Exploring and comparing adverse events between PARP inhibitors

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Ovarian cancer remains one of the most challenging malignancies to treat. Targeted therapies such as poly (ADP-ribose) polymerase (PARP) inhibitors have emerged as one of the most exciting new treatments for ovarian cancer, particularly in women with *BRCA1* or *BRCA2* mutations or those without a functional homologous recombination repair pathway. Perhaps the most advantageous characteristic of PARP inhibitors is their mechanism of action, which targets cancer cells on the basis of their inherent deficiencies while seemingly avoiding normally functioning cells. Although health-care providers might assume a low toxicity profile because of their specific mechanism of action, PARP inhibitors are not completely benign and overall show a class effect adverse-event profile. Further complicating this situation, three different PARP inhibitors have been approved by the US Food and Drug Administration since 2014, each with their own specific indications and individual toxicity profiles. The diversity of adverse events seen both within and across this class of drug underscores the importance of having a comprehensive reference to help guide clinical decision making when treating patients. This Review characterises and compares all toxicities associated with each PARP inhibitor, both in monotherapy and in novel combinations with other drugs, with a particular focus on potential management strategies to help mitigate toxic effects. Although the excitement surrounding PARP inhibitors might certainly be warranted, a thorough understanding of all associated toxicities is imperative to ensure that patients can achieve maximal clinical benefit.

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Introduction

The era of treating all patients with cancer with the same treatment is long over. The fact that contemporary management of cancer is increasingly being driven by individualised decision making is not surprising given the deeper understanding of oncogenesis that has emerged in recent years.

Poly (ADP-ribose) polymerase (PARP) inhibitors have the unique ability to selectively kill those cells that have loss of the homologous recombination repair pathway, also referred to as homologous recombination deficiency. Three PARP inhibitors have been approved for use in the USA to treat recurrent epithelial ovarian cancer: olaparib, niraparib, and rucaparib. These drugs rely on the principle of so-called synthetic sickness, which occurs when the deficiency of two or more cellular mechanisms lead to cell death, whereas loss of only one cellular mechanism does not. The exact mechanism for synthetic sickness with PARP inhibitors is still being investigated, although it has been extensively described.[1–4] An additional mechanism of action of PARP inhibition is the process of PARP trapping, in which PARP1 or PARP2 become trapped in DNA damage sites and prevent the recruitment of additional DNA repair proteins. Without the complete set of DNA repair proteins at a damage site, the cell is unable to properly repair its DNA during replication, which can lead to mitotic catastrophe and subsequent cell death.[5] Although all the developed PARP inhibitors (olaparib, niraparib, rucaparib, talazoparib, and veliparib) have shown effective and comparable inhibition of PARP1 and PARP2, they differ in their ability to cause PARP trapping.[6,7] This difference is thought to be the primary reason for the variation of the recommended doses across available PARP inhibitors, as increased PARP trapping has been shown to be associated with high myelosuppresion.[8]

Despite the fact that PARP inhibitors have the same mechanism of action, the specific toxicity profiles between them might differ substantially. Although differences in toxicity can also be found within other classes of drugs, such as the platinum drugs carboplatin and cisplatin, PARP inhibitors inhibit a family of proteins, with each protein having similar yet varied roles. Furthermore, PARP1 has been implicated in circadian metabolic activities and PARP2 has been shown to have a role in the regulation of red blood cell production.[9,10] Since the individual PARP inhibitors have different binding affinities for PARP1, PARP2, and PARP3, even the on-target effects of PARP inhibition can be varied between the members of this class of drugs. Moreover, unlike olaparib and niraparib, rucaparib inhibits PARP1, PARP2, and PARP3. Since PARP3 has been reported to activate the enzymatic activity of PARP1 in the absence of DNA, the additional inhibition of this member of the PARP family might potentiate the effects of rucaparib compared with olaparib or niraparib.[11]

In addition, the association between *BRCA* status and PARP inhibitor toxicities is not well described. As *BRCA1* or *BRCA2* germline mutation carriers have the inability to repair double-strand DNA breaks caused by platinum-based chemotherapy, a possible increase in treatment-related adverse events is a concern. Despite the paucity of prospective data, a retrospective analysis[12] evaluated the effect of an inherited *BRCA1* or *BRCA2* mutation on myelosuppression in 432 patients that received first-line platinum-based chemotherapy. Haematological toxicity did not differ based on *BRCA* mutation status. Whether toxicity of PARP inhibitors is associated with the proportion of patients who achieve a response is also unclear. Further research is required to evaluate the response to PARP inhibition in patients who had

mild-to-moderate versus severe adverse events to determine whether toxicity could be a predictive biomarker.[12]

This Review will provide a comprehensive overview on the indications for the use of each available PARP inhibitor and their individual toxicity profiles, and offer specific management recommendations if adverse events are encountered.

Companion diagnostics

A thorough understanding of companion diagnostics for PARP inhibitors is integral to the appropriate and safe use of this class of drugs in a patient population. Although the definition of a population that would receive no benefit from a PARP inhibitor might not be possible, companion diagnostics for PARP inhibitors allow clinicians to determine which patients have the greatest likelihood of achieving a response. In turn, this information might prove useful in selecting which treatments to use in either the maintenance or recurrent settings.

A substantial challenge inherent to the development of targeted therapies is the ability to predict which patients are most likely to benefit from their use. During the development of PARP inhibitors, researchers believed that only patients with germline *BRCA1* or *BRCA2* mutations would achieve a response, which is exemplified by the 2014 first US Food and Drug Administration (FDA) approval of olaparib and its companion diagnostic BRACAnalysis CDx test (Myriad Genetics, Salt Lake City, UT, USA), designed to detect only germline *BRCA1* or *BRCA2* mutations.[13] Since this initial approval, multiple other clinical trials have identified clinical activity of PARP inhibitors in a subset of patients that have somatic *BRCA1* or *BRCA2* mutations or possess another defect in the homologous recombination pathway.[14–16] The first FDA-approved test to detect homologous recombination deficiency was the myChoice HRD test (Myriad Genetics), which uses next-generation sequencing (NGS) of tumour tissue to create a composite score derived from the presence of loss of heterozygosity, telomeric allelic imbalance, and large-scale transitions. This test is an enhancement of BRACAnalysis CDx because it not only reliably detects germline *BRCA1* or *BRCA2* mutations but can also detect somatic *BRCA1* or *BRCA2* mutations as well as detect homologous recombination deficiency through its evaluation of genomic scarring.

The study by Mirza and colleagues,[15] published in 2016, led to the FDA approval of niraparib for maintenance treatment of recurrent ovarian cancer following response to platinum-based induction therapy, used myChoice HRD to stratify germline *BRCA1* or *BRCA2* patients into homologous recombination deficient or proficient cohorts. The FDA approval of rucaparib was primarily led by a phase 2 trial (ARIEL2)[16] and a phase 3 trial (ARIEL3),[14] which investigated the use of rucaparib in different clinical settings with slightly different cutoffs for the identification of homologous recombination deficiency. ARIEL2 examined rucaparib in the treatment of patients with recurrent ovarian cancer, whereas ARIEL3 examined its use in the maintenance setting.[14,16] To determine the presence of homologous recombination defects in these trials, the authors calculated the percentage of genomic loss of heterozygosity in tumour samples using the T5 NGS assay (Foundation Medicine, Cambridge, MA, USA), and labelled tumours as either those with a high loss of heterozygosity (ie, homologous recombination deficient) or those with a low loss of heterozygosity (ie, homologous recombination proficient) on the basis of a prespecified percentage cutoff. ARIEL2 used a prespecified cutoff greater than 14% to define high loss of heterozygosity, whereas ARIEL3 used a cutoff greater than 16%, optimised from an analysis of loss of heterozygosity and objective response in ARIEL2.[14,16] FoundationOne (Foundation Medicine, MA, USA) also received FDA approval as the first comprehensive genomic profiling test for all solid tumours, which involves massively parallel DNA sequencing of a panel of 324 genes to detect genomic alterations that are potentially therapeutically relevant.

