"Latest Advancements in Ovarian Cancer: The Role of Olaparib in Management".

Module IV

Safety and Management of Side Effects with Olaparib

CONTENT

Poly (ADP-ribose) Polymerase Inhibitors: Overview

The use of poly (ADP-ribose) polymerase (PARP) inhibitor therapy is standard care in the management of patients with various malignancies including ovarian, breast, prostate, and pancreatic cancers. PARP inhibitors have been approved in different settings for patients with specific hereditary pathogenic variants, most notably homologous recombination repair pathways such as BRCA1 and BRCA2 genes.

The vast experience with PARP inhibitors (olaparib, niraparib, rucaparib) has been in the management of epithelial ovarian cancer (EOC). Studies first focused on the treatment of recurrent EOC and then their use as a maintenance strategy after platinum-based therapy. In 2020, ASCO published a comprehensive guideline on PARP inhibitor therapy in the management of EOC after ground-breaking studies in the first-line maintenance setting.1 In 2022, a rapid update to the guidelines was issued to provide context to emerging survival data and revisions to the US Food and Drug Administration (FDA) indications, which occurred in the treatment setting and the maintenance therapy setting for the BRCA1/2 wild-type population. These are summarized in Table 1 and Figure 1.

The goal of this article is to highlight side effects of PARP inhibitors and focus on strategies to improve tolerance.

Adverse Side Effects of PARP Inhibitors

It is challenging to obtain reliable real-world estimates of PARP inhibitor adverse events (AEs; frequency, grade) and dose modifications. It is likely that real-world events are similar to those reported in randomized clinical trials; however, given that strict eligibility criteria often lead to trial participants who are younger and fitter compared with community practice, it is possible that side effects are under-reported in clinical trials.

The largest study of real-world experience was a longitudinal retrospective cohort analysis of the US MarketScan Commercial and Medicare Supplemental Databases. The adverse effects were generally consistent with the safety reports from the randomized trials, which are, however, somewhat lower than those reported in clinical trials, as common toxicities (nausea, fatigue) may not be recorded in health care claims data unless severe enough for medical intervention. There are inherent limitations of such studies because of potential biases with using health care data, which are recorded for billing as opposed to research purposes. Dose reductions were required in 23%, 35%, and 29% of patients on olaparib (n = 637), niraparib (n = 538), and rucaparib (n = 227), respectively, which are lower than those reported in clinical trials (Fig 2).For example, in the PRIMA trial of maintenance niraparib after response to first-line chemotherapy, 71% of participants required a dose reduction, which was similar to the 66% requiring a dose reduction in the NOVA trial of maintenance therapy in participants with platinum-sensitive recurrent ovarian cancer after response to chemotherapy.

An alternative source of real-world data is national databases of adverse drug reactions (ADRs) that are reported to regulatory authorities by clinicians even if they are uncertain whether there is a causal link with the drug. However, only a minority of ADRs are reported and may underestimate important AEs. Nonetheless, data repositories such as the FDA adverse event reporting system (FAERS) designed to support postmarketing surveillance provide important insights into ADRs including rare events that may not be observed in clinical trials.8 Our discussion and commentary are based on the key adverse effects reported in the pivotal ovarian cancer clinical trials that led to the regulatory approvals for olaparib, niraparib, and rucaparib, but we also highlight relevant safety data including postmarketing reporting of ADRs that have emerged from real-world experience and provide guidance on management.

There have not been any head-to-head comparisons of PARP inhibitors in randomized trials, and we can only perform cross-comparison on the basis of the reported literature. They appear to be equally effective at least on the basis of comparison of hazard ratios across trials for similar indications in ovarian cancer. The three approved PARP inhibitors for ovarian cancer share several common adverse effects because of a class effect including nausea, fatigue, and anemia, but there are also some notable differences likely because of variations in their polypharmacology and off-target effects. They exhibit different binding affinities to PARP isoforms and may also inhibit transporters, kinases, and ion channels to a greater or lesser extent. Rucaparib appears to be associated with higher incidence of adverse drug reactions reported probably because of many off-target effects.

There is high inter individual variability in pharmacokinetic exposure levels observed with olaparib, rucaparib, and niraparib, which could also account for some of the variability in adverse effects observed between patients as higher levels of exposure appear to be associated with greater toxicity, particularly hematologic.

The defining characteristics of the three PARP inhibitors are summarized in Table 2 and 3 lists the frequency of AEs reported in the registration clinical trials, whereas Figure 2 lists the frequency of dose interruptions, reductions, and discontinuations in different disease settings. Table 4 lists the recommended management for common AEs associated with PARP inhibitors. It is challenging to interpret the adverse effects reported in all clinical trials as they are typically presented in dense tables and include a long list of adverse effects including grading documented by clinicians over the long duration of the clinical trial. It is not possible to ascertain the timing, duration, and trajectory over time of the adverse effects from these tables or determine how they individually affect adherence and tolerability. Furthermore, it is important to acknowledge that there may be significant discordance in the frequency and grading of adverse effects reported by patients and clinicians.

This article is not intended to be a definitive source for detailed prescribing information, or all the possible adverse effects associated with PARP inhibitors, but rather a summary of the more common and important adverse effects and approaches to their management. There are several excellent papers published on this topic, which are referenced for interested readers. In addition, comprehensive prescribing information is provided by the pharmacologic companies for each of the approved PARP inhibitors. It is beyond the scope of this review to include adverse effects associated with PARP inhibitors combined with other agents.

Safe Prescribing and Strategies to Reduce the Likelihood of Adverse Effects

First and foremost, it is important to be proactive and take care to prevent and/or reduce the likelihood and impact of adverse effects associated with PARP inhibitors. This could allow patients to continue treatment and potentially derive clinical benefit while enjoying good quality of life. It is essential to ensure that the patient is fully educated and well informed before commencing a PARP inhibitor and understands the potential benefits, as well as the possible adverse effects, and what is recommended to mitigate adverse effects. In addition, the patient should be made aware of the importance of close surveillance particularly in the first 12 weeks when many of the adverse effects occur such as nausea, vomiting, and hematologic toxicities including anemia and thrombocytopenia and require prompt intervention and management (Table 4).

There are several factors to take into consideration before commencing a patient on maintenance treatment with a PARP inhibitor including the choice of PARP inhibitor, the starting dose, and when to commence maintenance therapy. Ideally, the patient should have recovered as much as possible from chemotherapy and should not start treatment <28 days after a last cycle chemotherapy to allow bone marrow recovery. The clinical trials allowed patients to commence maintenance therapy within 8-12 weeks depending on the trial. In SOLO2, the predictors for reduced dose intensity included nausea at baseline and a performance status of 1 and delaying the start of treatment until symptoms are controlled would be prudent in such patients. In NOVA, a weight of <77 kg and platelet counts of <150,000 μL were associated with greater hematologic adverse effects with 300 mg, once daily of niraparib, and this has led to recommendations to commence niraparib at 200 mg, once daily in patients who fit these criteria. In the maintenance trials of PARP inhibitors in ovarian cancer, patients typically had to meet eligibility criteria including a hemoglobin of ≥10.0 g/dose level with no blood transfusion in the past 28 days, an absolute neutrophil count of ≥1.5 × 109/L, a platelet count of ≥100 × 109/L, a total bilirubin level of ≤1.5 × upper limit of normal (ULN), and a serum creatinine level of ≤1.5 × ULN. These eligibility criteria should be kept in mind when prescribing a PARP inhibitor. Although there is more flexibility in clinical practice than in clinical trials, it would be prudent to adhere as closely as possible to these criteria in practice.

