

REVIEW ARTICLE

Practical guidance on the use of olaparib capsules as maintenance therapy for women with *BRCA* mutations and platinum-sensitive recurrent ovarian cancer

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Abstract

Olaparib is the first oral poly(ADP-ribose) polymerase inhibitor to be approved as maintenance monotherapy for treatment of patients with platinum-sensitive relapsed *BRCA*-mutated (*BRCAM*) serous ovarian cancer. This review provides practical guidance on the use of olaparib (capsule formulation) in the maintenance setting. The article focuses on the key toxicities that can arise with olaparib therapy and recommendations for their management. Nausea, vomiting, fatigue and anemia are the most commonly reported adverse events in olaparib clinical trials and are generally mild to moderate and transient in nature in most patients. Implementation of an effective and timely management plan can control many of the side effects. It is vital that health care providers effectively communicate the potential side effects of olaparib, as well as educate patients on management strategies to combat these symptoms. To this end, realistic expectations regarding the potential side effects need to be set, with an understanding that dose interruptions and modifications may be required to allow patients to continue receiving treatment.

Key words: olaparib, ovarian cancer, practical guidance, side effects, toxicity

INTRODUCTION

Up to 50% of patients with high-grade serous ovarian carcinoma are deficient in homologous recombination repair – a key pathway for repair of DNA damage – as a result of germline or somatic acquired *BRCA1* or *BRCA2* mutations, epigenetic inactivation of *BRCA1*,

or *BRCA*-independent defects in the homologous recombination pathway.^{1,2} It is estimated that 15–22% of high-grade serous ovarian cancers may be attributable to a germline *BRCA1* or *BRCA2* mutation.³ Poly(ADP-ribose) polymerase (PARP) plays an integral role in the repair of single-strand DNA breaks via the base excision pathway and likely maintains low-fidelity DNA repair mechanisms.^{4,5} PARP inhibitors have been developed as a new class of targeted anticancer treatments. On the basis of data obtained from a pivotal phase II trial in patients with platinum-sensitive relapsed serous ovarian cancer (NCT00753545; D0810C00019; Study 19),^{6,7} olaparib (Lynparza, Patheon Pharmaceuticals, Inc., Cincinnati, OH, USA) was the first PARP inhibitor to be approved.

In Australia, olaparib capsules are approved as monotherapy (400 mg taken twice daily, i.e. 8 × 50 mg capsules twice a day) for the maintenance treatment of patients with platinum-sensitive relapsed *BRCA*-mutated (*BRCAM*; germline or somatic) high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer

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who have responded (completely or partially) to their most recent platinum-based chemotherapy.⁸ The indication requires that patients have received at least two lines of platinum-based chemotherapy.⁸

As maintenance treatments are continued for a protracted period in order to maintain disease control after response to chemotherapy, it is important that they are well tolerated with limited side effects and minimal impact on patient quality of life. This review aims to provide practical advice on the use of olaparib (capsule formulation) in the maintenance setting, with a focus on the safety profile and guidance on how key toxicities should be managed.

CLINICAL EFFICACY OF OLAPARIB

Olaparib has demonstrated antitumor activity in phase II studies of patients with *BRCAM* breast and ovarian cancer.^{7,9–11} The pivotal phase II trial (Study 19) was an international, multicenter, randomized, double-blind, placebo-controlled trial in patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer with the histological subtype of high-grade serous, or with a high-grade serous component in mixed epithelial cancers.⁶ In this study, 265 patients were randomized to olaparib ($n = 136$) or placebo ($n = 129$) as maintenance therapy. The primary endpoint was progression-free survival (PFS) based on investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) 1.0. Key inclusion criteria were that patients should have completed at least two previous courses of platinum-based chemotherapy before randomization, have achieved complete or partial response following completion of their last platinum-based chemotherapy and be considered to have platinum-sensitive disease.

The phase II study met its primary objective of statistically significant improved PFS for olaparib maintenance monotherapy compared with placebo in the overall population.⁶ There was a 3.6-month increase in median PFS from the start of trial drug (median PFS of 8.4 *vs* 4.8 months for patients treated with olaparib and placebo, respectively; hazard ratio [HR] 0.35; 95% confidence interval [CI] 0.25–0.49; $P < 0.001$).⁶ In addition, a planned subgroup analysis showed that patients with germline *BRCAM* (g*BRCAM*) ovarian cancer ($n = 136$) derived the greatest clinical benefit from olaparib maintenance monotherapy.⁷ In this subset of *BRCAM* patients, there was a statistically significant improvement in PFS of 6.9 months for olaparib versus placebo (HR 0.18; 95% CI 0.10–0.31; $P < 0.0001$; median PFS 11.2 *vs* 4.3 months).