The availability of multiple FDA-approved companion diagnostic tests for PARP inhibitors might lead to confusion in choosing the most appropriate test. One of the main differences is that BRACAnalysis CDx offers a comprehensive analysis of germline *BRCA1* or *BRCA2* mutations but does not measure homologous recombination deficiency and might not identify patients who could potentially benefit from PARP inhibitors, whereas myChoice HRD offers detection of both germline and somatic *BRCA1* or *BRCA2* mutations and a composite homologous recombination deficiency score that can be used to determine eligibility for PARP inhibitors. Moreover, FoundationOne testing provides gene mutation analysis of 324 genes that are implicated in the tumourigenesis of many solid tumours. However, healthcare providers can still use this test, to focus on the genes relevant to ovarian cancer to determine if a patient is likely to respond to PARP inhibition.

Indications for use of PARP inhibitors

The three FDA-approved PARP inhibitors, olaparib, niraparib, and rucaparib, have similar yet slightly different indications for use in recurrent ovarian cancer (figure). Olaparib[17] is indicated for maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy. The SOLO2 trial[18] is the phase 3 trial that, in combination with Study 19,[19] led to the approval of olaparib for this indication in August, 2017. In this approval, SOLO2 provided data in the phase 3 maintenance setting among patients with germline *BRCA1* or *BRCA2* mutations and Study 19 provided data in the phase 2 setting of non-restricted (all-comer) patients following response to platinum-based therapy. Olaparib is also indicated for the treatment of

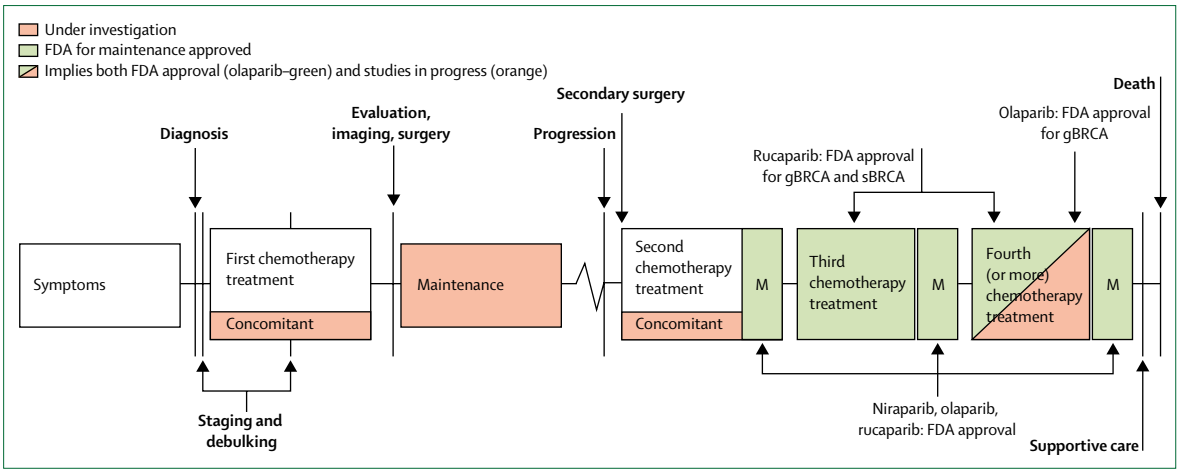

Figure: **Treatment paradigm for the use of poly (ADP-ribose) polymerase (PARP) inhibitors in ovarian cancer**
Olaparib, rucaparib, and niraparib are approved by the US Food and Drug Administration for use in ovarian cancer as a maintenance therapy in the platinum-sensitive recurrent setting. Rucaparib and olaparib are approved for recurrent disease. First-line and first-recurrence therapies are under investigation. FDA=Food and Drug Administration. gBRCA=germline BRCA mutation. M=maintenance. sBRCA=somatic BRCA mutation.

adult patients with deleterious or suspected deleterious germline *BRCA*-mutated advanced ovarian cancer who have been treated with three or more lines of chemotherapy. This indication was approved in December, 2014, after the phase 2 trial, Study 42.[20]

Niraparib[21] is indicated for maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. The NOVA trial is the phase 3 trial that led to the approval of this indication in March, 2017.[15]

Rucaparib[22] is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. ARIEL3 is the phase 3 trial that led to the approval of this indication in April, 2018.[14] Also, it is indicated for the treatment of adult patients with deleterious *BRCA* mutation (germline, somatic, or both) associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies. The ARIEL2 and Study 10 trials were the phase 2 trials that led to the approval of this indication in December, 2016.[16]

In addition to the three PARP inhibitors approved by the FDA, two others are in the developmental stage. Veliparib is a potent inhibitor of PARP1 and PARP2 and has been evaluated in a phase 2 trial for the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who have a germline *BRCA1* or *BRCA2* mutation.[23] Based on the results from this study, the upfront and maintenance settings are being evaluated in the phase 3 trial, Gynaecologic Oncology Group (GOG)-3005, which completed accrual in January, 2018. Talazoparib also targets PARP1 and PARP2, and results from a phase 1 trial that included patients with ovarian cancer who have a *BRCA* mutation showed that the proportion of patients who achieved an overall response was 42%.[24] This result has led to multiple phase 2 and 3 trials examining talazoparib for various cancer types, such as breast, head and neck, prostate, pancreatic, lung, haematological cancers, and advanced solid tumours. Most notably, the results from the EMBRACA phase 3 clinical trial (NCT01945775) in patients with HER2-negative locally advanced or metastatic breast cancer with deleterious or suspected deleterious germline BRCA mutations showed a significant increase in progression-free survival (8·6 *vs* 5·6 months, p<0·001) and the proportion of patients achieving a response (62·6 *vs* 27·2%, p<0·001) in patients receiving talazoparib compared with patients receiving standard chemotherapy.[25]

Pharmacokinetics and pharmacodynamics of PARP inhibitors

Niraparib has been shown to be metabolised in the liver by carboxylesterase-catalysed amide hydrolysis,[26] whereas rucaparib and olaparib are primarily metabolised by the cytochrome P450 enzymatic pathway (CYP) (table 1). Importantly, these two PARP inhibitors are metabolised to varying degrees by specific CYPs, leading to a unique set of drug–drug interactions for each PARP inhibitor. These interactions occur because of cytochrome enzyme inhibition or induction. Conversely, PARP inhibitors themselves can cause the inhibition or induction of CYP enzymes. On the one hand, common antibiotics and antifungals cause potent CYP inhibition (eg, ciprofloxacin inhibits CYP1A2; and clarithromycin, erythromycin, and ketoconazole inhibit CYP3A4/5), in addition to citrus foods, such as grapefruit and Seville oranges, that inhibit CYP3A4/5.[35] On the other hand, anticonvulsant drugs, such as phenytoin and carbamazepine, are potent