Doses may also need to be modified on the basis of the PARP inhibitor being prescribed depending on renal and hepatic function and concomitant medications (Table 2). For example, in patients with moderate renal impairment, olaparib should be started at a reduced dose of 200 mg twice a day, but dose reduction is not required for niraparib or rucaparib. Olaparib and rucaparib appear to be safe in patients with moderate hepatic impairment, but it is recommended that niraparib is reduced to 200 mg, once daily. There are no data in patients with severe hepatic impairment, and it is advisable to avoid PARP inhibitors if this is the case. It is particularly important to take note of all concomitant medications as there may be important drug-drug interactions particularly in patients on olaparib. Olaparib is primarily metabolized by CYP3A, and rucaparib is primarily metabolized by CYP2D6 and, to a lesser extent, by CYP1A2 and CYP3A4, whereas niraparib is metabolized by carboxylesterases. Inhibitors or inducers of CYP3A4 may interact with olaparib, and the dose of olaparib should be reduced if being coadministered with a strong or moderate CYP3A4 inhibitor.

If a strong CYP3A inhibitor must be coadministered, the recommended olaparib dose reduction is to 100 mg, twice daily; if a moderate CYP3A inhibitor must be coadministered, the recommended olaparib dose reduction is to 150 mg, twice daily.

The patient should be carefully monitored for AEs. Strong or moderate inducers of CYP3A4 should be avoided in patients on olaparib. There are good sources that can provide guidance on which drugs could interact with olaparib. Dietary recommendations are also required for, in particular, advising patients on olaparib to avoid Seville oranges, starfruit, and grapefruit as they inhibit CYP3A4J5. In addition, over-the-counter medications such as St John's Wort, which is among the most commonly used herbal medications in the United States, should be avoided as it is an inducer of CYP3A4. It is important to take care in the choice of antibiotics if required later in patients on olaparib because of potential drug-drug interactions (eg, ciprofloxacin, erythromycin) and a pharmacist should be consulted if in doubt. There is also a risk for drug-drug interactions when rucaparib is coadministered with substrates of multidrug and toxin extrusion transporters MATE-1 and MATE-2K and the organic ion transporters OCT1 and OCT2 such as metformin. It is suggested that dose adjustments and close monitoring of patients on rucaparib should be considered for CYP 1A2, CYP2C9, and CYP3A4 substrates particularly for drugs with a narrow therapeutic index such as theophylline.

Managing Adverse Effects of PARP Inhibitors

GI Adverse Effects

A recent meta-analysis of phase II and III randomized trials with PARP inhibitors across all cancer types found that PARP inhibitors significantly increased the risk of all-grade nausea, vomiting, diarrhea, and decreased appetite although not constipation. Patients with ovarian cancer have a higher risk of all-grade nausea and vomiting compared with other cancers for reasons that are unclear. There is a paucity of real-world data on the incidence of GI side effects with PARP inhibitors apart from relatively small single-institution reports, which mirror the experience in clinical trials. There is a tendency to report only severe adverse effects in the FAERS or similar reporting systems in other countries, and it is likely that GI side effects would be under-reported in them.

Nausea and vomiting.

Nausea and, to a lesser extent, vomiting are among the most common adverse effects associated with all the three FDA-approved PARP inhibitors (olaparib, niraparib, and rucaparib) in patients with ovarian cancer and thought to be mediated through off-target kinase inhibition. They are a class effect and reported in over 75% of patients although grade 3 or 4 nausea and vomiting are uncommon at 1%-2% (Table 3). According to National Comprehensive Cancer Network (NCCN) guideline criteria, they would all be considered moderately high emetogenic agents although they are quite different from chemotherapy on which the guidelines are based.

Nausea typically occurs within the first few days to weeks of starting treatment, is usually low grade in most patients, and lessens and/or resolves over time although it may persist in a subset. In patients who only develop these symptoms of nausea and vomiting after the first 3 months of starting treatment, alternative causes such as tumor progression should be excluded. The median time to first onset of nausea with olaparib tablets in the SOLO1 trial was 4 days (range, 0.03-21.49 months), and the median duration was 1.4 months. The median time to first onset of vomiting was 1.46 months (range, 0.03-20.60 months), and the median duration was 2 days. Relatively few patients discontinue PARP inhibitors because of nausea or vomiting, and proactive efforts should be taken to prevent and treat nausea and vomiting given the high incidence across all studies. In SOLO1, 3% of patients discontinued olaparib because of nausea, which was similar in the placebo arm (2%), and 1.9% ceased because of vomiting.

Nonetheless, even low-grade nausea and vomiting can affect quality of life particularly if persistent, and it is therefore important to educate and inform the patient of these adverse effects including the time course and trajectory over time, the approaches to mitigate them, and strategies to prevent or lessen their impact.

There have not been any controlled trials of antiemetics in patients treated with PARP inhibitors, and guidance is based on expert opinion and experience (Table 4).

First and foremost, supportive treatment including antiemetics for prophylaxis and treatment are usually effective and dose interruption and dose reduction were only required in 5% of patients in SOLO1 for nausea and in none for vomiting. Antiemetics such metoclopramide or domperidone or olanzapine are usually sufficient in most patients, whereas serotonin 5-hydroxytryptamine-3 receptor antagonists may be of value in selected patients for a short duration but are commonly associated with constipation.

There are anecdotal reports that pyridoxine (vitamin B6), which is commonly used for pregnancy-associated nausea and vomiting, may be effective in some patients and is cheap and safe. Dexamethasone is rarely used if ever needed and ideally avoided. The neurokinin-1 receptor antagonist aprepitant should be avoided with olaparib as it is a CYP3A4 inhibitor and can interact with it. Anecdotally, advising patients to take the PARP inhibitor with food or shortly after eating and administering a prokinetic agent such as metoclopramide 30-60 minutes before the PARP inhibitor can help prevent or reduce nausea, which is prevalent in the first few weeks of starting treatment. In patients on niraparib, which is administered once a day, taking the capsules at night before bed may be associated with less nausea and may be complemented by taking metoclopramide 30 minutes before if needed. In some patients with troublesome nausea, dose interruptions can be helpful and if ongoing despite antiemetics, dose reductions are usually effective. Patients who had dose reductions for any reasons in clinical trials could not re-escalate to the starting dose, whereas this may be considered in clinical practice for adverse effects such as nausea or vomiting although it would be ill advised if the dose reduction was for grade 3 or 4 anemia or thrombocytopenia. It should be noted that recent analyses showed no adverse outcomes with respect to progression-free survival in patients with protocol-mandated dose reductions or interruptions for adverse effects.

Other GI AEs.

There are several other GI adverse effects including reduced appetite, dysgeusia constipation, diarrhea, abdominal pain, and symptoms of reflux. These can differ between the three PARP inhibitors (Table 3). For example, there was more constipation with niraparib on the basis of ADR reports in the United Kingdom. These adverse effects can be managed effectively on the basis of standard practice, for example, proton pump inhibitors or prokinetic agents such as metoclopramide for reflux symptoms, laxatives for constipation, and loperamide for diarrhea. GI symptoms may also herald recurrence of ovarian cancer and include cramping abdominal pain, bloating, nausea, and vomiting.

