring, and the doses of these two PARPi should be adjusted if necessary (Level II evidence).

Olaparib and niraparib are P-gp substrates, but there are few pharmacokinetic data on DDIs between olaparib, niraparib and strong P-gp inhibitors/inducers in human. Mechanism-wise, such combinations can either increase or decrease the concentrations of olaparib and niraparib, thus Medscape and DDInter databases included such interactions (see Table 3).

Table 3 Recommendations for PARPi DDI Management

Medicine	Interacting Drugs or Foods	Interaction	Level of Evidence

Olaparib	CYP3A strong/moderate inhibitors	+++[a]	Level I
	CYP3A4 weak inhibitors	+	Level III
	CYP3A strong/moderate inducers	+++	Level I
	P-gp strong inhibitors/inducers	+[b]	Level II
	Foods containing CYP3A inhibitors, such as grapefruit (juice) and lime (juice)	+++	Level I
Niraparib	P-gp strong inhibitors/inducers	+[b]	Level II
Fuzuloparib/fluzoparib	CYP3A4 strong inhibitors	+++[c]	Level I
	CYP3A4 moderate inhibitors	+++[d]	Level I
	CYP3A4 weak inhibitors	+	Level III
	CYP3A4 strong inducers	+++	Level I
	Foods containing CYP3A inhibitors, such as grapefruit (juice) and lime (juice)	+++	Level I
Pamiparib	CYP3A strong/moderate/weak inhibitors	-	Level I
	CYP3A strong inducers	+	Level I
	CYP2C8 strong inhibitors	+	Level I

Note: PARPi: Poly ADP-ribose polymerase inhibitors; P-gp: P-glycoprotein; +++: Strong interaction, so the combination should be avoided; +: Mild to moderate interaction, so more attention should be paid to efficacy and/or the adverse reactions when used in combination; -: The combination is allowed, and there is no known interaction or the interaction has little effect on pharmacokinetics; [a]If the combination is inevitable, it is suggested that the dosage of olaparib be reduced to 150 mg bid (in combination with CYP3A moderate inhibitors) and 100 mg bid (in combination with CYP3A strong inhibitors); [b]When initiating or suspending the use of P-gp strong inhibitors/inducers, more attention should be paid to the pharmacological reaction of olaparib/niraparib and the dosage should be adjusted if necessary; [c]It is suggested to discontinue fuzuloparib/fluzoparib if the combination is inevitable, and its use can be restored after CYP3A4 strong inhibitor is cleared for 5-7 half lives. [d]If the combination is inevitable, it is suggested that the dosage of fuzuloparib/fluzoparib be reduced to 50 mg bid.

IV. DDI between PARPi and Commonly Used Drugs and Treatment Recommendations

1. Antiemetics

Consensus 8: For patients treated with olaparib, it is suggested that the use of aprepitant, netupitant and dexamethasone should be avoided (Level I evidence); For patients treated with 5-hydroxytryptamine 3 (5-HT_3) receptor antagonists, metoclopramide, thalidomide and olanzapine, more attention should be paid to efficacy and adverse effects (Level II-III evidence).

Olaparib is metabolized by CYP3A4/5, while aprepitant and netupitant are modetrate CYP3A4 inhibitors, and dexamethasone is a strong CYP3A4 inducer. Their combination can affect the metabolism of olaparib. As indicated clearly in the label of olaparib, "the combination of CYP3A strong/moderate inhibitors should be avoided. If the combination is inevitable, the dosage of olaparib should be reduced; The combination of CYP3A strong/moderate inducers should be avoided. If the combination cannot be avoided, the efficacy of olaparib may be reduced"[2]. Therefore, the combination of aprepitant, netupitant and dexamethasone is not recommended. If dexamethasone is needed in clinical practices, more attention should be paid to the efficacy of olaparib. For patients who have to use neurokinin-1 (NK-1) receptor antagonists, fosaprepitant and rolapitant are recommended for fewer interactions, and more attention should be paid to the adverse reactions of olaparib. Fosaprepitant, a weak CYP3A4 inhibitor, and rolapitant, a P-gp inhibitor, inhibit the metabolism and excretion of olaparib, respectively. Therefore, their combination with olaparib may increase the incidence of adverse reactions.

Olanzapine and thalidomide are CYP2B6 substrates, and olaparib is a CYP2B6 inhibitor. The incidence of adverse reactions may increase when combining olaparib and olanzapine or

thalidomide, so more attention should be paid to adverse reactions. Thalidomide and olaparib may cause myelosuppression, so blood routines should be monitored. The combination of 5-HT_3 receptor antagonists and olaparib can increase the risk of constipation, thus more attention should be paid to this adverse effect in case of such combinations[12-14]. Metoclopramide, mainly metabolized by CYP2D6 and CYP3A4, can compete with olaparib for the metabolizing enzyme CYP3A4 when used together, which may slow the metabolism of olaparib, so more attention should be paid to the adverse reactions of olaparib.

Consensus 9: Aprepitant, fosaprepitant, dexamethasone, olanzapine and metoclopramide can be given safely to patients treated with niraparib; More attention should be paid to the adverse reactions when combined with rolapitant, netupitant, 5-HT_3 receptor antagonists and thalidomide (Level II-III evidence).