	Enzymes used for metabolism	Effect of PARP inhibitors on other drugs	Effect of other drugs on PARP inhibitors	Effect on renal and hepatic uptake transporters	Pharmacokinetics	Effect with food
Rucaparib[14,27,28]	Is metabolised predominantly by CYP2D6, and by CYP1A2 and CYP3A4 to a lesser extent	Reversibly inhibits CYP1A2, CYP2C19, CYP2C9, and CYP3A; increased area under the curve (ie, total drug exposure over time) of caffeine, midazolam, warfarin, omeprazole, and digoxin*[29]	No known clinically significant effect	Inhibits MATE1 and MATE2-K (potent effect), and OCT1 (moderate effect)	Mean half-life=17 h; median time to maximal concentration=1·9 h	Coadministration of a high-fat meal delayed Tmax by 2·5 h and increased area under the curve by 38%, although between-subject variability of the area under the curve and maximum concentration were the same in high-fat intake and fasting groups
Olaparib[30–32]	Is metabolised primarily by CYP3A4	Induces CYP2B6 and inhibits CYP3A†[31]	CYP3A inhibitors increased area under the curve (ie, total drug exposure over time) in 170% (strong effect) or 121% (moderate effect); CYP3A inducers decreased area under the curve in 87% (strong effect) or 60% (moderate effect)	Inhibits OATP1B1, OCT1, OCT2, OAT3, MATE1, and MATE2-K	Mean half-life=14·9 h (tablet) or 11·9 hours (capsule); median time to maximal concentration=1·5 h	Coadministration of a high-fat meal delayed Tmax by 2·5 h but did not alter the extent of olaparib absorption
Niraparib[26,33,34]	Is metabolised by carboxylesterase-catalysed amide hydrolysis (primarily hepatic metabolism)	Has negligible effect on CYP450 enzymes†[33]	No formal drug interaction studies have been performed with niraparib	No known interaction with the major hepatic or renal transporters	Mean half-life=~36 h; median time to maximal concentration=3 h	Coadministration of a high-fat meal did not affect the pharmacokinetics

*Data from clinical studies. †Data from in vitro studies only.

Table 1: **Absorption, distribution, metabolism, and excretion of poly (ADP-ribose) polymerase (PARP) inhibitors**

inducers of CYP1A2, CYP2C19, and CYP3A4/5.[35] The review of all concomitant medications and the instruction of patients regarding specific foods and drugs that should be avoided before the use of PARP inhibitors are important measures that need to be considered before initiating treatment. Notably, olaparib was initially delivered via a capsule formulation that was used in Studies 19, 41, and 42, whereas the newer tablet formulation has been used in the SOLO1 and SOLO2 clinical trials. It is important to note that the dosing and pharmacokinetic and pharmacodynamic properties are not the same between the tablet and capsule formulations (as shown in table 1),[36] and substitutions on a milligram-to-milligram basis should not be made. To help prevent this confusion, the capsules are no longer manufactured and are being phased out from clinical practice. Regarding ingestion, olaparib and niraparib can both be taken with or without food.[30,32–34] Rucaparib can also be taken with or without food, but its pharmacokinetic parameters are different when taken with food versus without food, probably because of its solubility in the small intestine.

PARP inhibitors have been shown to cause teratogenicity, and embryo-fetal toxicity and death in animal reproduction studies, and should, therefore, be avoided during pregnancy.[28,30,33] Furthermore, women of reproductive age should be counselled to use effective birth control during treatment and until 6 months after the last dose of PARP inhibitor. Data regarding the concentration of PARP inhibitors in human breast milk are not available but because of potential serious adverse events, lactating women should not breastfeed during treatment or until 2 to 4 weeks after the last dose of the drug.[28,30,33]

Toxicities and approaches for management

Haematological toxicities

Haematological toxicities are a very common class effect of PARP inhibitors (table 2). They tend to occur early after treatment initiation with recovery after a few months. In patients treated with niraparib, haematological adverse events represented the majority of grade 3 and 4 events, and were the most common cause of dose modification, interruption, and discontinuation.[15]

Anaemia is the most common haematological toxicity among PARP inhibitors. In the three phase 3 maintenance trials,[14,15,18] all-grade anaemia occurred in 85 (44%) of 195 patients treated with olaparib, in 184 (50%) of 367 patients treated with niraparib, and in 139 (37%) of 372 patients treated with rucaparib. Grade 3 and 4 adverse events were slightly higher for niraparib (93 [25%] of 367 patients), followed by rucaparib (70 [19%] of 372 patients) and olaparib (38 [19%] of 195 patients). Haemoglobin concentrations were lower with olaparib and rucaparib until the fifth or sixth cycle and then stabilised with continued treatment.[14,18] Anaemia might be an on-target adverse effect related to PARP2 inhibition and erythrogenesis. Farres and colleagues[10] showed that deletion of PARP2 impairs the differentiation of erythroid progenitors and reduces the life expectancy of erythrocytes in mice when erythropoietin plasma concentrations are increased, suggesting that exogenous supplementation might not be the most efficacious method to manage anaemia, although (to our knowledge) no studies in humans are available. Transfusions are generally recommended for symptomatic anaemia and for haemoglobin values of more than 7 g/dL. Neutropenia was the third most common haematological toxicity observed

	Niraparib (n=367)		Placebo (n=179)		Olaparib (n=195)		Placebo (n=99)		Rucaparib (n=372)		Placebo (n=189)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Anaemia	184 (50%)	93 (25%)	12 (7%)	0	85 (44%)	38 (19%)	8 (8%)	2 (2%)	139 (37%)	70 (19%)	11 (6%)	1 (<1%)
Thrombocytopenia	225 (61%)	124 (34%)	10 (6%)	1 (<1%)	27 (14%)	2 (1%)	3 (3%)	1 (1%)	104 (28%)	19 (5%)	5 (3%)	0
Neutropenia	111 (30%)	72 (20%)	11 (6%)	3 (2%)	38 (19%)	10 (5%)	6 (6%)	4 (4%)	67 (18%)	25 (7%)	9 (5%)	2 (1%)
Nausea	270 (74%)	11 (3%)	63 (35%)	2 (1%)	148 (76%)	5 (3%)	33 (33%)	0	280 (75%)	14 (4%)	69 (37%)	1 (<1%)
Constipation	146 (40%)	2 (<1%)	36 (20%)	1 (<1%)	40 (21%)	0	20 (20%)	3 (3%)	136 (37%)	7 (2%)	45 (24%)	2 (1%)
Vomiting	126 (34%)	7 (2%)	29 (16%)	1 (<1%)	73 (37%)	5 (3%)	19 (19%)	1 (1%)	136 (37%)	15 (4%)	28 (15%)	2 (1%)
Decreased appetite	93 (25%)	1 (<1%)	26 (15%)	1 (<1%)	43 (22%)	0	11 (11%)	0	87 (23%)	2 (<1%)	26 (14%)	0
Abdominal pain	83 (23%)	4 (1%)	53 (30%)	3 (2%)	47 (24%)	5 (3%)	31 (31%)	3 (3%)	111 (30%)	9 (2%)	49 (26%)	1 (<1%)
Diarrhoea	70 (20%)	1 (<1%)	37 (21%)	2 (1%)	64 (33%)	2 (1%)	20 (20%)	0	118 (32%)	2 (<1%)	41 (22%)	2 (1%)
Dyspepsia	42 (11%)	0	17 (10%)	0	22 (11%)	0	8 (8%)	0	54 (15%)	1 (<1%)	9 (5%)	0
Dysgeusia	37 (10%)	0	7 (4%)	0	52 (27%)	0	7 (7%)	0	146 (39%)	0	13 (7%)	0
Fatigue	218 (59%)	30 (8%)	74 (41%)	1 (<1%)	128 (66%)	8 (4%)	39 (39%)	2 (2%)	258 (69%)	25 (7%)	83 (44%)	5 (3%)
Dizziness	61 (17%)	0	13 (7%)	0	26 (13%)	1 (<1%)	5 (5%)	0	54 (15%)	0	15 (8%)	1 (<1%)
Headache	95 (26%)	1 (<1%)	17 (10%)	0	49 (25%)	1 (<1%)	13 (13%)	0	67 (18%)	1 (<1%)	30 (16%)	1 (<1%)
Dyspnoea	71 (19%)	4 (1%)	15 (8%)	2 (1%)	23 (12%)	2 (1%)	1 (1%)	0	50 (13%)	1	14 (7%)	0
Nasopharyngitis	41 (11%)	0	13 (7%)	0	21 (11%)	0	11 (11%)	0	41 (11%)	0	6 (3%)	2 (1%)
Cough	55 (15%)	0	8 (5%)	0	33 (17%)	1 (<1%)	5 (5%)	0	54 (15%)	0	25 (13%)	0
Arthralgia	43 (12%)	1 (<1%)	22 (12%)	0	29 (15%)	0	15 (15%)	0	57 (15%)	2 (1%)	24 (13%)	0