Fatigue

Fatigue is a very common adverse effect associated with all PARP inhibitors and has been reported to occur in up to 60%-70% of patients with most having low-grade fatigue. For example, in SOLO1, 64% of patients reported any-grade fatigue compared with 42% on placebo, with 4% of patients having grade 3 or 4 fatigue on olaparib and 2% on placebo. Perhaps more important than the percentage of patients reported to have fatigue over the duration of the trial are the timing, duration, and trajectory over time. This was analyzed by Colombo et al who reported that about 40% of patients experienced fatigue at 1 month after starting olaparib, which was mostly low grade, but importantly persisted over 2 years and was about twice as high as a placebo. Interestingly, the findings are somewhat different from the responses of patients in SOLO1 to the question (GP1) in functional assessment of cancer therapy - ovarian, “I have a lack of energy,” which could be considered as a surrogate for fatigue.

Almost 80% of patients on olaparib reported lack of energy compared with 70% on placebo, which was mostly mild-moderate in both groups with a similar number of patients reporting more severe symptoms in the olaparib and placebo arms over 2 years. These data underscore the high prevalence and impact of fatigue/lack of energy in ovarian cancer survivors including those not on a PARP inhibitor and the need to address this symptom. It is beyond the scope of this review to cover management in detail, but approaches include exercise programs and cognitive behavioral therapy as well as excluding reversible and treatable causes such as anemia, hypothyroidism, and depression. Insomnia is also very common in ovarian cancer survivors and could exacerbate symptoms of fatigue (see Table 4 and NCCN guidelines).

Hematologic Adverse Effects

Hematologic adverse effects including anemia, neutropenia, and thrombocytopenia are common with all the PARP inhibitors, but there are some notable differences between them. A recent meta-analysis that included over 9,000 patients enrolled in 29 randomized controlled trials reported that PARP inhibitors significantly increased the risk of all-grade anemia (risk ratio (RR), 2.32; 95% CI, 1.78 to 3.01; P < .00001), neutropenia (RR, 1.69; 95% CI, 1.38 to 2.07; P < .00001), and thrombocytopenia (RR, 2.54; 95% CI, 1.87 to 3.45; P < .00001). Inhibition of PARP-2, in particular, as well as PARP trapping, is believed to be responsible at least in part for the hematologic toxicities.In addition, thrombocytopenia may also be related to the volume of distribution (Vd) and bone marrow exposure, which could explain the higher risk of thrombocytopenia with niraparib as it has a Vd value of 1,074/L compared with 420/L for rucaparib and 158/L for olaparib.

Close monitoring of patients particularly in the first 12 weeks after commencing a PARP inhibitor is required as hematologic adverse effects usually occur early but not invariably, and regular blood counts should continue while patients are on treatment. Anemia is the most common hematologic toxicity observed with PARP inhibitors and typically is macrocytic, and although it is not due to folate or B12 deficiency, grade 3/4 anemia was observed in 22% of patients on olaparib, 27% of patients on rucaparib, and 31% of patients on niraparib in the first-line maintenance therapy ovarian cancer trials. Anemia should be managed with dose interruptions and dose reductions if dose interruption for symptomatic anemia is required. Transfusions should be used if the hemoglobin level falls to <7 g/dL accompanied by a dose reduction (Table 4).

Thrombocytopenia is also an important adverse effect. All-grade thrombocytopenia was observed in 11% of patients in SOLO1, 24% in ATHENA, and 46% in PRIMA. More importantly, grade 3 or 4 thrombocytopenia was reported in 29% of patients in the PRIMA trial, 7% in ATHENA, and 1% in SOLO1. Given the high incidence of thrombocytopenia with niraparib, it is recommended that patients with baseline platelet counts of <150,000/μL and/ a body weight of <77 kg should be treated with a reduced dose of 200 mg, once daily instead of 300 mg, once daily as they appear to have a higher risk of thrombocytopenia. In the PRIME trial, which is a first-line maintenance trial of niraparib vs placebo that was performed in China, the incidence of grade 3 or 4 thrombocytopenia was 14% using the reduced dose of niraparib according to the above criteria. It is worth noting that in the PRIME trial, which used individualized starting doses of niraparib, 40% of patients commenced on 200 mg, once daily still required further dose reductions. The median time to first dose reduction or interruption was 29 days. Dose reductions did not compromise patient outcomes.

The niraparib prescribing information advises that patients should have weekly full blood counts in the first month of starting niraparib as thrombocytopenia typically occurs early, then monthly for the next 11 months, and periodically thereafter. If the platelet count falls to <100 × 109/L, niraparib should be discontinued until the platelet count increases to above 100,000/μL, and if it falls to <75 × 109/L, it should be restarted with a dose reduction once the level rises to >100,000/μL, provided that the count has recovered within 28 days (Table 4). The prescribing information also recommends platelet transfusions if the platelet count drops to <10 × 109/L. If patients are on anticoagulants or antiplatelet agents, then consider interrupting these agents and have a lower threshold for platelet transfusions. Thrombopoietin receptor agonists such as avatrombopag have been reported to rapidly mitigate niraparib-associated thrombocytopenia and, in a small case series, enabled patients to continue therapy.The dose interruption criteria are somewhat different with olaparib and rucaparib, and prescribing recommendations are that treatment should be temporarily discontinued only if the platelet count falls <50 × 109/L and recommenced once it has recovered at either the same dose or a dose reduction depending on how low and how long the thrombocytopenia persists, with guidance provided in prescribing information for each agent. Close monitoring is recommended for platelet count between 50-75 × 109/L, and dose interruption can be considered at the clinician's discretion.

Grade 3/4 neutropenia is common (20% with niraparib in PRIMA; 9% with olaparib in SOLO1, and 15% with rucaparib in ATHENA), and febrile neutropenia is rare.Grade 3 or 4 neutropenia is managed with dose interruption until the platelet count recovered to >1.5 × 109/L and dose reduction as well. Growth factors are not required.

Cardiovascular Adverse Effects

The most important cardiovascular adverse effect is hypertension. Niraparib is the only PARP inhibitor reported to cause hypertension, which may be due to an off-target inhibition of the kinase DYRK1A, which may increase levels of neurotransmitters in the dopaminergic system. Hypertension was reported in 17% of patients in the PRIMA trial, with only 6% being grade 3 or greater. The median time to first onset was 43 days in PRIMA, and there were no discontinuations because of hypertension. Hypertension can be managed with antihypertensive agents, but care should be taken to ensure that blood pressure is well controlled before commencing niraparib in patients with a history of hypertension. On commencing niraparib, blood pressure should be monitored regularly, at least weekly for the first 2 months, then monthly for the first year, and periodically thereafter. It should be noted that rare cases of hypertensive crises were reported postmarketing and could develop as early as within the first month of niraparib. In cases of hypertensive crisis or medically significant hypertension that cannot be adequately controlled with antihypertensive therapy, niraparib should be discontinued.

Arrhythmias including tachycardia and palpitations have also been reported with niraparib. Postmarketing ADR reports include rare cases of hypotension with olaparib and rucaparib and arrhythmias with rucaparib.