As a P-gp substrate, niraparib can reduce its excretion and increase the incidence of its adverse reactions when combined with P-gp inhibitors rolapitant and netupitant, so more attention should be paid to the adverse reactions of niraparib. When 5-HT_3 receptor antagonists, thalidomide and niraparib are used together, the risk of constipation and myelosuppression increases, so more attention should be paid to constipation and blood routine test. Aprepitant, fosaprepitant, dexamethasone, olanzapine and metoclopramide have no known or mechanism-deducted interaction with niraparib, so they can be safely given concomitantly.

Consensus 10: Patients treated with fuzuloparib/fluzoparib can safely use rolapitant and olanzapine; Aprepitan, netupitant and dexamethasone are not recommended (Level I evidence); For patients who have to use NK-1 antagonists, rolapitant is preferred, followed by fosaprepitant, and it is suggested that the dosage of fuzuloparib/fluzoparib be reduced appropriately when given concomitantly with aprepitant and netupitant. For patients treated with 5-HT_3 receptor antagonists, thalidomide and metoclopramide, more attention should be paid to adverse reactions (Level II-III evidence).

Fuzuloparib/fluzoparib is metabolized by CYP3A4, and dexamethasone is a strong CYP3A4 inducer. Their combination can accelerate metabolism and reduce efficacy. Therefore, the label of fuzuloparib/fluzoparib clearly indicates that "the combination of fuzuloparib/fluzoparib and strong CYP3A4 inducers should be avoided in clinical practices."[7]. If dexamethasone is clinically needed, more attention should be paid to the efficacy of olaparib and increase its dosage when necessary. Arepitant and netupiptant are moderate CYP3A4 inhibitors. It is pointed out in the literature that fluconazole, a moderate CYP3A4 inhibitor, can increase the C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of fuzuloparib/fluzoparib by 1-2 times, so it is suggested that the dosage of fuzuloparib/fluzoparib be reduced to 50 mg bid when used in combination with moderate CYP3A4 inhibitors[8]. Fosaprepitant is a weak CYP3A4 inhibitor, which may cause an increase in the incidence of adverse reactions of fuzuloparib/fluzoparib, but only to a limited extent, so more attention should be paid to the adverse reactions of fuzuloparib/fluzoparib in this case. The combination of fuzuloparib/fluzoparib and 5-HT_3 receptor antagonists or thalidomide can increase the risk of constipation and myelosuppression, so more attention should be paid to constipation and blood routine test. There are no known or mechanism-related interactions between rolapitant, olanzapine and fuzuloparib/fluzoparib, rendering such combinations safe. Metoclopramide is mainly metabolized by CYP2D6 and CYP3A4, and can compete with fuzuloparib/fluzoparib for the metabolizing enzyme CYP3A4 when used in combination, which may slow down the metabolism of fuzuloparib/fluzoparib, so more attention should be paid to the adverse reactions of this PARPi.

Consensus 11: Patients treated with pamiparib can safely use aprepitant, fosaprepitant, rolapitant, netupitant, metoclopramide and olanzapine (Level I evidence); When using dexamethasone, 5-HT_3 receptor antagonists (Level II evidence) and thalidomide, more attention should be paid to efficacy and adverse effects (Level III evidence).

Pamiparib is metabolized by CYP3A, and its combination with dexamethasone, a strong CYP3A inducer, can accelerate its metabolism. It should be noted that the efficacy of pamiparib may decrease. The risk of constipation can increase when used concomitantly with 5-HT_3 receptor

antagonists, and that of myelosuppression may rise when used in combination with thalidomide. Pamiparib is metabolized by both CYP2C8 and CYP3A rather than depending on a single metabolizing enzyme, and CYP3A inhibitors have less influence on pamiparib, so it can be safely used with aripipitan and netupitant, moderate CYP3A4 inhibitors, as well as fosaprepitant, a weak CYP3A4 inhibitor. There is no known interaction between rolapitant, metoclopramide, olanzapine and pamiparib, so they can be used together safely.

Interactions between commonly used antiemetics and PARPi and the level of evidence are shown in Table 4.

Table 4 Interactions between Commonly Used Antiemetics and PARPi and the Level of Evidence

Medicine Category	Name and Nature of Medicine	Olaparib		Niraparib		Fuzuloparib/fluzoparib		Pamiparib	
		Interaction	Level of Evidence	Interaction	Level of Evidence	Interaction	Level of Evidence	Interaction	Level of Evidence
NK-1 antagonists	Aprepitant (CYP3A4 moderate inhibitor)	+++[a]	Level I	-	-	+++[b]	Level I	-	-
	Fosaprepitant (CYP3A4 weak inhibitor)	+[c]	Level II	-	-	+[c]	Level III	-	-
	Rolapitant (P-gp inhibitor)	+[c]	Level III	+[c]	Level III	-	-	-	-
	Netupitant (CYP3A4 moderate inhibitor, P-gp inhibitor)	+++[a]	Level I	+[c]	Level III	+++[b]	Level I	-	-
5-HT_3 receptor antagonists	All agents in the category	+[d]	Level III	+[d]	Level III	+[d]	Level III	+[d]	Level III
Glucocorticoids	Dexamethasone (CYP3A4 strong inducer)	+++[e]	Level I	-	-	+++[e]	Level I	+[e]	Level I
Other antiemetics	Olanzapine (CYP 2B6 substrate)	+[f]	Level II	-	-	-	-	-	-
	Metoclopramide (Mainly metabolized by CYP2D6 and CYP3A4)	+[c]	Level III	-	-	+[c]	Level III	-	-
	Thalidomide (CYP3A substrate and inducer, CYP 2B6 substrate)	+[fg]	Level II	+[g]	Level II	+[g]	Level II	+[g]	Level II