Table 2: **Toxicities of poly (ADP-ribose) polymerase (PARP) inhibitors described in the three phase 3 trials**

in the phase 3 maintenance trials. Although all-grade neutropenia was observed in 18–30% of patients, grade 3 and 4 adverse events were higher with niraparib (72 [20%] of 367 patients) compared with rucaparib (25 [7%] of 372 patients) and olaparib (10 [5%] of 195 patients).[14,15,18]

Thrombocytopenia of any grade is also more pronounced with niraparib, occurring in 225 (61%) of 367 patients, compared with 104 (28%) of 372 patients with rucaparib and 27 (14%) of 195 patients with olaparib. Grade 3 or 4 thrombocytopenia occurred in 124 (34%) of 367 patients with niraparib, compared with 19 (5%) of 372 with rucaparib and 2 (1%) of 195 patients with olaparib.[14,15,18]

Berek and colleagues,[37] in a study published in 2018, reported updated information on the toxicities associated with niraparib. Baseline bodyweight and platelet counts were each identified as predictors of dose modification in patients treated with niraparib at 300 mg/day. Specifically, patients with a baseline bodyweight of less than 77 kg or platelet counts less than 150 000 cells per mL had more events of grade 3 or more thrombocytopenia during the first month (35% *vs* 12%) compared with patients with baseline values above both these thresholds. Overall, thrombocytopenia typically occurred during the first month of treatment. The authors suggested that patients with either of these characteristics might benefit from a starting dose of 200 mg/day. The cause of thrombocytopenia in the context of PARP inhibitor use has been shown to be associated with a reversible decrease in megakaryocyte proliferation and maturation.[37,38] Importantly, however, the platelet decrease with either niraparib or rucaparib occurred predominantly during the first cycle and concentrations plateaued after cycle 2 or 3.[14,15,37] No data are available for platelet trends with olaparib.

In general, all patients starting a PARP inhibitor or those who undergo a dose modification should have a complete blood count with differential monthly to monitor haematological toxicity (table 3, panel).[28,30] The niraparib FDA label recommends that those patients starting niraparib should have weekly testing in the first month to monitor platelet concentrations.[33]

Gastrointestinal toxicities

Gastrointestinal adverse events are common for all PARP inhibitors, with nausea being the most prevalent (table 2).[14,15,18] Nausea was reported by 148 (76%) of 195 patients treated with olaparib, 280 (75%) of 372 patients treated with rucaparib, and 270 (74%) of 367 patients treated with niraparib. Symptoms were mainly mild and only 3–4% of patients had grade 3 or 4 nausea.[14,15,18] The treatments for gastrointestinal toxicities are mostly based on expert opinion and are similar to the management of chemotherapy-induced gastrointestinal toxicities.[39–41]

Patients should be counselled about the high potential for nausea and to be vigilant or even prophylactically prevent its occurrence. Daily prokinetic and antihistamine (eg, 5-HT3) drugs are generally helpful to ameliorate symptoms. Having a light meal with an antiemetic 60 min before taking the PARP inhibitor can also be helpful. Recalcitrant nausea or vomiting can

	Grade 1	Grade 2	Grade 3 or 4
Anaemia[33]	Monitor and continue PARP inhibitor	Withhold for maximum of 28 days and monitor blood counts weekly until haemoglobin returns to ≥9 g/dL; resume PARP inhibitor at reduced dose; discontinue if haemoglobin has not returned to acceptable concentrations after 28 days	Consider transfusion; withhold for maximum of 28 days; resume PARP inhibitor at reduced dose; if already at the lowest dose, discontinue; discontinue if haemoglobin has not returned to acceptable concentrations after 28 days
Neutropenia[33]	Monitor and continue PARP inhibitor	Withhold for maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1500 cells/μL; resume PARP inhibitor at reduced dose; discontinue if neutrophils have not returned to acceptable concentrations after 28 days	Withhold for maximum of 28 days; resume PARP inhibitors at reduced dose; if already at the lowest dose, discontinue; discontinue if neutrophils have not returned to acceptable concentrations after 28 days
Thrombocytopenia[33]	First occurrence (platelets <100 000/μL): CBC should be monitored at least weekly depending on the degree of platelet decrease, although twice weekly might be considered;* withhold for maximum of 28 days and monitor blood counts weekly until platelets return to ≥100 000/μL; resume PARP inhibitor at same or reduced dose; if platelets <75 000/μL, reduce dose. Second occurrence (platelets <100 000/μL): withhold for maximum of 28 days and monitor blood counts weekly until platelets return to ≥100 000/μL; resume PARP inhibitor at reduced dose; discontinue if platelets have not returned to acceptable concentrations after 28 days or if patient was on lowest dose	Withhold for maximum of 28 days and monitor blood counts weekly until platelets returns to ≥100 000/μL; resume PARP inhibitor at reduced dose; if platelets <75 000/μL, reduce dose	Platelet transfusion for concentrations of platelets <10 000/μL or bleeding; resume PARP inhibitor at reduced dose; if already at the lowest dose, discontinue; consider interruption of anticoagulation and antiplatelet drugs

CBC=complete blood count. *Although these guidelines are specific from the niraparib packaging label for management of niraparib haematological adverse events (especially the weekly CBC upon initiation), they can also be applied to the other PARP inhibitors.