The investigator assessment of PFS was consistent with a blinded independent central radiological review of PFS.

The phase II trial was not designed to assess statistically significant differences in overall survival (OS), and analyses conducted at 38% and 58% maturity showed no significant OS benefit with olaparib.^{6,7} A third updated OS analysis (77% maturity; data cutoff 30 September 2015), representing an additional follow-up of 3 years since the previous analyses, has recently been reported.¹² A trend to improved OS was observed for patients who received olaparib maintenance therapy compared with placebo (HR 0.73, 95% CI 0.55–0.96), with the greatest benefits observed for the *BRCAM* subgroup (HR 0.62, 95% CI 0.41–0.94). However, the criterion for statistical significance ($P < 0.0095$) was not met.¹² Of patients receiving placebo, 23% switched to a PARP inhibitor after progression. An exploratory *post hoc* analysis that excluded all patients from sites where ≥ 1 placebo patient received postprogression PARP inhibitor treatment resulted in an OS HR of 0.52 (95% CI 0.28–0.97; $P = 0.039$) for the 97 *BRCAM* patients included in the analysis.¹³ This suggested that postprogression PARP inhibitor treatment had a confounding influence on the interim OS analysis for *BRCAM* patients.

Assessment of health-related quality of life (HRQoL) in the phase II study showed that olaparib maintenance treatment had no detrimental impact on global HRQoL compared with placebo, both for the overall study population and in patients with a *BRCAM* or g*BRCAM*.¹⁴

CLINICAL SAFETY OF OLAPARIB

Olaparib is generally well tolerated in both *BRCAM* and wild-type patients. Adverse reactions associated with olaparib monotherapy are typically of mild or moderate severity (Common Terminology Criteria for Adverse Events [CTCAE] grade 1 or 2) and, in most cases, are short term in nature, self-limiting and do not require treatment discontinuation.

In the pivotal phase II trial, the most commonly reported adverse events (AEs) with an incidence $>10\%$ higher in the olaparib than in the placebo group were nausea, fatigue, vomiting and anemia.^{6,7} The tolerability profile of olaparib in patients with *BRCAM* cancer did not differ to that of the overall population.⁷ Subsequent analyses of the common safety events of nausea, vomiting, fatigue and anemia showed that, in the majority of patients, these events occurred early during the treatment (within the first 4–8 weeks) and were mainly grade 1 or 2, generally transient and managed with supportive care without the need to change the dose of olaparib.^{15,16} For

the total population, serious AEs (SAEs) were reported in 25 patients (18%) who received olaparib and 11 patients (9%) who received placebo (eight patients [5.9%] and one patient [0.8%], respectively, had SAEs considered by the investigator to be causally related to olaparib).⁷ Treatment to progression was achieved in most patients, with interruption of or a dose reduction in olaparib therapy used to manage AEs in 28% and 23% of patients, respectively.⁶

Safety data for olaparib from the phase II trial after a median follow-up of 5.9 years showed no new safety findings.¹² Few AEs led to permanent discontinuation of treatment – only eight patients (6%) receiving olaparib and two patients (2%) receiving placebo discontinued treatment because of AEs over this period.¹² In those patients receiving olaparib for at least 2 years, frequencies of the common AEs (nausea, fatigue, vomiting and anemia) were consistent with those in the overall population, with AEs generally initially reported during the first 2 years of treatment.^{6,7,12} These long-term data demonstrate the feasibility of extended olaparib maintenance therapy. In the olaparib treatment group, 18% of patients remained on treatment for more than 3 years⁷ and 13% of patients remained on treatment for at least 5 years.¹² As of September 2015, at a median follow-up of 5.9 years, 15 patients (11%) were still receiving olaparib, with one patient (<1%) still receiving placebo.¹²

The safety results from the phase II study are consistent with findings across clinical trials with olaparib monotherapy. Overall, the most frequently seen adverse reactions ($\geq 10\%$) in patients receiving olaparib monotherapy were nausea, vomiting, diarrhea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, anemia, neutropenia, lymphopenia, mean corpuscular volume elevation and increase in creatinine.¹⁷ The specific management and monitoring of key olaparib side effects is described in the section “Management of toxicities.”

PRACTICAL CONSIDERATIONS FOR ADMINISTRATION

Choosing the right patient

Patients selected for treatment with olaparib monotherapy should ideally have characteristics comparable to the inclusion criteria used in the phase II olaparib trial; that is, patients should have pathogenic *BRCAm* (either germline or somatic), high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer, responded to platinum-based therapy and received at least two lines of platinum-based regimens. It is essential that

BRCAm status is confirmed prior to initiating olaparib treatment, with testing carried out by an accredited laboratory using a validated test method. The monotherapy dose of olaparib (400 mg twice daily) is approved in the maintenance setting and is not suitable for use in patients receiving other anticancer agents.