Note: PARPi: Poly ADP-ribose polymerase inhibitors; P-gp:P-glycoprotein; +++: Strong interaction, so the combination should be avoided; +:Mild to moderate interaction, so more attention should be paid to efficacy and/or adverse reactions when used in combination; -: The combination is allowed, and there is no known interaction or the interaction has little effect on pharmacokinetics; [a]If the combination is inevitable, it is suggested

that the dosage of olaparib be reduced to 150 mg bid, and the initial dose can be restored after discontinuing the combined agent for 3-5 half lives; [b]If the combination is inevitable, the dosage of fuzuloparib/fluzoparib should be reduced to 50 mg bid; [c]The adverse reactions of PARPi increased; [d]The risk of constipation increased; [e]The efficacy of PARPi decreased; [f]The efficacy of combined drugs decreased; [g]The risk of myelosuppression increased.

2. Analgesics

Consensus 12: All PARPi can be given concomitantly with commonly used analgesics, but more attention should be paid to constipation, bleeding and other adverse reactions (Level II-III evidence).

Morphine/celecoxib are P-gp substrates, and olaparib is a P-gp inhibitor. Their combination can lead to decreased excretion and possibly increased adverse reactions. Oxycodone is metabolized by CYP3A4/5 and CYP2D6, and tramadol is metabolized by CYP2D6, CYP3A4 and CYP2B6. They compete for the metabolizing enzymes of olaparib, which may slow down the metabolism of this PARPi, so more attention should be paid to the adverse reactions of olaparib. Fentanyl and methadone are P-gp inhibitors, and olaparib and niraparib are P-gp substrates. Their combined use may slow down the PARPi metabolism, and increase the incidence of adverse reactions.

PARPi can cause thrombocytopenia, with an incidence between 13.8% - 50.8% as indicated in the label. Hemorrhage is a common adverse reaction of non-steroidal anti-inflammatory drugs (NSAIDS), and its risk can increase in case of such combinations, so more attention should be paid in this scenario. In addition, there is an increased risk of constipation in the combination of PARPi and opioids, and monitoring should be strengthened when given together.

Interactions between commonly used analgesics and PARPi and the level of evidence are shown in Table 5.

Table 5 Interactions between Commonly Used Analgesics and PARPi and the Level of Evidence

Medicine Category	Name and Nature of Medicine	Olaparib		Niraparib		Fuzuloparib/fluzoparib		Pamiparib	
		Interaction	Level of Evidence	Interaction	Level of Evidence	Interaction	Level of Evidence	Interaction	Level of Evidence
Strong opioids	Morphine (P-gp substrate)	++[ab]	Level III	+[b]	Level III	+[b]	Level III	+[b]	Level III
	Oxycodone (Metabolized by CYP3A4/5 and CYP2D6)	++[bc]	Level II	+[b]	Level III	+[b]	Level III	+[b]	Level III
	Fentanyl (P-gp inhibitor)	++[bc]	Level III	++[bc]	Level III	+[b]	Level III	+[b]	Level III
	Methadone (P-gp inhibitor)	++[bc]	Level II	++[bc]	Level III	+[b]	Level III	+[b]	Level III
Weak opioids	Tramadol (Metabolized by CYP2D6, CYP3A4 and CYP2B6)	++[bc]	Level II	+[b]	Level III	+[b]	Level III	+[b]	Level III
Non-steroidal anti-inflammatory drugs	Celecoxib (P-gp substrate, CYP3A substrate)	++[ad]	Level II 级	+[d]	Level III	+[d]	Level III	+[d]	Level III
	Rofecoxib (CYP3A substrate and inducer)	++[de]	Level II	+[d]	Level III	++[de]	Level III	+[d]	Level III
	Etoricoxib (CYP3A substrate and inhibitor)	++[d]	Level II	+[d]	Level III	++[d]	Level III	+[d]	Level III

	Nimesulide (CYP3A substrate)	++[dc]	Level II	+[d]	Level III	++[dc]	Level III	+[d]	Level III
	Other non-steroidal anti-inflammatory drugs	+[d]	Level III	+[d]	Level III	+[d]	Level III	+[d]	Level III

Note: PARPi: Poly ADP-ribose polymerase inhibitors; P-gp: P-glycoprotein; ++: Two or more mechanisms of DDI; +: One mechanism of DDI; [a]The adverse reactions of combined drugs increased; [b]The risk of constipation increased; [c]The adverse reactions of PARPi increased; [d]The risk of bleeding increased; [e]The efficacy of PARPi decreased.

3. Sedative Hypnotics

Consensus 13: When combining olaparib with diazepam, alprazolam, triazolam, zaleplon, (de)zopiclone, fuzuloparib/fluzoparib with diazepam, and pamiparib with triazolam, more attention should be paid to the adverse reactions of PARPi and/or the combined agents (Level II-III evidence).

Diazepam is a CYP3A inhibitor, and olaparib and fuzuloparib/fluzoparib are metabolized by CYP3A. Their combinations may increase the incidence of adverse reactions of olaparib and fuzuloparib/fluzoparib. Triazolam is a CYP2C8 inhibitor, and pamiparib is metabolized by CYP2C8 and CYP3A. Their combined use can slow down the metabolism of the PARPi. CYP3A is involved in the metabolism of alprazolam, (de)zopiclone, triazolam and zaleplon, and olaparib and fuzuloparib/fluzoparib are metabolized by CYP3A. Such combinations can cause competitive inhibition, which may lead to a high incidence of adverse reactions.