Table 3: **Management for haematological adverse events for poly (ADP-ribose) polymerase (PARP) inhibitors (grading by Common Terminology Criteria for Adverse Events, version 5·0)***

Panel: Management of non-haematological adverse events (according to the Common Terminology Criteria for Adverse Events) for poly (ADP-ribose) polymerase PARP inhibitors*

Grade 1[28,30,33]
- Continue PARP inhibitor
- Symptomatic treatment if necessary

Grade 2[28,30,33]
- Continue PARP inhibitor
- Consider dose interruption, reduction, or both, if toxicity remains uncontrolled despite symptomatic or prophylactic therapies

Grade 3 or 4[14,15,18]
- Withhold until resolution of adverse event for niraparib is classified grade 1 or less for olaparib (ie, resolved or grade 1 event), or grade 2 or less for rucaparib (resolved, grade 1, or grade 2)
- Might continue treatment if adverse event is nausea, vomiting, or diarrhoea, and controlled on medication
- If treatment was interrupted, consider dose reduction upon resumption (particularly if after second time withholding)

Grade 3 or 4 lasting more than 28 days with the lowest dose of PARP inhibitor[7,27,30]
- Discontinue PARP inhibitor

* Although these guidelines are specific for niraparib (except where indicated in the panel), they can also be applied to the other PARP inhibitors.

be addressed through appropriate use of a variety of antiemetic drugs, such as metoclopramide, prochlorperazine, phenothiazine, dexamethasone, olanzapine, haloperidol, or lorazepam. The neurokinin-1 receptor antagonist aprepitant should be avoided with olaparib since it is a strong CYP3A4 inhibitor and might affect olaparib plasma concentrations.[26,34]

Other frequent gastrointestinal symptoms reported by patients are constipation, vomiting, and diarrhoea. They were reported of any grade by 20–40% of patients, but grade 3 or 4 toxicities occurred in 4% of patients or less with all three drugs. Over-the-counter medications, such as senna (twice daily) or polyethylene glycol 3350 for constipation, or loperamide for diarrhoea, can be used to treat these symptoms; however, patients must be counselled to contact the medical team if symptoms do not ameliorate. Any grade abdominal pain was reported between 23 and 30% of patients with olaparib having the most grade 3 or 4 events (3%) of the three PARP inhibitors; however, this symptom is difficult to isolate from the underlying disease process and proper evaluation to exclude other causes should be considered. Dyspepsia is more common in patients using rucaparib (54 [15%] of 372 patients) compared with olaparib (22 [11%] of 195 patients) or niraparib (42 [11%] 367 patients), although severe toxicity is rare (<1%). Proton pump inhibitors and prokinetics can be prescribed to alleviate these symptoms. Dysgeusia was seen more frequently with rucaparib, occurring in 146 (39%) of 372 patients. Dietary changes and improvement in oral hygiene can be helpful to ameliorate symptoms.

Renal toxicities

Another common adverse event that occurs with PARP inhibitors is an increase in creatinine concentrations.

Rucaparib use in the ARIEL3 trial resulted in an elevation of creatinine (any grade) in 15% of patients versus 2% in the placebo group, which was typically observed within the first few weeks of treatment and then stabilised with continued cycles. Rucaparib inhibits MATE1 and MATE2-K renal transporter proteins, which have a role in the secretion of creatinine.[14] Similarly, veliparib interacts with these same proteins as well as the OCT2 transporter, which is related to the renal secretion of cations and anions. In the SOLO2 trial,[18] 21 [11%] of 195 patients treated with olaparib had grades 1 or 2 elevation in creatinine (no grades 3 and 4) compared with 1% in the placebo group. Notably, niraparib was not associated with elevated serum creatinine.[33] Importantly, elevations of serum creatinine might not reflect a true decline in glomerular filtration rate (GFR) or kidney insufficiency. Expert opinion recommends that if concern exists for renal disease based on clinical signs, symptoms, biochemical, or radiographic abnormalities, other methods to assess GFR, such as radionucleotide scan, should be used. If GFR is appropriate (ie, GFR is typical or not in congruence with the elevated creatinine), dose reductions or interruptions can be avoided. In addition, all-grade hypomagnesemia was reported in 28 (14%) of 195 patients on olaparib and 40 (11%) of 372 patients on rucaparib, probably due to their inhibition of cation transporters.

Fatigue

Fatigue is a nearly universal toxicity for all PARP inhibitors and seems to be a class effect. 59–69% of patients had fatigue of any grade with the three approved PARP inhibitors, and grade 3 or higher fatigue was seen in 30 (8%) of 367 patients using niraparib, 25 (7%) of 372 patients using rucaparib, and 8 (4%) of 195 patients using olaparib.[14,15,18] Expert opinion recommends that non-pharmacological treatments, such as exercise, massage therapy, and cognitive behavioural therapy, can be effective in reducing symptoms. A systematic review and a phase 2 trial showed that for more symptomatic patients, pharmacological interventions with psychostimulants, such as methylphenidate and ginseng, can be prescribed.[43,44]

Investigational toxicities

Common laboratory abnormalities associated with PARP inhibitors are increased amounts of cholesterol and serum aminotransferase. Rucaparib led to increased cholesterol of any grade in 40–84% of patients, although only 2–4% of patients had grade 3 or 4 elevation.[16,28] Persistent hypercholesterolemia should be managed with appropriate statin therapy as indicated,[45] with careful attention to liver enzymes that can also be elevated PARP inhibitors. ARIEL3 showed that 126 [34%] of 372 patients treated with rucaparib had an increase in either alanine aminotransferase or aspartate aminotransferase of any grade, with 39 [10%] of 372 patients having a grade 3 or 4 event. These increases, however, were generally transient, self-limiting, and not associated with other signs of liver toxicity. Niraparib has also been reported to cause an any-grade increase of alanine aminotransferase in 36% of patients or of aspartate aminotransferase in 28% of patients, with 2% of patients having a grade 3 or 4 elevation, in contrast with olaparib, which has an incidence of 5% elevation of alanine aminotransferase and 2% elevation of aspartate aminotransferase.

Timing of adverse events

Briefly, adverse events led to treatment discontinuation in 21 (11%) of 195 patients on olaparib versus 2 (2%) of 99 patients on placebo in the SOLO2 trial,[18] 19 [9%] of 204 patients on rucaparib in the ARIEL2 trial,[16] 50 [13%] of 372 patients on rucaparib versus 3 [2%] of 189 patients on placebo in the ARIEL3 trial,[14] and 54 [15%] of 367 patients on niraparib versus 4 [2%] of 179 patients on placebo in the NOVA trial.[15]

With niraparib, toxicities leading to dose reductions occurred early in treatment and most patients reached their ultimate individual-adjusted dose after the third month of treatment (after month 3, the incidence of grade >3 events decreased to 0·7% for thrombocytopenia and 1·6% for neutropenia). Non-haematological toxicities also decreased after the third month of treatment, including nausea (61·9% of patients at month 1 *vs* 1·6% at month 4), vomiting (19·6% *vs* 2·0%), and fatigue (32·4% *vs* 4·9%).[37]

Similar to niraparib, rucaparib toxicities also occurred early on in treatment that were resolved in later cycles. The supplementary data from ARIEL3 showed that the proportion of patients with anaemia was highest in the first five cycles with a return to baseline haemoglobin concentrations afterwards. Platelet concentrations were the lowest in cycles 1 and 2 (primarily grade 1 or 2), but also began to return to baseline during cycle 3 without any further drops. Alanine aminotransferase, aspartate aminotransferase, and bilirubin concentrations also had the largest increase from cycle 1 to cycle 2 (also primarily grade 1 or 2 elevations), but these concentrations decreased quickly thereafter with resolution around cycle 20. Creatinine concentrations also increased the most from cycle 1 to cycle 2 (approximately 30% above baseline), but stabilised thereafter. Elevated creatinine is probably more an effect of the inhibition of renal transporters than true kidney injury.[14]

The safety data regarding olaparib have remained relatively similar since the initial phase 2 trial that was published in 2012.[46] In that trial (Study 19), the most common adverse events in the olaparib group compared with placebo were nausea, vomiting, fatigue, and anaemia. Further analyses of these common safety events showed that the majority were mild to moderate grade (1 or 2), which occurred within the first 4–8 weeks of treatment, and were generally transient and able to be managed symptomatically without the need for dose reduction.[31,47]

Less common toxicities

The spectrum of infrequent adverse events continues to expand as the use of PARP inhibitors increases, particularly in novel combination regimens. Some of the more common, yet overall infrequent, toxicities of PARP inhibitors affect the neurological, respiratory, musculoskeletal, cutaneous, and cardiovascular systems.