There are limited data in patients with impaired hepatic and renal function. As a result, olaparib should not be used in patients with significant hepatic impairment (serum bilirubin >1.5 times the upper limit of normal) or severe renal impairment (creatinine clearance <30 mL/min). Olaparib can be administered in patients with mild renal insufficiency (creatinine clearance >50 mL/min) at the recommended dose, but patients should be monitored closely for toxicity. There are no data in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min) or patients on dialysis.

Based on its mechanism of action, olaparib could cause fetal harm and should not be administered to pregnant women. Women of childbearing potential must use effective contraception during therapy and for at least 1 month after receiving the last dose of olaparib.

Recommended dosing schedule

The recommended dose of olaparib is 400 mg (eight 50 mg capsules) taken twice daily, equivalent to a total daily dose of 800 mg. Although this is a large number of capsules to take, compliance was very high in all the clinical trials. Nevertheless, a tablet formulation has been developed to reduce the capsule burden. The dose used in current phase III trials of the tablet formulation is 300 mg twice daily, that is four tablets a day. The treatment should be continued until progression, as determined by imaging or cancer-related symptoms (asymptomatic rising CA125 or small volume progression does not necessitate cessation of treatment if the patient is considered to be deriving clinical benefit). The Australian and EU product information states that olaparib should be taken at least 1 h after food and that patients should refrain from eating for a further 2 h after taking the medication^{8,17}; however, other countries have not provided any specific recommendations on food intake with olaparib capsules.¹⁸ In a food-effect study, the presence of food was shown to decrease the rate of absorption of olaparib (time to maximal plasma concentration [t_{max}] was delayed by approximately 2 h) and increase the extent of absorption (by approximately 20%).¹⁹ However, there was less impact on maximum plasma concentration (increased by 10%), which likely reflects the delayed t_{max} . The authors concluded that the effects of food on olaparib pharmacokinetics were not deemed clinically important.¹⁹

Table 1 Inhibitors/inducers of CYP3A4/5[†]

Inhibitors	Inducers
Itraconazole	Phenytoin
Clarithromycin	Rifampicin
Boosted protease inhibitors with ritonavir or cobicistat	Rifabutin
Indinavir	Carbamazepine
Saquinavir	Nevirapine
Boceprevir	St John's wort
Aciprofloxacin	
Erythromycin	
Diltiazem	
Fluconazole	
Verapamil	
Grapefruit	
Starfruit	
Seville oranges	

[†]This list is not intended to be exhaustive.

Given that the CYP3A4/5 enzymes are predominantly responsible for the metabolic clearance of olaparib, it is recommended to avoid concomitant administration with, or use suitable substitutes of, known potent inducers and inhibitors of CYP3A4/5 isoenzymes (Table 1). If concomitant use of strong or moderate CYP3A inhibitors cannot be avoided, the olaparib dose can be reduced to 150 mg (three 50 mg capsules) taken twice daily for a strong CYP3A inhibitor or 200 mg (four 50 mg capsules) taken twice daily for a moderate CYP3A inhibitor.¹⁸

No data are available about the impact of olaparib on wound healing. Dose interruption is not recommended for minor surgical procedures. However, for other types of surgery, it is the authors' opinion to stop olaparib for several days prior to surgery and not recommence olaparib until wound healing has occurred.

PARP inhibitors are known to be a radiation sensitizer. Therefore, discussion with the treating radiation oncologist should determine whether it is appropriate to stop olaparib for any patient planned to receive radiotherapy, depending on the field size, site to be treated and the planned dose. Dose interruption would generally not be required for patients planned to receive a single fraction or short course of palliative radiation (e.g. to bone).

The olaparib dose can be adjusted as a strategy for managing AEs and this is described in more detail below.

Patient counseling points

It is important that patients have a clear understanding of the dosage instructions of olaparib. Patients should be instructed that if they miss a dose, they should not take

an extra dose to make up for the one that they missed; instead, they should take their next normal dose at the next scheduled time. Patients should be advised that each capsule should be swallowed whole and that they should not chew, dissolve or open the capsules. It should also be mentioned that if patients take too much olaparib, they need to call their health care provider or go to the nearest emergency room for assessment and advice.

Patients should also be advised to avoid grapefruit, grapefruit juice and Seville oranges during the treatment with olaparib. It should also be clearly communicated to patients that they need to notify their doctor if they start taking any new medications or supplements.