Interactions between commonly used sedative hypnotics and PARPi and the level of evidence is shown in Table 6.

Table 6 Interactions between Commonly Used Sedative Hypnotics and PARPi and the Level of Evidence

Medicine Category	Name and Nature of Medicine	Olaparib		Niraparib		Fuzuloparib/fluzoparib		Pamiparib	
		Interaction	Level of Evidence	Interaction	Level of Evidence	Interaction	Level of Evidence	Interaction	Level of Evidence
Benzodiazepines	Diazepam (CYP3A inhibitor)	+[a]	Level II	-	-	+[a]	Level III	+[a]	Level III
	Flurazepam	-	-	-	-	-	-	-	-
	Oxazepam	-	-	-	-	-	-	-	-
	Clonazepam	-	-	-	-	-	-	-	-
	Lorazepam	-	-	-	-	-	-	-	-
	Alprazolam (Metabolized by CYP3A)	+[ab]	Level II	-	-	+[ab]	Level III	-	-
	Estazolam	-	-	-	-	-	-	-	-
	Triazolam (CYP2C8 inhibitor, CYP3Asubstrate)	+[ab]	Level II	-	-	+[ab]	Level III	+[a]	Level III
Non-benzodiazepines	Zaleplon (Very few of them are metabolized by CYP3A4, CYP3A4 substrate)	+[a]	Level II	-	-	-	-	-	-
	(De)zopiclone (Mainly metabolized by CYP3A)	+[b]	Level II	-	-	+[ab]	Level III	-	-

Zolpidem	-	-	-	-	-	-	-	-

Note: PARPi: Poly ADP-ribose polymerase inhibitors; +: Mild to moderate interaction, so more attention should be paid to efficacy and/or adverse reactions when used in combination; -: The combination is allowed, and there is no known interaction or the interaction has little effect on pharmacokinetics; [a]The adverse reactions of PARPi increased; [b]The adverse reactions of combined drugs increased.

4. Antibacterials

Consensus 14: Olaparib can be safely given with β-lactams, carbapenems, aminoglycosides, moxifloxacin, (lev)ornidazole, vancomycin and micafungin; The combination of olaparib with ciprofloxacin, erythromycin, clarithromycin, metronidazole and triazole antifungal agents should be avoided (Level I evidence); When combining olaparib with levofloxacin, azithromycin, linezolid and caspofungin, more attention should be paid to the adverse reactions of olaparib (Level II-III evidence).

Voriconazole, posaconazole, itraconazole and clarithromycin are strong CYP3A4 inhibitors, while fluconazole, ciprofloxacin, erythromycin and metronidazole are moderate CYP3A4 inhibitors. If they are used concomitantly with olaparib metabolized by CYP3A4, the metabolism of this PARPi can be affected, leading to an increase in concentration. Levofloxacin is a P-gp inhibitor, azithromycin is a CYP3A4 inhibitor and a P-gp inhibitor, and caspofungin is a CYP3A inhibitor and a P-gp inhibitor. Their combinations with olaparib can affect the metabolism/excretion of this PARPi. Interactions between linezolid and olaparib and other PARPi are mainly added risks of platelet inhibition.

Consensus 15: Niraparib can be safely given with β-lactams, carbapenems, aminoglycosides, ciprofloxacin, moxifloxacin, metronidazole, (lev)ornidazole, vancomycin, micafungin, fluconazole, voriconazole and posaconazole; When combining niraparib with levofloxacin, erythromycin, clarithromycin, azithromycin, linezolid, itraconazole and caspofungin, more attention should be paid to the adverse reactions of niraparib (Level II-III evidence).

Levofloxacin, erythromycin, clarithromycin, azithromycin, itraconazole and caspofungin are all P-gp inhibitors, and niraparib is a P-gp substrate. Their combined use can slow down the excretion of niraparib, and increase the incidence of its adverse reactions. Both linezolid and niraparib can lead to thrombocytopenia, so the monitoring of platelet count should be strengthened in case of such combinations. Carbapenems, β-lactams, aminoglycosides, ciprofloxacin, moxifloxacin, metronidazole, (lev)ornidazole, vancomycin, micafungin, fluconazole, voriconazole and posaconazole have no known interaction with niraparib, so they can be safely used concomitantly.

Consensus 16: Fuzuloparib/fluzoparib can be safely used with β-lactams, carbapenems, aminoglycosides, levofloxacin, moxifloxacin, (lev)ornidazole, vancomycin and micafungin; The combination of fuzuloparib/fluzoparib with ciprofloxacin, erythromycin, clarithromycin, metronidazole and triazole antifungal agents should be avoided, and it is suggested to reduce the dosage of fuzuloparib/fluzoparib appropriately if necessary when used in combination (Level I evidence); When combining fuzuloparib/fluzoparib with azithromycin, linezolid and caspofungin, more attention should be paid to the adverse reactions of fuzuloparib/fluzoparib (Level II-III evidence).

Ciprofloxacin, erythromycin, clarithromycin, metronidazole and triazoles are all strong/moderate CYP3A4 inhibitors, and their combination with fuzuloparib/fluzoparib can increase the exposure of fuzuloparib/fluzoparib. When the combination with strong CYP3A4 inhibitors (clarithromycin, voriconazole, posaconazole, itraconazole) is inevitable, fuzuloparib/fluzoparib should be discontinued; When used concomitantly with moderate CYP3A4 inhibitors (ciprofloxacin, erythromycin, metronidazole and fluconazole), it is suggested in literature[8] that the dosage of fuzuloparib/fluzoparib be adjusted to 50 mg bid. Azithromycin and caspofungin are inhibitors of CYP3A4 and CYP3A, respectively, with unknown inhibition potency, so more attention should be paid to the adverse reactions of fuzuloparib/fluzoparib.