Neurological toxicities

Neurological symptoms are not reported as common toxicities related to PARP inhibitors, although their frequency cannot be entirely ignored. Headache and insomnia are often reported with the use of olaparib, niraparib, and rucaparib. These symptoms are usually mild but can have a substantial impact on quality of life. Headache was reported in 95 (26%) of 367 patients with niraparib in the NOVA trial,[14] 49 (25%) of 195 patients with olaparib in the SOLO2 trial,[15] and 67 [18%] of 372 patients in the ARIEL3 trial[18] using rucaparib. Across the same trials, tthe occurrence of insomnia was highest in patients using niraparib (89 [24%] of 367 patients), followed by 53 (14%) of 372 patients using rucaparib, and 11 (6%) of 195 patients using olaparib. Dizziness was also reported at a frequency of 17% (61 of 367 patients) for niraparib, 15% (54 of 372 patients) for rucaparib, and 13% (26 of 195 patients) for olaparib.

Excessive activation of PARP enzymes can result in a type of neuronal death caused by the overexpression of calcium-permeable AMPA receptors in the hippocampal region, an activation that is similar to that seen in neurodegenerative disorders.[48] Preclinical studies have reported that these effects could be prevented with PARP1 but not PARP2 inhibitors.[48] In addition, PARP1 has shown to have an important role in maintaining the transcription of circadian genes, with PARP1 inhibition leading to a disconnect in key circadian rhythm transcriptional components.[9] These molecular studies might help to explain some of the neurological symptoms reported by patients on PARP inhibitors.

Since most symptoms are not severe, symptomatic therapies alone might lead to resolution. It is also important to educate patients to manage their expectations before starting PARP inhibitor therapy. For symptoms that persist despite symptomatic management, we recommend following the guidelines and dose reductions outlined in the panel, based on the FDA label for the three PARP inhibitors.[28,30,33]

Respiratory toxicities

Respiratory side-effects are not commonly associated with PARP inhibition; however, they should not be overlooked. Dyspnoea of any grade was reported in 71 (19%) of 367 patients in the niraparib group of the NOVA trial,[15] 14 (7%) of 189 patients using rucaparib in the ARIEL3 trial,[14] and 23 (12%) of 195 patients in the SOLO2 trial[18] using olaparib. Dyspnoea was usually mild and was reported as grade 3 or more in only 1% of patients across the three trials.

Another respiratory symptom associated with the three approved PARP inhibitors is cough. In the NOVA[15] and SOLO2 trials,[18] 15% of patients had coughing using niraparib and olaparib, with a frequency of 16% of patients using rucaparib in the ARIEL3 trial.[14] Similar to dyspnoea, cough was usually mild and reported as grade 3 in 1% of patients on olaparib only. Nasopharyngitis and upper respiratory tract infection have also been reported with PARP inhibitors. Nasopharyngitis grade 1 or 2 was reported in 11% of patients using niraparib or olaparib and upper respiratory tract infection was reported in 11% of patients using rucaparib.[14,15,18] Both toxicities were mild with no grade 3 or 4 events. The use of over-the-counter antihistamines should be considered for nasopharyngitis treatment. Pneumonitis, including fatal cases, occurred in less than 1% of patients treated with olaparib. The mechanism of respiratory toxicities is not well known; however, preclinical data have shown that PARP activation is associated with bronchial hyperreactivity and airway remodelling.[49] If a patient presents with new or worsening respiratory symptoms such as cough, dyspnoea, or both, the PARP inhibitor should be interrupted and other causes of symptoms, such as pulmonary embolus or pneumonia, should be ruled out. If pneumonitis is suspected or confirmed by endoscopic lavage, the PARP inhibitor should be held. Treatment should follow accepted guidelines for drug-induced pneumonitis (eg, corticosteroids, antibiotics, or both).[50] If the symptoms are mild, reinstitution of PARP therapy might be attempted and carefully monitored.

Musculoskeletal toxicities

Musculoskeletal and connective tissue toxicities are common to different types of antineoplastic drugs. Arthralgia and back pain were reported in 11–15% of patients in the three phase 3 PARP inhibitor trials, although toxicities grade 3 or higher occurred in only 1% of patients.[14,15,18]

Cutaneous toxicities

Although cutaneous toxicities have been reported for all three approved PARP inhibitors, only the ARIEL3 trial specifically catalogued toxicities associated with rucaparib use. The authors reported any-grade photosensitivity reactions (64 [17%] of 372 patients), pruritis (47 [13%] of 372 patients), rash (46 [12%] of 372 patients), and peripheral oedema (39 [10%] of 372 patients).[14] The toxicities were mild with only 1% or less grade 3 adverse events. It is important to counsel patients about the importance of sun protection with suncream and hats, and also to liberally use skin moisturisers when initiating PARP inhibitor therapy.

Although rare, allergic reactions to PARP inhibitors consisting of urticaria have been reported. In severe cases, a desensitization protocol for olaparib has been

	Starting dose	1st dose reduction	2nd dose reduction	3rd dose reduction	Presence of hepatic impairment*	Presence of renal impairment†
Niraparib[15,33]	300 mg daily‡	200 mg daily	100 mg daily	Discontinue	Mild: no dose adjustment; moderate or severe: unknown	Mild or moderate: no dose adjustment; severe or ESRD: unknown
Rucaparib[14,28]	600 mg twice daily	500 mg twice daily	400 mg twice daily	300 mg twice daily	Mild: no dose adjustment; moderate or severe: unknown	Mild or moderate: no dose adjustment; severe or ESRD: unknown
Olaparib[18,30]	300 mg twice daily	250 mg twice daily	200 mg twice daily	Discontinue	Mild: no dose adjustment; moderate or severe: unknown	Mild: no dose adjustment; moderate: 200 mg twice daily; severe or ESRD: unknown

*Hepatic impairment defined according to Organ Dysfunction Working Group criteria. †Mild: creatinine clearance=60–89 mL/min. Moderate: creatinine clearance=30–59 mL/min. Severe: creatinine clearance <30 mL/min. ESRD: end-stage renal disease. ‡Although not yet in the US prescribing information, for patients with baseline body weight of less than 77 kg or a baseline platelet count less than 150 000/mL, starting dose of 200 mg daily should be considered.

Table 4: **Dose reduction guide**

previously developed which can be used to prevent discontinuation of treatment.[51]

Cardiovascular toxicities

The PARP inhibitor most associated with cardiovascular toxicity is niraparib. Cardiovascular toxicities included hypertension, tachycardia, and palpitations. In the NOVA trial,[15] 71 (19%) of 367 patients treated with niraparib had any-grade hypertension (compared with 8 [4·5%] of 179 patients in the placebo group), 30 (8%) patients had grade 3 or 4 hypertension, and 38 (10%) patients had any-grade palpitations. The mechanism of cardiovascular toxicity is not well characterised but might be due to an off-target disruption of dopamine and norepinephrine metabolism. The FDA label for niraparib states that it can bind to dopamine, norepinephrine, and serotonin transporters, leading to inhibited uptake of dopamine and norepinephrine within cells.[33] Conversely, however, PARP1 activation has been implicated in the pathogenesis of myocardial dysfunction and hypertension,[52] and also associated with angiotensin-II activation.[53] These studies suggest a possible cardioprotective effect of PARP inhibitor therapy. Regardless, patients on niraparib should have their blood pressure and heart rate monitored monthly for the first year of treatment and periodically thereafter, particularly if they have a history of cardiovascular disease.[33] Hypertension should be managed with antihypertensive medications and adjustment of PARP inhibitor dosing (tables 3, 4).[28,30,33]