Neurologic Adverse Effects

Headaches have been reported in between 20% and 25% of patients treated with olaparib, niraparib, and rucaparib (Table 3). However, the incidence is similar to that reported in the placebo arms of all the trials. For example, in SOLO1, headache was reported in 23% of patients on olaparib and 24% on placebo and was in the majority low-grade and likely incidental rather than related. Rarely, psychiatric adverse effects have been reported in postmarketing reports including mania, anxiety, and depression. They have been reported with all PARP inhibitors although there was a trend suggesting that they may be higher with niraparib, which may be due to its higher blood brain barrier penetration. Posterior reversible encephalopathy syndrome has been reported with niraparib in 0.1% of patients treated and can occur in association with hypertension or with normal blood pressure during the first month of niraparib.The diagnosis should be suspected in patients who present with seizures, headaches, cortical blindness, or visual disturbance and should be confirmed with an magnetic resonance imaging. This is potentially life-threatening, and niraparib should be ceased and not restarted.

Laboratory Abnormalities That May Occur on PARP Inhibitors

There are a number of abnormal nonhematologic laboratory results that may occur in patients on PARP inhibitors and can vary depending on the PARP inhibitor. An elevated creatinine (grade 1 or 2) is observed in 10%-15% of patients on olaparib and rucaparib although not niraparib. This is due to inhibition of renal transporter proteins such as MATE 1 and MATE 2 and does not necessarily imply a decline in glomerular filtration rate or require dose modification, but alternative causes should be excluded. Rucaparib is commonly associated with elevated levels in ALT/AST, with elevated levels occurring in just over 40% of patients in ATHENA-MONO. These mostly grade 1 or 2 and transient but grade 3 or 4 elevations occur in 10%, which requires dose interruptions until levels are grade 2 or lower and dose reduction. Elevated ALT/AST is also observed in about 11% of patients treated with niraparib but almost always low grade. Dose interruption/reductions are not required for grade 1 or 2 elevations in ALT/AST. Elevated cholesterol levels are common with rucaparib, but grade 3 or 4 is reported in only 2%-4% of patients. Statins may be required depending on the level and other risk factors.

Myelodysplastic Syndrome and AML

Treatment-related myeloid neoplasms (t-MNs), myelodysplastic syndrome (MDS), and AML are the most significant and clinically important adverse effects that have been associated with PARP inhibitors. A recent meta-analysis that included 5,693 patients treated with a PARP inhibitor and 3,406 with placebo reported that PARP inhibitors increased the risk of MDS and AML with an overall risk of 2.63 (CI, 1.13 to 6.14; P = .026). The incidence of MDS/AML was 0.73% across all PARP inhibitors compared with 0.47% in controls. The risk is related in part to the number of previous lines of chemotherapy, with a lower incidence of MDS/AML observed in the first-line maintenance trials compared with the recurrent setting. In SOLO1, which has the longest follow-up of all the first trials, one additional case was reported in the 7-year follow-up since the primary analysis in 2018 in the olaparib arm and 1 case in the placebo arm.The overall incidence of MDS/AML was 1.5% in the olaparib arm (n = 260) and 0.8% in the placebo arm (n = 130) in SOLO1.Similar findings have been reported in PAOLA, PRIMA, and ATHENA-MONO. By contrast, the 5-year follow-up of SOLO2 reported that 8% of 195 patients were diagnosed with MDS (5%) or AML (3%) compared with 4% treated with placebo (n = 99). Some of the patients in the placebo arm were diagnosed with AML/MDS after receiving subsequent chemotherapy and a PARP inhibitor.
The authors of the meta-analysis referred to above also interrogated the WHO pharmacovigilance database, which included 178 cases of MDS/AML, and looked at median treatment duration, latency, presenting features, and outcomes. There was clinical information available for only about 30% of cases; the median treatment duration was 9.8 months, the median latency period since first exposure and diagnosis of MDS/AML was 17.8 months, and the mortality was 45% in the 104 cases.

Delayed cytopenia after the first 3 months of commencing a PARP inhibitor with pancytopenia, bicytopenia, or thrombocytopenia may be an early safety signal and identify patients at potential risk of t-MNs.

There is evidence to suggest that pre-existing TP53 clonal hematopoiesis of indeterminate potential variants before commencing a PARP inhibitor may be associated with t-MN and that in patients with cytopenias, the risk of t-MN is increased in the presence of these variants. Clinicians should be alert to this possibility, treatment should be interrupted, and a hematologic consultation and bone marrow biopsy are advised. Conventional cytogenetics is recommended as about 30% of cases of t-MN may not meet morphologic dysplasia criteria as reported in a comprehensive study from France. Complex karyotypes, frequent TP53 mutations, and a high rate of mutations in DNMT3A and TET2 are commonly observed. The mortality of MDS and AML is high and a devastating consequence of treatment. It is beyond the scope of this review to discuss the management of patients with t-MNs.

Pneumonitis

PARP inhibitors have been linked to a risk of pneumonitis, most notably with olaparib and niraparib. According to a recent meta-analysis involving 5,771 patients treated with a PARP inhibitor (or control), PARP inhibitors increased the risk of pneumonitis with the Peto odds ratio of 2.68 (95% CI, 1.31 to 5.47; P = .007). In patients treated with a PARP inhibitor, the incidence of all-grade pneumonitis was 0.79% (28 of 3,551), whereas it was 0.24% (5 of 2,060) in those treated with control. The median time to event onset for pneumonitis associated with PARP inhibitors was 81 days, with most cases occurring during the first 6 months of treatment (IQR, 27-131). The diagnosis should be suspected in patients with unexplained shortness of breath and confirmed on radiologic investigations where the features are consistent with interstitial lung disease. Treatment includes cessation of the PARP inhibitor and commencement of corticosteroids.

Cutaneous Toxicities

All three of the licensed PARP inhibitors have been associated with cutaneous toxicities, but only the ARIEL3 trial specifically reported incidence of rash (12%, n = 46 of 372), pruritus (13%, n = 47 of 372), any-grade photosensitivity reactions (17%, n = 64 of 372), and peripheral edema (10%, n = 39 of 372). There were only a few grade 3 AEs (1% or less), and the toxicities were mainly low grade. When starting PARP inhibitor therapy, it is important to alert patients to the possibility of photosensitivity and to consider sun protection using sunscreen and hats and liberal use of skin moisturizers when appropriate.

Special Populations

Older Age

Women older than 65 years are under-represented in clinical trials, and there is a paucity of data on the efficacy and safety of PARP inhibitors in older patients. Only 20% of patients in SOLO2 were older than 65 years and met eligibility criteria to be enrolled in the trial limiting interpretation of analyses of safety and efficacy.65 However, there did not appear to be any differences in dose interruptions and dose reductions in older patients or any safety signals. By contrast, very different findings were reported in ARIEL 3, which reported higher incidence of grade 3 toxicities in patients older than 65 years (70% v 54%) and higher percentage of dose reductions (71% v 47%) and dose discontinuations (21% v 12%) in older patients versus younger. In PAOLA, patients older than 70 years had higher rates of grade 3 or 4 anemia and grade 3 or 4 neutropenia and higher incidence of severe hypertension than patients younger than 70 years. A recent meta-analysis that included 4,364 patients enrolled in eight phase III trials of PARP inhibitors demonstrated that they were as effective in patients older than 65 years as in younger patients. Safety information was limited to hematologic toxicities that were available in only a subset of patients and suggested that there may be a higher risk of thrombocytopenia in older patients. It has been suggested that geriatric assessment should be considered in older patients before commencing a PARP inhibitor, which we agree with. Real-world studies of PARP inhibitors in older populations are required as participants in clinical trials may not be representative.