Consensus 17: Pamiparib can be safely given with other commonly used antibacterials except linezolid.

Although many antibacterials are CYP3A4 inhibitors, pamiparib is metabolized by CYP2C8 and CYP3A, less dependent on CYP3A4, so it can be safely used with strong/moderate/weak CYP3A inhibitors. The interaction between linezolid and pamiparib mainly lead to an added risk of thrombocytopenia.

Interactions between commonly used antibacterials and PARPi and the level of evidence are shown in Table 7.

Table 7 Interactions between Commonly Used Antibacterials and PARPi and the Level of Evidence

Medicine Category	Name and Nature of Medicine	Olaparib		Niraparib		Fuzuloparib/fluzoparib		Pamiparib	
		Interaction	Level of Evidence	Interaction	Level of Evidence	Interaction	Level of Evidence	Interaction	Level of Evidence
β-lactams	Amoxicillin	-	-	-	-	-	-	-	-
	Piperacillin-tazobactam	-	-	-	-	-	-	-	-
	Cefuroxime	-	-	-	-	-	-	-	-
	Cefperazone-sulbactam	-	-	-	-	-	-	-	-
	Ceftriaxone	-	-	-	-	-	-	-	-
	Ceftazidime	-	-	-	-	-	-	-	-
	Cefotaxime	-	-	-	-	-	-	-	-
Carbapenems	Imipenem	-	-	-	-	-	-	-	-
	Meropenem	-	-	-	-	-	-	-	-
	Ertapenem	-	-	-	-	-	-	-	-
	Faropenem	-	-	-	-	-	-	-	-
Quinolones	Levofloxacin (P-gp substrate, inhibitor)	+[ab]	Level III	+[a]	Level III	-	-	-	-
	Ciprofloxacin (CYP3A4 moderate inhibitor, P-gp substrate)	+++[c]	Level I	-	-	+++[d]	Level I	-	-
	Moxifloxacin	-	-	-	-	-	-	-	-

Macrolides	Erythromycin (CYP3A4 moderate inhibitor, P-gp inhibitor)	+++[c]	Level I		+[a]	Level III		+++[d]	Level I		-	-
	Clarithromycin (CYP3A4 strong inhibitor, P-gp inhibitor)	+++[e]	Level I		+[a]	Level III		+++[f]	Level I		-	-
	Azithromycin (CYP3A4 inhibitor, P-gp substrate and inhibitor)	+[ab]	Level II		+[a]	Level III		+[a]	Level III		-	-
Aminoglycosides	Gentamicin	-	-		-	-		-	-		-	-
	Amikacin	-	-		-	-		-	-		-	-
	Etimicin	-	-		-	-		-	-		-	-
	Netilmicin	-	-		-	-		-	-		-	-
Anti-anaerobic bacteria	Metronidazole (CYP3A4 moderate inhibitor)	+++[c]	Level I		-	-		+++[d]	Level I		-	-
	(Lev)ornidazole	-	-		-	-		-	-		-	-
Glycopeptides	Vancomycin	-	-		-	-		-	-		-	-
Oxazolidinones	Linezolid	+[g]	Level II		+[g]	Level II		+[g]	Level II		+[g]	Level III
Antifungal drugs	Fluconazole (CYP3A4 moderate inhibitor)	+++[c]	Level I		-	-		+++[d]	Level I		-	-

	Voriconazole (CYP3A4 strong inhibitor)	+++[e]	Level I		-	-		+++[f]	Level I		-	-
	Posaconazole (CYP3A4 strong inhibitor)	+++[e]	Level I		-	-		+++[f]	Level I		-	-
	Itraconazole (CYP3A4 strong inhibitor, P-gp strong inhibitor)	+++[e]	Level I		+[a]	Level II		+++[f]	Level I		-	-
	Caspofungin (CYP3A inhibitor, P-gp inhibitor)	+[a]	Level III		+[a]	Level III		+[a]	Level III		-	-
	Micafungin	-	-		-	-		-	-		-	-

Note: PARPi: Poly ADP-ribose polymerase inhibitors; P-gp: P-glycoprotein; +++: Strong interaction, so the combination should be avoided; +: Mild to moderate interaction, so more attention should paid to efficacy and/or adverse reactions when used in combination; -: The combination is allowed, and there is no known interaction or the interaction has little effect on pharmacokinetics; [a]The adverse reactions of PARPi increased; [b]The adverse reactions of combined drugs increased; [c]If the combination is inevitable, it is suggested that the dosage of olaparib be reduced to 150 mg bid; [d]If the combination is inevitable, it is suggested that the dosage of fuzuloparib/fluzoparib be reduced to 50 mg bid; [e]If the combination is inevitable, it is suggested that the dosage of olaparib be reduced to 100 mg bid; [f]If the combination is inevitable, it is suggested to discontinue fuzuloparib/fluzoparib, and it can be restored after discontinuing the strong CYP3A4 inhibitor for 5-7 half lives; [g]The risk of myelosuppression increased.

5. Anticoagulants

Consensus 18: When combining any anticoagulant with PARPi, more attentions should be paid to bleeding and other adverse reactions (Level II-III evidence).