Secondary malignancies

As the primary mechanism of PARP inhibition involves interference with DNA repair pathways, secondary malignancies, such as myelodysplastic syndrome and acute myeloid leukaemia, are severe adverse events that have a substantial impact as they increase the burden of the patient's condition, require discontinuation of a treatment that might be sustaining their lives, and complicates any further treatment. Fortunately, as the clinical experience expands under various indications and durations of therapy, both these severe adverse events appear only rarely with an incidence of 0·5%–1·4%, and usually after long-term treatment.[14,15,18] All patients who developed myelodysplastic syndrome or acute myeloid leukaemia received previous platinum-based chemotherapy or other DNA-damaging drugs, meaning that it is difficult to specifically identify PARP inhibitors as the cause of secondary malignancies. Some of these patients also had a history of bone marrow dysplasia or another primary malignancies. [14,15,18] If a patient develops pancytopenia while using PARP inhibitors, an appropriate investigation should be done to rule out other causes, such as nutritional deficiencies or viral infections. Unexplained cases should prompt referral for bone marrow aspiration to evaluate for dysplasia. If myelodysplastic syndrome or acute myeloid leukaemia is confirmed, the drug must be discontinued.

Quality of life

Given the wide spectrum of adverse events observed with PARP inhibitors, health-care providers might assume a negative impact on quality of life. Importantly, however, the improvement in disease-specific symptoms following cancer regression and also the typical drug tolerability observed after dosage titration, is generally associated with an improved quality of life. Objectively assessing this effect is especially important among studies with largely asymptomatic patients, specifically those using maintenance therapy. A quality of life (QoL) study[54] on olaparib reported that mean quality-adjusted progression-free survival and time without clinically significant symptoms of toxicity were both significantly longer with olaparib compared with placebo (quality-adjusted progression-free survival: 13·96 months [SD 10·96] *vs* 7·28 months [5·22, 95% CI 4·98–8·54], p<0·0001; time without symptoms of toxicity: 15·03 months [SD 12·79] *vs* 7·7 months [6·42, 95% CI 4·7–8·96], p<0·0001). This unique analysis of quality-adjusted progression-free survival subtracted the impact of adverse events from both treatment and placebo groups, and the progression-free survival endpoint remained significantly increased in the olaparib group. Furthermore, the adjusted average mean change in Trial Outcome Index (which measures physical and functional wellbeing) from baseline over the first 12 months was –2·90 (95% CI –4·13 to –1·67) with olaparib and –2·87 (–4·64 to –1·10) with placebo, showing no detrimental loss of quality of life in patients using olaparib in the

maintenance setting.[54] In addition, Oza and colleagues[55] reported QoL data from patients treated with niraparib as maintenance therapy. The results showed no difference in QoL parameters between the niraparib and placebo groups from initial screening up to pre-progression, as assessed by the scores from the Functional Assessment of Cancer Therapy-Ovarian Symptoms Index and from the European QoL Five-Dimension Five-Level questionnaire. Aside from nausea, all reported symptoms improved or remained stable during niraparib treatment.

In combination with other agents

Similar to nearly all contemporary therapy for patients with recurrent ovarian cancer, efficacy decreases with successive lines of therapy, particularly among those deemed platinum-resistant. The proportion of patients with *BRCA1* or *BRCA2* mutations who achieve a response using olaparib as monotherapy in the platinum-resistant setting is approximately 31–33%.[56,57] Efforts to improve these results are the focus of several ongoing trials; however, combination therapy raises the potential for unique or augmented adverse events. Considering these concerns, most ongoing PARP combination strategies are using rationally designed biologicals. For this Review, we have selected clinical trials that use PARP inhibitors in doublet or triplet combinations.

PARP inhibitors and antiangiogenic drugs

The rationale for combining PARP inhibitors with anti-angiogenic drugs has two purposes. Firstly, PARP inhibition has been shown to decrease angiogenesis[58] and secondly, studies have reported that both hypoxic conditions and VEGFR3 inhibitors induce down-regulation of homologous recombination repair proteins.[59–62] A phase 2 trial[63] combining cediranib (30 mg daily) with olaparib (200 mg twice daily) in recurrent, platinum-sensitive ovarian cancer, in comparison with olaparib monotherapy, showed a significant increase in progression-free survival in the combination group (17·7 *vs* 9·0 months, p=0·005); however, adverse events of grade 3 or higher were reported by 70% of patients. The most common of these were hypertension (41% *vs* 0%), diarrhoea (23% *vs* 0%), and fatigue (27% *vs* 11%).

Additional trials are in progress to assess this doublet combination. The NRG-GY004 (NCT02446600) and NRG-GY005 (NCT02502266) will evaluate olaparib and cediranib, the Niraparib Versus Niraparib-bevacizumab Combination in Women With Platinum-sensitive Epithelial Ovarian Cancer (also known as AVANOVA, NCT02354131) will evaluate the combination of niraparib and bevacizumab, and the Platine, Avastin and OLAparib in 1st Line trial (also known as PAOLA-1, NCT02477644) is evaluating the addition of olaparib versus placebo for maintenance treatment after upfront platinum chemotherapy in patients receiving bevacizumab.

PARP inhibitors and PI3K drugs

Dysregulation of the PI3K/AKT/mTOR pathway is common in epithelial ovarian cancer, particularly in clear cell and endometrioid carcinomas, with alterations occurring in up to 30% of patients.[64] A phase 1 trial (NCT01623349) examined a pan-PI3K inhibitor (BKM120) in combination with olaparib and included patients with recurrent high-grade serous ovarian cancer or any recurrent ovarian histology with a germline *BRCA* mutation. Overall, the combination was well tolerated with the most common toxicities being nausea in 54 (78%) of 69 patients and fatigue in 45 (65%) of 69 patients. Expected PI3K inhibitor toxicities were hyperglycaemia in 27 (39%) of 69 patients, transaminase elevations in 14 (20%) of 69 patients, depression in 25 (36%) of 69 patients (4 [6%] of 69 with grade >3), and anxiety in 19 (28%) of 69 patients. The most common toxicities related to olaparib were expectedly haematological and mostly grade 1 and 2.[65] A phase 1b trial (NCT02208375) is in progress to examine either an AKT inhibitor (AZD5363) or an mTOR inhibitor (AZD2014) in combination with olaparib for metastatic triple-negative breast cancer or recurrent ovarian or endometrial cancers.

PARP inhibitors and immunotherapy

Immunotherapy as monotherapy in platinum-resistant epithelial ovarian cancer has shown only modest responses.[66–68] Combination of immune checkpoint inhibitors and PARP inhibitors might have a more promising efficacy than PARP therapy alone since tumours with alterations in the homologous recombination pathway have increased mutational burden, predicted neoantigen load, and expression of programmed cell death 1 or programmed cell death ligand-1.[69] A phase 2 trial[70] combining olaparib and durvalumab is in progress for patients with platinum-sensitive, recurrent epithelial ovarian cancer with a germline *BRCA* mutation. Preliminary data showed that 20 (63%) of 32 enrolled patients had a complete or partial response and, overall, a low incidence of grade 3 or more or immune-mediated adverse events. The most common adverse events of grade 3 or more were anaemia (4 [12%] of 34 patients) and increase lipase (3 [9%] of 34 patients), along with any-grade hypothyroidism (5 [15%] of 34 patients) and rash (4 [12%] of 34 patients).[70] In the platinum-resistant setting, a phase 2 trial[71] evaluated niraparib with pembrolizumab and showed that 18 (62%) of 29 patients achieved either a partial response or stable disease. Preliminary safety data revealed that grade 3 or more adverse events occurred in 16 [44%] of 36 patients. The most common adverse events of any grade were fatigue, nausea, constipation, anaemia, and thrombocytopenia, and those for grade 3 or more were anemia (17%), fatigue (6%), and thrombocytopenia (3%).[71]

PARP inhibitors and chemotherapy

PARP inhibitors have also been combined with various chemotherapy drugs to increase response and efficacy.