Ethnicity

White patients dominate the patient populations enrolled into most trials of PARP inhibitors, and it is possible that there might be differences in safety and efficacy in different ethnic and racial groups. However, on the basis of limited information, it appears that safety and tolerability of PARP inhibitors are similar in Asian populations to White populations although there is a trend toward higher incidence of hematologic adverse effects, but this is an area that requires more research.

Summary

• PARP inhibitors are playing an increasingly important role in the treatment of EOC and breast, prostate, and pancreatic cancers, particularly in patients with pathogenic variants in BRCA1 and BRCA2 but also among those with other mechanisms of homologous recombination deficiency.

• The benefits and the adverse effects associated with PARP inhibitors have been very well documented in clinical trials, but less well so in real-world settings. Patients included in clinical trials are often younger with a good performance status and less comorbidities than the real-world population, and hence, the potential benefits and adverse effects of treatment with PARP inhibitors may not be superimposable in older patients or those with medical comorbidities or those who are on medications that might have precluded them from entry onto clinical trials.

• It is incumbent on us as clinicians to be aware of the long list of potential adverse effects associated with PARP inhibitors and to ensure that where possible they are prevented or mitigated and managed effectively.

• It is also imperative to educate and inform patients and their families about what to expect including the potential adverse effects including their timing, trajectory, and treatment and stress the importance of close monitoring in the first few months of starting treatment with appropriate management of adverse effects as outlined above.

• Awareness of the potential for drug-drug interactions as well as identifying those patients at greater risk of adverse effects is important and affects the choice of PARP inhibitor, the starting dose, and intensity of follow-up. Meticulous attention to all these factors is likely to improve tolerability and permit patients to continue treatment.

• It appears that the adverse effect profile will be less with the next generation of selective PARP1 inhibitors but for the foreseeable future, we need to focus on the PARP inhibitors that we have access to in clinical practice and take the effort to understand how best to use them and how to avoid and manage the adverse effects.

Implications for Practice:

1. Olaparib therapy represents a new approach to treating recurrent ovarian cancer.

2. Some associated adverse events can have a substantial effect on quality of life. It is therefore important for patients, caregivers, and health care providers to have realistic expectations and a thorough understanding of the safety and tolerability profile of olaparib to prevent or alleviate key symptoms so that therapy can continue uninterrupted if possible.

3. Fatigue and GI toxicities can be particularly problematic in patients with ovarian cancer because they may have baseline disease-related fatigue, overlapping myelosuppression from conventional chemotherapy, and GI symptoms from disease burden.

4. Given the established toxicity profile of olaparib, prophylactic measures should be discussed and enacted to minimize the GI toxicities from treatment outset

5. Dose interruption followed by dose modification of olaparib is an acceptable way to manage significant treatment-related diarrhea.

Figures

TABLE 1. PARP Inhibitors: FDA Indications (March of 2023) for Epithelial Ovarian Cancer[a]

Maintenance Therapy	PARP Inhibitor
First-line maintenance after response to platinum-based chemotherapy for newly diagnosed, advanced-stage, high-grade ovarian cancer	Olaparib (germline or somatic deleterious *BRCA* alteration) Olaparib with bevacizumab (germline or somatic deleterious *BRCA* alteration and/or HRD score positive) Niraparib (all—any *BRCA* or HRD status)
Second- or greater-line maintenance after response to platinum-based chemotherapy for recurrent platinum-sensitive ovarian cancer	Olaparib (all—any *BRCA* or HRD status) Rucaparib (all—any *BRCA* or HRD status) Niraparib (germline or suspected germline *BRCA* deleterious alteration)

Abbreviations: FDA, US Food and Drug Administration; HRD, homologous recombination–deficient; PARP, poly (ADP-ribose) polymerase.

[a]Of note, change in FDA approvals (as of March of 2023): (1) withdrawn indications for maintenance: second- or greater-line maintenance after response to platinum-based chemotherapy for recurrent platinum-sensitive ovarian cancer—niraparib in nongermline *BRCA* is no longer FDA-approved in this setting and (2) withdrawn indications for treatment—olaparib, rucaparib, and niraparib are no longer FDA-approved in this setting.