Interactions between anticoagulants and PARPi mainly lead to an added risk of bleeding, and the bleeding risk of PARPi is mainly caused by thrombocytopenia. Some anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban and ticagrelor) are P-gp substrates. Their combinations with olaparib, which inhibits P-gp, can slow down the excretion of anticoagulants, and increase the incidence of adverse reactions. If patients need to use the above orally administered anticoagulants for a long time due to comorbidities, PARPi other than olaparib are recommended; If olaparib has been used, heparin is preferred for anticoagulation.

Consensus 19: Patients treated with olaparib should use warfarin with caution (Level II evidence).

Warfarin is a CYP3A inducer, and olaparib is metabolized by CYP3A. Such combination can slow down the metabolism of olaparib, and may increase the incidence of adverse reactions. CYP3A4 is involved in the metabolism pathway of warfarin, and olaparib can inhibit/induce CYP3A4. According to Drug Bank database, olaparib may increase the serum concentration of warfarin. Therefore, patients treated with olaparib should use warfarin with caution.

Consensus 20: Pamiparib is preferred among PARPi for patients who have been using ticagrelor for a long time (Level III evidence).

Ticagrelor is an inhibitor of CYP3A and P-gp. Its combined use with P-gp substrates (olaparib and niraparib) can slow down the excretion of these PARPi, and may increase the incidence of adverse reactions. As olaparib and fuzuloparib/fluzoparib are mainly metabolized by CYP3A, ticagrelor can inhibit the metabolism of the two PARPi, resulting in an increase of concentration and incidence of adverse reactions. Therefore, pamiparib is preferred among PARPi for patients who have been using ticagrelor for a long time.

Interactions between commonly used anticoagulants and PARPi and the level of evidence are shown in Table 8.

Table 8 Interactions between Commonly Used Anticoagulants and PARPi and the Level of Evidence

Medicine Category	Name and Nature of Medicine	Olaparib		Niraparib		Fuzuloparib/fluzoparib		Pamiparib	
		Interaction	Level of Evidence	Interaction	Level of Evidence	Interaction	Level of Evidence	Interaction	Level of Evidence
Coumarins	Warfarin (CYP3A inducer, CYP3A4 substrate)	++[abc]	Level II	+[b]	Level III	++[ab]	Level III	++[ab]	Level III
Novel oral anticoagulants	Rivaroxaban (P-gp substrate)	++[bd]	Level II	++[bd]	Level II	+[b]	Level III	+[b]	Level III
	Apixaban (P-gp substrate)	++[bd]	Level II	++[bd]	Level II	+[b]	Level III	+[b]	Level III
	Edoxaban (P-gp substrate)	++[bd]	Level III	++[bd]	Level II	+[b]	Level III	+[b]	Level III
	Ticagrelor (CYP3A and P-gp inhibitor)	++[bd]	Level II	++[bd]	Level II	++[bd]	Level III	+[b]	Level III
	Dabigatran (P-gp substrate)	++[bd]	Level II	+[b]	Level III	+[b]	Level III	+[b]	Level III
Heparins	All medicines	+[b]	Level II	+[b]	Level II	+[b]	Level III	+[b]	Level III

Note: PARPi: Poly ADP-ribose polymerase inhibitors; P-gp: P-glycoprotein; ++: Two mechanisms of DDI, so more attention should be paid to efficacy and/or adverse reactions when used in combination; +: One mechanism of DDI, so more attention should be paid to efficacy and/or adverse reactions when used in combination; [a]The efficacy of PARPi decreased; [b]The risk of bleeding increased; [c]The adverse reactions of drug combination increased; [d]The adverse reactions of PARPi increased.

V. Interactions between Food, Traditional Chinese Medicine and PARPi and Treatment Recommendations

Grapefruit (juice) and lime (juice) are strong CYP3A inhibitors, and hyperforin perforatum (also known as St. John's wort) is a strong inducer of CYP3A and P-gp, which can affect the metabolism of PARPi, thus such combinations should be avoided. Fupu granule and polygonum capitatum can also induce CYP3A4[15-16]. Some Chinese medicine or proprietary Chinese medicine can also inhibit CYP3A4, such as ginseng, ginkgo biloba, motherwort, epimedium, myricetin, rutaceae Chinese medicines containing flavonoid hesperidin (including tangerine peel, orange peel and bergamot), and Chinese medicines containing coumarin (including angelica dahurica, peucedanum root and angelica sinensis), all of which can inhibit CYP3A4 activity[16-17].

VI. Conclusion

PARPi are mostly metabolized by hepatic microsomal enzymes, and can interact with many other drugs commonly used in cancer patients. Verification should be highlighted in clinical practices. Interaction databases should be fully used to avoid severe DDIs, and the dosage of drugs should be adjusted when necessary. For interactions not included in databases, the existence of a potential one can be deducted from the mechanism considering the characteristics of drug metabolism and metabolic enzymes, and the observation and monitoring of dosing should be strengthened to better ensure the safety and efficacy of PARPi. Currently, relevant researches on the interactions between traditional Chinese medicine or proprietary Chinese medicine and PARPi is inadequate, which can be seen as a prospect for future research.