A phase 2 trial[72] of patients with recurrent platinum-sensitive ovarian cancer compared olaparib, carboplatin, and paclitaxel followed by olaparib maintenance versus carboplatin or paclitaxel alone. Any-grade adverse events occurred in all patients in the combination group compared with 73 [97%] of 75 patients in the chemotherapy alone group. The adverse events that were substantially greater in the combination group were alopecia (60 [74%] of 81 patients *vs* 44 [59%] of 75 patients), nausea (56 [69%] of 81 patients *vs* 43 [57%] of 75 patients), fatigue (52 [64%] of 81 patients *vs* 43 (57%) of 75 patients), diarrhoea (34 [42%] of 81 patients *vs* 20 [27%] of 75 patients), headache (27 [33%] of 81 patients *vs* 7 [9%] of 75 patients), peripheral neuropathy (25 [31%] of 81 patients *vs* 14 [19%] of 73 patients), and neutropenia (40 [49%] of 81 patients *vs* 29 [39%] of 75 patients). With the exception of neutropenia (40 [49%] of 81 patients with grade ≥3), most adverse events were mild.[72] A phase 1b–2 trial[73] with olaparib and weekly metronomic carboplatin and paclitaxel in heavily pretreated patients with ovarian cancer relapse was safely administered. Olaparib was administered orally in capsule formulation at 150 mg dose (twice daily) administered orally for three consecutive days each week of a 4-week cycle, with paclitaxel and carboplatin being given intravenously for three out of the 4 weeks at 60 mg/m² and AUC2 (ie, area under the plasma drug concentration–time curve), respectively.[73] The common grade 3 toxicities caused by this regimen were neutropenia, anaemia, and thrombocytopenia with no cardiac, hepatic, or pulmonary toxicities reported. Additional phase 1 trials have evaluated olaparib with different chemotherapy drugs.[73–77] Unfortunately, these combinations resulted in substantial toxicities that have discouraged future trials for this combination.

Veliparib has also been examined in a phase 1 trial[78] in combination with carboplatin and gemcitabine for patients with metastatic or unresectable breast or ovarian cancer. The safety profile was similar to that seen with carboplatin only, with the most common adverse events being haematological toxicities and nausea.[78] The phase 3 trial GOG-3005 (NCT02470585) examining veliparib combined with carboplatin and paclitaxel has recently completed accrual and results are awaited.

Other novel PARP inhibitors combination trials

Considering the promising results from PARP inhibitor doublets with antiangiogenics or immune checkpoint inhibitors, multiple trials examining the efficacy of PARP inhibitors in combination with more than one drug have been undertaken. A phase 1 trial examined the use of veliparib, carboplatin, and liposomal doxorubicin, followed by the addition of bevacizumab in platinum-sensitive recurrent ovarian cancer. The addition of veliparib to chemotherapy resulted in dose limiting toxicities of thrombocytopenia and neutropenia in a few patients. Adding bevacizumab, however, proved to be very toxic with the majority of patients having dose-limiting toxicities. The addition of veliparib to chemotherapy in the dose escalation phase resulted in dose-limiting toxicities of thrombocytopenia (4 of 27 patients) and neutropenia (3 of 27 patients). Adding bevacizumab to the maximal tolerated dose of the three other drugs, however, proved to be very toxic with 9 of 12 patients having dose limiting toxicities (grade 4 thrombocytopenia, grade 3 hypertension, grade 5 sepsis, and prolonged neutropenia).[79]

Currently, two phase 1 trials in the upfront setting are in progress with triplet combinations: carboplatin and paclitaxel, veliparib, and bevacizumab (GOG-9923, NCT00989651) and carboplatin and paclitaxel, rucaparib, and bevacizumab (NCT03462212). Carboplatin, veliparib, and bevacizumab will be evaluated in platinum-sensitive recurrent ovarian cancer (NCT01459380).

Another hypothesis that is currently being investigated is the use of PARP inhibitors after disease progression in patients who have been previously treated with a different PARP inhibitor. Since all PARP inhibitors have distinct chemical structures with various off-target effects, patient treatment with an alternative PARP inhibitor after disease progression or who had no clinical response might be a feasible treatment strategy. As more information emerges on the various mechanisms of adaptive PARP inhibitor resistance, including upregulation of other PARP proteins, different PARP inhibitors might have the ability to uniquely target these so-called escape PARP proteins (ie, PARP proteins that escape being inhibited by PARP inhibitors).

Search strategy and selection criteria

We compiled information for this Review from PubMed and Medline using the search terms "ovarian cancer", "PARP inhibitors", "PARP1", "PARP2", "antioangiogenic agents", "immunotherapy", "immune checkpoints", "PARP inhibitor combinations", "PIK3CA agents", "P3KCA and PARP", "toxicity", "side effects", and "unique PARP inhibitor toxicities". We included papers published from March 26, 1992, to Nov 29, 2018 without language restrictions. Information regarding clinical trials for poly (ADP-ribose) polymerase (PARP) inhibitors and their inclusion in combined regimens was obtained from: http://www.clinicaltrials.gov and http://www.nci.nih.gov/clinical-trials. Relevant published abstracts from scientific meetings were also considered.

Conclusion

Although PARP inhibitors have a common class effect toxicity profile, individual PARP inhibitors have unique adverse events that require a thorough understanding of the specific toxicities, as well as knowledge regarding monitoring and dose regime customisation. Typically, toxicity is easily managed with supportive care and dose reduction, and the therapeutic window for all drugs is wide, which provides scope for dose modification.

Appropriate counselling should be provided before starting treatment to manage the expectations of both patients and caregivers to prevent treatment interruption or premature discontinuation. The majority of adverse events typically occur during the first cycles of treatment and patients should be closely monitored during this time. QoL does not appear to be affected by specific or global symptoms in any of the phase 3 maintenance trials. Combination regimens have been investigated with the purpose of improving efficacy while maintaining a safe toxicity profile, but data are awaited to make conclusive recommendations on monotherapy versus combination treatment options.

PARP inhibitors are a new class of chemotherapeutic drugs which have transformed the oncology landscape. A thorough knowledge of their mechanism, indications, and safety profile—particularly in emerging clinical trials—is imperative for their safe use in patients.

Contributors

All authors contributed in the literature search, creation of the content, choice of figures, and writing and revising of this manuscript. CJL and GZDM both contributed equally to this manuscript and share co-first authorship.

Declaration of interests

RLC reports personal fees from Cell Medica, DelMar Pharmaceuticals, Geistlich, Genmab, ImmunoGen, Perthera, Takeda, Tesaro, TRM Oncology, Clovis, Aravive Biologics Inc, ArQule, AstraZeneca, Bayer, Caris Life Sciences, Eisai-Morphotek, Gamamabs, Janssen, Medscape, Merck, Myriad, and Roche, outside the submitted work; and grants from Clovis, AstraZeneca, Janssen, Merck, and Roche, outside the submitted work. AKS is part of the advisory board of Kiyatec, is a stockholder for Biopath, a consultant at Tesaro, and reports grants from M-Trap, all outside the submitted work. The remaining authors declare no competing interests.

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