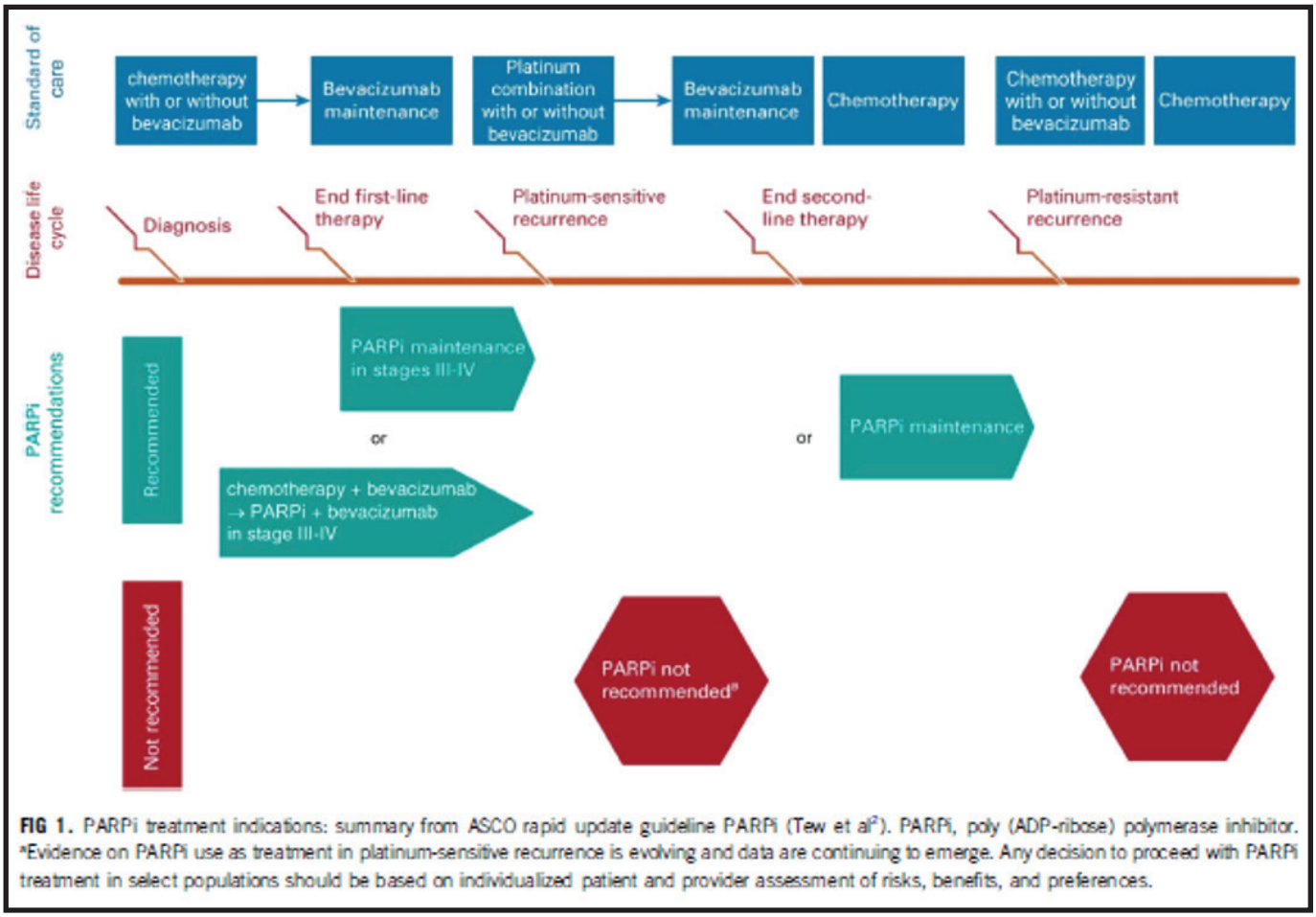


FIG 1. PARPi treatment indications: summary from ASCO rapid update guideline PARPi (Tew et al[2]). PARPi, poly (ADP-ribose) polymerase inhibitor. [a]Evidence on PARPi use as treatment in platinum-sensitive recurrence is evolving and data are continuing to emerge. Any decision to proceed with PARPi treatment in select populations should be based on individualized patient and provider assessment of risks, benefits, and preferences.

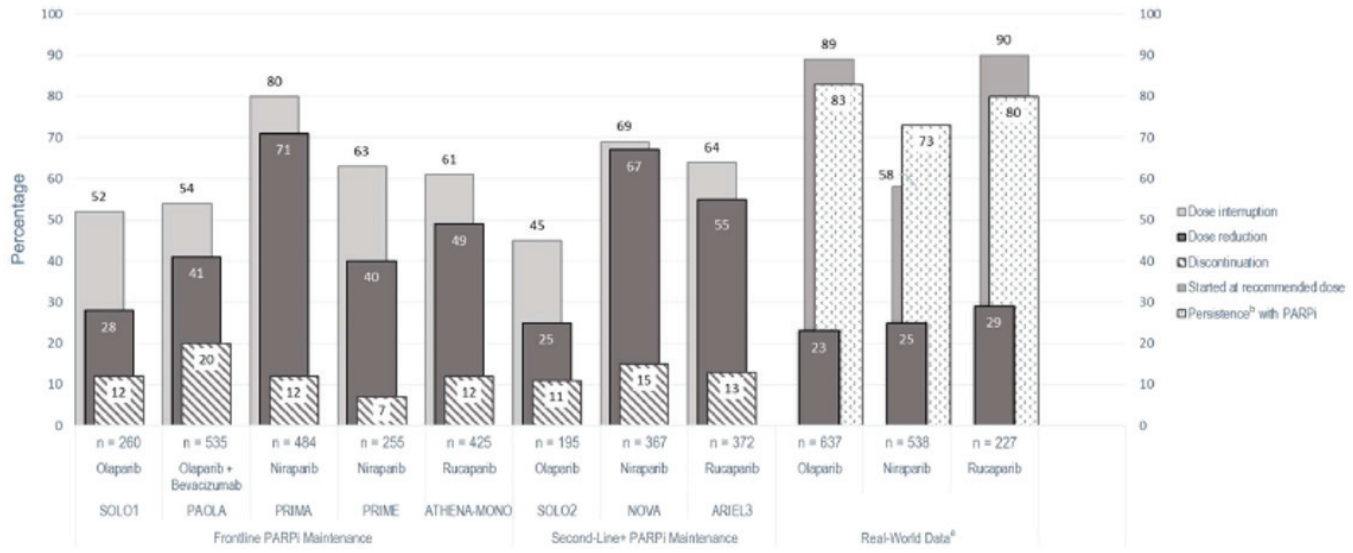
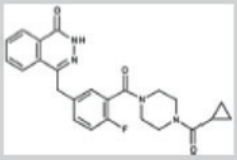
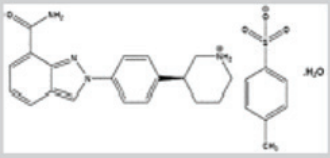
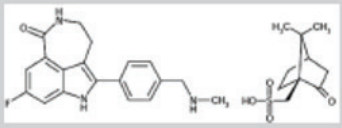


FIG 2. Dose interruptions, reduction, and discontinuation in studies of PARPi in frontline and second-line onward maintenance settings and real-world data. PARPi, poly (ADP-ribose) polymerase inhibitor. [a]Real-word data reported by O'Malley et al.[5] [b]Persistence was defined as the percentage of patients with no index PARPi regimen treatment gaps of >90 days of those with at least 6 months of continuous enrollment.

TABLE 2. Specific Characteristics of PARP Inhibitors

PARP Inhibitors	Olaparib	Niraparib	Rucaparib
Chemical structure			
Target	PARP-1, PARP-2, and PARP-3	PARP-1 and PARP-2	PARP-1, PARP-2, PARP-3
Formulation	Tablet[a]	Capsule	Tablet
Dose forms	150 mg, 100 mg	300 mg, 200 mg, 100 mg	300 mg, 250 mg, 200 mg
Storage	2°C-30°C	Up to 25°C	20°C-25°C
Method of administration	Swallowed whole, with or without food	Swallowed whole, with or without food	Swallowed whole, with or without food
Starting dose	300 mg BD	200 mg daily; or 300 mg daily if the weight is ≥77 kg or the platelet is ≥150,000/μL	600 mg BD
Dose adjustment because of AEs	DL-1: 250 mg BD DL-2: 200 mg BD DL-3: discontinue	If starting dose at 200 mg daily, DL-1: 100 mg daily DL-2: discontinue If starting dose at 300 mg daily, DL-1: 200 mg daily DL-2: 100 mg daily DL-3: discontinue	DL-1: 500 mg BD DL-2: 400 mg BD DL-3: 300 mg BD DL-4: discontinue
Mean terminal half-life	15 hours	36 hours	25.9 hours
Metabolism	CYP3A4	Carboxylesterase and conjugation (UDP-glucuronosyltransferases)	CYP2D6, CYP1A2, CYP3A, CYP2C9, and CYP2C19 substrates
Drug-drug interactions	CYP inhibitors,[b] CYP inducers[c]	NA	CYP inhibitors,[d] CYP inducers[d] Multidrug and toxin extrusion transporters (MATE-1, MATE-2K) Organic ion transporters (OCT1, OCT2)
Drug-food interactions	Grapefruit, star fruit, pomegranate, and seville oranges[e]	NA	NA
Elderly (older than 65 years)	No adjustments in starting dose, limited clinical data in patients older than 75 years	No adjustments in starting dose, but greater sensitivity of some older individuals cannot be ruled out	Safety data unknown
Renal adjustment	CrCl 51-80 mL/min: no adjustment CrCl 31-50 mL/min: 200 mg BD CrCl < 30 mL/min: not recommended	CrCl 30-89 mL/min: no adjustment Severe impairment/on dialysis: safety data unknown	CrCl 30-89 mL/min: no adjustment Severe impairment/on dialysis: safety data unknown
Hepatic adjustment	Child-Pugh grade A or B: no adjustment Child-Pugh grade C: not recommended	Mild impairment[f]: no dose adjustment Moderate impairment[f]: 200 mg daily Severe impairment[f]: safety data unknown	Mild impairment[f]: no dose adjustment Moderate—severe impairment[f]: safety data unknown