Consensus Guiding Group

TONG Rongsheng, Sichuan Provincial People's Hospital
WANG Danbo, Liaoning Cancer Hospital and Institute
WANG Jianliu, Peking University People's Hospital
WU Lingying, Department of Gynecology and Oncology, Cancer Hospital, China Academy of Medical Sciences
KONG Beihua, Department of Obstetrics and Gynecology, Qilu Hospital of Shandong University
ZHAO Rongsheng, Department of Pharmacy, Peking University Third Hospital
LIU Jihong, Department of Gynecology, Cancer Hospital Affiliated to Sun Yat-sen University
ZHANG Bikui, Department of Pharmacy, The Second Xiangya Hospital of Central South University
ZHU Jianqing, Department of Gynecologic Surgery, Zhejiang Cancer Hospital

Expert Group Leaders

HUANG Ping, Department of Pharmacy, Zhejiang Provincial People's Hospital
LI Guohui, Department of Pharmacy, Cancer Hospital, China Academy of Medical Sciences
DONG Mei, Department of Pharmacy, Harbin Medical University Cancer Hospital
LU Liqin, Cancer Center of Zhejiang Provincial People's Hospital

Lead Writer

ZHENG Xiaowei, Department of Pharmacy, Zhejiang Provincial People's Hospital

Consensus Expert Group (in alphabetical order)

BIAN Xiaolan, Department of Pharmacy, Ruijin Hospital, Shanghai Jiaotong University School of Medicine
CHEN Yun, Department of Oncology, Zhejiang Provincial People's Hospital
DONG Mei, Department of Pharmacy, Harbin Medical University Cancer Hospital
FENG Weiyi, Department of Pharmacy, The First Affiliated Hospital of Xi'an Jiaotong University
GAO Yunong, Department of Gynecology and Oncology, Peking University Cancer Hospital
HU Chuanwen, Department of Pharmacy, Zhejiang Provincial People's Hospital
HU Ying, Department of Pharmacy, Zhejiang Provincial People's Hospital
HUANG Ping, Department of Pharmacy, Zhejiang Provincial People's Hospital
HUANG Hongbing, Department of Pharmacy, Sun Yat-sen University Cancer Center
KONG Beihua, Department of Obstetrics and Gynecology, Qilu Hospital of Shandong University
LAO Haiyan, Department of Pharmacy, Guangdong Provincial People's Hospital
LI Guohui, Department of Pharmacy, Cancer Hospital, China Academy of Medical Sciences

LI Zhengxiang, Department of Pharmacy, Tianjin Medical University General Hospital
LIU Jihong, Department of Gynecology, Sun Yat-Sen University Cancer Hospital
LIU Jiyong, Department of Pharmacy, Fudan University Cancer Hospital
LIU Lijuan, Department of Pharmacy, Jiangxi Cancer Hospital
LIU Maobai, Department of Pharmacy, Fujian Medical University Union Hospital
LIU Yuguo, Shandong Cancer Hospital
LU Liqin, Cancer Center of Zhejiang Provincial People's Hospital
PAN Zongfu, Department of Pharmacy, Zhejiang Provincial People's Hospital
SHEN Chengwu, Department of Pharmacy, Shandong Provincial Hospital
SONG Feifeng, Department of Pharmacy, Zhejiang Provincial People's Hospital
SUN Yancai, Department of Pharmacy, Anhui Provincial Cancer Hospital
TAO Gang, Department of Gynecology, Zhejiang Medical and Health Group Hangzhou Hospital
TAO Xia, Department of Pharmacy, Shanghai Changzheng Hospital Affiliated to Naval Medical University
TONG Rongsheng, Sichuan Provincial People's Hospital
WANG Dong, Gynecological Cancer Center, Chongqing University Cancer Hospital
WANG Li, Department of Gynecology and Oncology, Henan Cancer Hospital
WANG Wei, Department of Pharmacy, Zhejiang Provincial People's Hospital
WANG Danbo, Liaoning Cancer Hospital and Institute
WANG Jianliu, Peking University People's Hospital
WANG Yingmei, Department of Obstetrics and Gynecology, Tianjin Medical University General Hospital
WEI Jifu, Department of Pharmacy, Jiangsu Cancer Hospital
WU Lingying, Department of Gynecology and Oncology, Cancer Hospital, China Academy of Medical Sciences
WU Junyan, Department of Pharmacy, Sun Yat-sen Memorial Hospital, Sun Yat-sen University
XIA Jun, Nottingham Ningbo GRADE Center
XU Donghang, Department of Pharmacy, The Second Affiliated Hospital of Zhejiang University School of Medicine
YANG Xiuli, Department of Pharmacy, Zhejiang Provincial People's Hospital
YIN Rutie, Department of Tumor Radiotherapy and Chemotherapy, West China Second Hospital of Sichuan University
YIN Wenjuan, Department of Pathology, Zhejiang Cancer Hospital
ZHANG Bikui, Department of Pharmacy, The Second Xiangya Hospital of Central South University
ZHANG Wenzhou, Department of Pharmacy, Henan Cancer Hospital
ZHANG Yiwen, Department of Pharmacy, Zhejiang Provincial People's Hospital
ZHANG Min, Nursing Department of Zhejiang Cancer Hospital
ZHAO Rongsheng, Department of Pharmacy, Peking University Third Hospital
ZHAO Hongying, Department of Pharmacy, Zhejiang Provincial People's Hospital
ZHENG Xiaowei, Department of Pharmacy, Zhejiang Provincial People's Hospital
ZHOU Yubing, Department of Pharmacy, The First Affiliated Hospital of Zhengzhou University
ZHU Jianqing, Department of Gynecologic Surgery, Zhejiang Cancer Hospital
ZUO Xiaocong, Department of Pharmacy, The Third Xiangya Hospital of Central South University

Data Group
LAN Xinyu, Zhejiang Chinese Medical University
WANG Qi, Zhejiang University of Technology
MA Peiyu, Zhejiang University of Technology
WEI Guoliang, Hangzhou Medical College

Statement of Conflicts of Interest
All authors declare no conflicts of interest.