Abbreviations: AE, adverse event; BD, twice daily; DL, dose level; NA, not available; PARP, poly (ADP-ribose) polymerase; ULN, upper limit of normal.

aOlaparib is also available as 50 mg capsule formulation; however, this is not to be substituted with olaparib tablets on a milligram-to-milligram basis because of differences in the dosing and bioavailability of each formulation.

bCoadministration with strong or moderate CYP3A inhibitors is not recommended. If a strong CYP3A inhibitor must be coadministered, the recommended olaparib dose reduction is to 100 mg, twice daily; if a moderate CYP3A inhibitor must be coadministered, the recommended olaparib dose reduction is to 150 mg, twice daily. The patient should be carefully monitored for AEs.

cCoadministration with a strong or moderate CYP3A inducer is not recommended. The efficacy of olaparib may be substantially reduced if coadministered with strong or moderate CYP3A inducer.

dStrong CYP3A4 inhibitors and inducers are not recommended. Dose adjustment should be considered for CYP1A2, CYP2C9, and CYP3A4 substrates with a narrow therapeutic window. CYP1A2 or CYP2D6 inhibitors did not affect rucaparib exposure.

eThese fruits are known to inhibit CYP3A4 and may increase olaparib plasma concentration.

fMild hepatic impairment was defined as total bilirubin _1.5_ ULN and any AST level, or bilirubin _ULN and AST . ULN; moderate hepatic impairment was defined as total bilirubin .1.5 to 3.0 _ ULN and any AST; severe hepatic impairment was defined as total bilirubin .3.0 _ ULN and any AST.

TABLE 3. AEs of Poly (ADP-ribose) Polymerase Inhibitors Reported in Front-Line Maintenance Trials and Real-World Data

	SOLO1[17,18]				PAOLA1[20]				PRIMA[6] (overall)				PRIMA[6] (individualized dosing subgroup)				ATHENA-MONO[19]				Real-World Data[4]		
	Olaparib (n = 260)		Placebo (n = 130)		Olaparib + Bevacizumab (n = 535)		Placebo + Bevacizumab (n = 267)		Niraparib (n = 484)		Placebo (n = 244)		Niraparib (n = 169)		Placebo (n = 86)		Rucaparib (n = 429)		Placebo (n = 110)		Olaparib	Niraparib	Rucaparib
Adverse Events	All	≥G3	All	≥G3	All	≥G3	All	≥G3	All	≥G3	All	≥G3	All	≥G3	All	≥G3	All	≥G3	All	≥G3	CEI	CEI	CEI
Hematologic, %																							
Anemia	**39**	*22*	10	2	**41**	*17*	10	<1	**63**	*31*	18	2	**50**	*23*	**28**	1	**47**	*29*	9	0	**39**	**48**	**42**
Neutropenia	23	9	12	5	18	6	16	3	**26**	*13*	7	1	**24**	*10*	7	1	**28**	*15*	7	1	17	24	23
Thrombocytopenia	11	1	4	2	8	2	3	<1	**46**	*29*	4	<1	**34**	*15*	5	1	24	7	1	0	19	**42**	**31**
Leukopenia	13	3	8	0	18	2	10	1	**28**	5	9	<1	**28**	5	11	0	NR	NR	NR	NR	17	24	23
General, %																							
Fatigue	**64**	4	**42**	2	**53**	5	**32**	1	**35**	2	**30**	<1	**48**	3	**36**	0	**56**	5	**37**	1	**26**	**28**	**30**
Musculoskeletal pain[a]	10	0	10	0	22	1	24	1	18	<1	19	0	**37**	1	**41**	0	**33**	<1	**32**	0	**28**	**26**	22
Hypertension	3	<1	8	2	**46**	*19*	**60**	*30*	17	6	7	1	17	5	9	2	NR	NR	NR	NR	**32**	**46**	**40**
Rash	10	0	11	0	3	0	4	<1	NR	NR	NR	NR	NR	NR	NR	NR	14	<1	7	0	5	3	7
Respiratory, %																							
Cough	18	0	22	0	NR	NR	NR	NR	15	0	14	<1	15	0	21	0	12	0	10	0	NR	NR	NR
Dyspnea	15	0	6	0	8	1	3	<1	18	<1	12	1	19	0	12	1	11	1	11	0	NR	NR	NR
GI, %																							
Nausea	**77**	1	38	0	**53**	2	22	1	**57**	1	**28**	1	**53**	1	21	0	**56**	2	**30**	0	**26**	**33**	43
Vomiting	**40**	<1	15	1	22	1	11	2	22	1	12	1	17	0	9	1	24	1	12	0	3	5	8
Diarrhea	**34**	3	**25**	0	18	2	17	2	19	1	23	<1	14	1	23	0	24	1	21	2	13	19	19
Constipation	**28**	0	19	0	10	0	10	<1	**39**	<1	19	0	**33**	1	16	1	19	0	16	0	7	6	11
Dysgeusia	**26**	0	4	0	8	<1	1	0	NR	NR	NR	NR	NR	NR	NR	NR	21	<1	6	0	NR	NR	NR
Abdominal pain	24	2	18	1	19	1	20	2	22	1	31	<1	**28**	2	**37**	2	**25**	1	**28**	2	NR	NR	NR
Decreased appetite	20	0	10	0	8	<1	4	<1	19	1	8	0	19	1	5	0	18	1	15	0	NR	NR	NR
AST/ALT elevation	NR	NR	NR	NR	NR	NR	NR	NR	11	2	7	0.4	8	2	7	1	**43**	11	8	1	0	1	2
Acute kidney injury[b]	8	0	2	0	6	0	1	0	12	<1	4	0	12	1	5	0	11	<1	6	0	9	14	18
Nervous system disorders, %																							
Headache	23	<1	24	2	14	<1	13	1	**26**	<1	15	0	22	1	17	0	20	1	15	0	NR	NR	NR
Dizziness	20	0	15	1	5	<1	4	<1	15	0	11	<1	11	0	11	0	13	0	8	0	NR	NR	NR
Insomnia	10	0	12	0	4	<1	4	0	**25**	1	14	<1	21	0	14	0	14	<1	7	0	5	10	10

NOTE. AEs with ≥10% G3 reported are given in italics, and AEs with ≥25% all grade reported are given in bold.

Abbreviations: AE, adverse event; CEI, clinical events of interest; G3, grade 3; NR, no response.

[a]Musculoskeletal pain includes arthralgia, backpain, pain in extremity, myalgia, and other related terms.

[b]Acute kidney injury includes blood creatinine increased, blood urea increased, and renal failure.

TABLE 4. Recommended Management for Common AEs Because of PARP Inhibitors[a]

General approach	Ensure that the patient has adequately recovered from chemotherapy; aim to start maintenance PARP inhibitor within 8-12 weeks of last cycle of chemotherapy Consider potential drug interactions with PARP inhibitors, which may affect the starting dose or choice of PARP inhibitor Proactively educate patients about the range of possible AEs, action plans, and frequency of investigations Implement close surveillance particularly in the first 12 weeks of treatment when AEs commonly occur	
AE	**Low-Grade Symptoms (or initial management)**	**High-Grade Symptoms (or follow-up management)**
Nausea with or without vomiting	Do not replace vomited dose; take next dose at scheduled time Consider prophylactic metoclopramide 30-60 minutes before PARP inhibitor and taking with a light meal Treat gastroparesis and dyspepsia when indicated Consider antiemetics such as metoclopramide or 5-HT3 antagonist for symptom management Consider taking PARP inhibitor later in the day (10 AM instead of 8 AM) at twice daily dose schedule or at night before bed for daily dose schedule (niraparib)	Dose interruption until AE resolves to grade 1 or less Exclude other causes (partial or complete bowel obstruction) Resume the same dose with prophylactic antiemetic therapy Dose reduction if AE recurs despite prophylactic therapy
Fatigue	Encourage a balance of physical activity and energy conservation. Tailor realistic expectations with structured daily routine Consider nonpharmacologic intervention: massage therapy and psychosocial interventions Optimize treatment for depression, sleep dysfunction, and nutritional deficit	Dose interruption until AE resolves to grade 1 or less Exclude anemia, electrolyte imbalance, or endocrine dysfunction as the contributing cause Exclude depression as a contributor Resume the same dose or consider dose reduction if AE recurs despite supportive management
Anemia	Workup investigations to exclude other causes of anemia including iron, vitamin B12, folate deficiencies, or hypothyroidism Consider a short period of dose interruptions without dose reduction	Dose interruption when Hb < 8 g/dL, and bloods should be monitored weekly until Hb returns to ≥9 g/dL Blood transfusion is recommended when Hb < 7 g/dL or higher levels if symptomatic or significant comorbidities are present Once recovered, resume PARP inhibitor at the same or reduced dose level (if dose interruption took place because of symptomatic anemia) If AE not recovered after 4 weeks or repeated occurrence, the patient should be referred to a hematologist to exclude MDS/AML
Neutropenia	Observe asymptomatic cases	Dose interruption when the neutrophil count is $<1.0 \times 10^9$/L, and bloods should be monitored weekly until recovery Once recovered, resume PARP inhibitor at a reduced dose level If AE is not recovered after 4 weeks or repeated occurrence, the patient should be referred to a hematologist to exclude MDS/AML
Thrombocytopenia	Review concomitant medications to exclude other causes of thrombocytopenia For niraparib Ensure that weight-based dosing was used for those <77 kg Dose interruption when the platelet count is $<100 \times 10^9$/L, and bloods should be monitored weekly until the platelet count is $\geq 100 \times 10^9$/L For olaparib and rucaparib, Dose interruption when the platelet count is $<50 \times 10^9$/L, and bloods should be monitored weekly until the platelet count is $\geq 100 \times 10^9$/L	Platelet transfusion recommended when the platelet count is $<10 \times 10^9$/L or higher if bleeding or on anticoagulants For niraparib: dose reduction if the platelet count falls to $<75 \times 10^9$/L or higher if bleeding For olaparib/rucaparib: dose reduction if the platelet count falls to $<50 \times 10^9$/L or higher if bleeding If AE is not recovered after 4 weeks or repeated occurrence, the patient should be referred to a hematologist to exclude MDS/AML

Abbreviations: 5-HT3, 5-hydroxytryptamine-3; AE, adverse event; MDS, myelodysplastic syndrome; PARP, poly (ADP-ribose) polymerase.
[a]It is important to refer to prescribing information for guidance on dosing, dose interruptions, and dose reductions for each PARP inhibitor.

Table 4. Examples of self-report screening instruments used for identification of psychosocial distress in cancer patients

Title	No. of items	Time (min)	Constructs measured
Distress Thermometer and Problem List [25, 26]	Varies	2–3	Distress and problems related to the distress
Brief Symptom Inventory [43]	105	7–10	Somatization, anxiety, interpersonal sensitivity, depression, hostility, phobic anxiety, paranoid ideation, psychoticism, obsessive-compulsiveness
Brief Symptom Inventory-18 [43]	18	3–5	Somatization, depression, anxiety, general distress
Hospital Anxiety and Depression Scale [44–46]	14	5–10	Symptoms of clinical depression and anxiety
Functional Assessment of Chronic Illness Therapy (FACIT; formerly the FACT) [47]	27	5–10	4 domains of quality of life: physical, functional, social/family, emotional well-being
Profile of Mood States [48]	65	3–5	6 mood states: anxiety, fatigue, confusion, depression, anger, vigor
Zung Self-Rating Depression Scale [49]	20	5–10	Symptoms of depression

Data obtained from [42].

Table 6. Practical approach to supportive care for patients on olaparib therapy: fatigue

Evaluation and treatment planning	Nonpharmacologic approaches	Pharmacologic
• Screen all patients	• Conserve energy	• Prescribe psychostimulants
• Evaluate for all causes of fatigue	• Use distractions	• Treat underlying pain or depression
• Educate, counsel, reassure patients and advise to self-monitor	• Exercise (adapted to patient status); 150 min/wk	• Prescribe sleep aid medications
• Consider referring to supportive/palliative care specialist	• Massage, psychosocial interventions, stress reduction	• Address sleep dysfunctions, nutritional issues, comorbidities
	• Address sleep hygiene	• Interrupt olaparib dosing until fatigue returns to baseline, then either restart at same dose or modify olaparib daily dose if necessary
	• Refer for nutritional counseling	

Detailed and specific guidelines are given in published guidelines [27, 28].

Table 7. Practical approach to supportive care for patients on olaparib therapy: gastrointestinal symptoms

Initial management or low-grade symptoms	Follow-up or higher-grade symptoms
Dyspepsia	
Consider starting or giving prescription for PPIs concomitantly with initiation of olaparib	For grade ≥2, consider dose interruption until dyspepsia back to baseline. Can restart at starting dose or dose modify (e.g., 1 level) depending on the severity of symptoms and other contributing factors. Consider referral to gastroenterology for evaluation of *Helicobacter pylori*, possible endoscopy if grade ≥2 symptoms persist despite appropriate therapy with PPIs and dose interruption.
Diarrhea	
Prescribe loperamide or diphenoxylate/atropine; begin if diarrhea ≤grade 1	Grade 2: interrupt olaparib; restart when it is grade ≤1 at same dose or at dose reduction, depending on severity of symptoms and other contributing factors.
Nausea/emesis	
Pretreatment with antiemetics is not required for olaparib. Patient education regarding this common side effect is essential, and prescriptions for prochlorperazine, 5-HT_3 antagonists, or other antiemetics of choice should be given along with instructions and indications for use if nausea/emesis is grade 1.	Grade 2: interrupt olaparib; consider adding a second antiemetic per NCCN guidelines [32]; restart olaparib when it is grade ≤1 at same dose or at a dose reduction based on the severity of symptoms.

Detailed and specific guidelines are given in published guidelines [32].
Abbreviations: NCCN, National Comprehensive Cancer Network; PPI, proton-pump inhibitor.

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