Acknowledgments
Thanks to Professor MENG Lihua from Chinese Pharmacists Association and Professor WU Yang from Zhejiang Anti-cancer Association for their support and help.

References

[1] McCormick A, Swaisland H. In vitro assessment of the roles of drug transporters in the disposition and drug-drug interaction potential of olaparib[J]. Xenobiotica, 2017, 47(10):903-915. DOI:10.1080/00498254.2016.1241449.

[2] Drug label information of olaparib tablet[DB/OL]. (2022-10-27)[2023-05-01]. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=741ff3e3-dc1a-45a6-84e5-2481b27131aa.

[3] Drug label information of niraparib capsule[DB/OL]. (2023-04-26)[2023-05-01]. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c15c7b7e-4b7f-4489-bbbc-884caeee0669.

[4] Dirix L, Swaisland H, Verheul HM, et al. Effect of itraconazole and rifampin on the pharmacokinetics of olaparib in patients with advanced solid tumors: results of two phase Ⅰ open-label studies[J]. Clin Ther, 2016, 38(10):2286-2299. DOI:10.1016/j.clinthera.2016.08.010.

[5] Pilla Reddy V, Bui K, Scarfe G, et al. Physiologically based pharmacokinetic modeling for olaparib dosing recommendations: bridging formulations, drug interactions, and patient populations[J]. Clin Pharmacol Ther, 2019, 105(1):229-241. DOI:10.1002/cpt.1103.

[6] Lee A. Fuzuloparib: first approval[J]. Drugs, 2021, 81(10):1221-1226. DOI:10.1007/s40265-021-01541-x.

[7] Instructions for Fluzopali Capsules[DB/OL]. (2021-06-22)[2023-05-01]. https://www.hengrui.com/uploads/20220111145544/f.pdf.

Drug label information of fluzoparib capsule[DB/OL]. (2021-06-22)[2023-05-01]. https://www.hengrui.com/uploads/20220111145544/f.pdf.

[8] Chen X, Yang F, Zhao J, et al. Effect of fluconazole on the pharmacokinetics of fuzuloparib: an open-label, crossover study in Chinese healthy male volunteers[J]. Cancer Chemother Pharmacol, 2022, 89(1):141-148. DOI:10.1007/s00280-021-04376-1.

[9] Zhang Q, Kai J, Zhai Y, er al. The impact of rifampicin on the pharmacokinetics of fuzuloparib in healthy Chinese male volunteers[J]. Br J Clin Pharmacol, 2022, 88(1):84-90. DOI:10.1111/bcp.14926.

[10] Mu S, Lin C, Skrzypczyk-Ostaszewicz A, et al. The pharmacokinetics of pamiparib in the presence of a strong CYP3A inhibitor (itraconazole) and strong CYP3A inducer (rifampin) in patients with solid tumors: an open-label, parallel-group phase 1 study[J]. Cancer Chemother Pharmacol, 2021, 88(1):81-88. DOI:10.1007/s00280-021-04253-x.

[11] Instructions for Pampali Capsules[DB/OL]. [2023-05-01]. http://drugs.dxy.cn/drug/I1aW3n5I8mepepmxImZz8M4ujqw==.

Drug label information of pamiparib capsule[DB/OL]. [2023-05-01]. http://drugs.dxy.cn/drug/I1aW3n5I8mepepmxImZz8M4ujqw==.

[12] Madariaga A, Bowering V, Ahrari S, et al. Manage wisely: poly (ADP-ribose) polymerase inhibitor (PARPi) treatment and adverse events[J]. Int J Gynecol Cancer, 2020, 30(7):903-915. DOI:10.1136/ijgc-2020-001288.

[13] Stacher G, Weber U, Stacher-Janotta G, et al. Effects of the 5-HT_3 antagonist cilansetron vs placebo on phasic sigmoid colonic motility in healthy man: a double-blind crossover trial[J]. Br J Clin Pharmacol, 2000, 49(5):429-436. DOI:10.1046/j.1365-2125.2000.00180.x.

[14] Leng QN, Sheng JZ, Ren ZB. TCM diagnosis thoughts and methods on constipation caused by 5-HT_3 receptor antagonist[J]. Clin J Chin Med, 2013, 5(4):113-114. DOI:10.3969/j.issn.1674-7860.2013.04.070.

[15] Lou YY, Du WF, Zhang T, et al. Study on the effect of anti-cold Chinese medicines on the hepatic enzyme P450 and subtypes[J]. J Liaoning Univ Tradit Chin Med, 2018, 20(12):16-19. DOI:10.13194/j.issn.1673-842x.2018.12.004

[16] Gao S, Tang XQ. Research progress on the influence of traditional Chinese medicine on CYP450 enzyme activity[J]. Prac Pharm Clin Remed, 2016, 19(12):1563-1568. DOI: 10.14053/j.cnki.ppcr.201612030.

[17]Zhang B, Zhang LT. Research progress on the effect of traditional Chinese medicine on CYP450 enzyme system in recent years[J]. Pharm Clin Chin Mate Med, 2005, 21(6):92,15. DOI:10.3969/j.issn.1001-859X.2005.06.048.