In particular, several commonly prescribed antibiotics (ciprofloxacin, erythromycin and fluconazole) are moderate CYP3A4 inhibitors, which may increase olaparib plasma concentrations. If it is clinically imperative that patients receive concurrent treatment with moderate or strong CYP3A4 inhibitors, a dose reduction of olaparib is recommended during the treatment course.¹⁸

Additionally, when counseling patients on dosing and administration of olaparib capsules, patients need to be made aware of the risk of fetal harm associated with olaparib and given advice on contraception during the treatment. Women should be instructed to inform their health care provider if they are pregnant or become pregnant. Patients should also be advised not to breastfeed while taking olaparib.

MANAGEMENT OF TOXICITIES

Prior to initiating olaparib treatment, patients should be counseled on what side effects to expect and what to do if they experience specific symptoms.

For all toxicities, implementation of a timely management plan and tailoring interventions according to the individual needs of the patient is usually effective. From the outset, realistic expectations regarding the potential side effects need to be set, with an understanding that dose interruptions and modifications may be required to allow patients to continue receiving treatment. Patients should recognize that the aim is to provide long-term therapy with minimal impact on their quality of life. They should be aware that it is common to experience nausea and fatigue in the first few months, but these can usually be controlled. If patients have a clear understanding prior to starting treatment about what is likely to happen, the natural history and likely duration of expected toxicities, and what they can do to treat the symptoms, they are more likely to be compliant with the recommended strategies to manage their side effects and thereby adhere to treatment.

Table 2 Recommended management strategies of important toxicities observed with olaparib maintenance monotherapy

Adverse event	Prior to treatment	Following treatment initiation
Nausea and vomiting	<ul style="list-style-type: none"> • Patient counseling regarding frequency of side effect, including awareness that events are more common at the start of treatment and improve over time • Provide prescriptions for antiemetics, with instructions and indications for use. Advise patients that pretreatment with antiemetics is not required 	<ul style="list-style-type: none"> • Prompt treatment of mild/moderate nausea/vomiting with antiemetics (e.g. metoclopramide or prochlorperazine) • If not controlled with medication, interrupt olaparib treatment; when symptoms are grade ≤ 1, restart olaparib treatment at same or lower dose[†]
Fatigue	<ul style="list-style-type: none"> • Patient counseling regarding frequency of side effect, including awareness that events are more common at the start of treatment and improve over time • Advise patients that fatigue management is considered a routine part of cancer care – provide any tools, as required, for self-monitoring 	<ul style="list-style-type: none"> • Evaluate for other possible causes of fatigue • Supportive care to cope with fatigue (e.g. strategies to conserve energy and exercise) • If not controlled with supportive care, interrupt olaparib treatment; when symptoms are grade ≤ 1, restart olaparib treatment at same or lower dose[†]
Dysgeusia	<ul style="list-style-type: none"> • Patient counseling regarding frequency of side effect and self-management strategies that can be used to combat this symptom 	<ul style="list-style-type: none"> • Supportive care to cope with dysgeusia • If not controlled with supportive care, interrupt olaparib treatment; when symptoms are grade ≤ 1, restart olaparib treatment at same or lower dose[†]
Hematological toxicity	<ul style="list-style-type: none"> • Patient counseling regarding frequency of side effect • Baseline testing of complete blood counts • Ensure recovery (grade ≤ 1) from any existing hematological toxicity caused by previous chemotherapy 	<ul style="list-style-type: none"> • Monthly assessment of complete blood counts for first 12 months and periodically thereafter (every 3 months if blood counts remain in normal range) • Toxicities can be managed by dose interruptions. However, treatment-related anemia may be managed by transfusions without interruption of treatment • Grade 3/4 events should be managed by dose interruption. If toxicity resolves to grade ≤ 1 within a maximum of 28 days, patients can restart treatment at a lower dose[†] • For severe hematological toxicity or in cases where blood transfusion is still required despite dose reductions, interrupt olaparib and initiate appropriate hematological investigation. If blood parameters remain clinically abnormal after 4 weeks of dose interruption, bone marrow biopsy and cytogenetic analysis should be considered
MDS/AML	<ul style="list-style-type: none"> • Patient counseling regarding potential risks 	<ul style="list-style-type: none"> • Long-term monitoring to determine the risk of MDS/AML • If MDS/AML confirmed, treat appropriately and discontinue olaparib
Pneumonitis	<ul style="list-style-type: none"> • Patient counseling regarding potential risks; advise to report new onset of shortness of breath, cough, wheezing or fever 	<ul style="list-style-type: none"> • Interrupt olaparib and investigate patients with new or worsening respiratory symptoms, such as dyspnea, cough and fever, or a radiological abnormality consistent with pneumonitis • If pneumonitis confirmed, discontinue olaparib and treat appropriately (glucocorticoids)

[†]The recommended dose reduction is to 200 mg (four 50 mg capsules) twice daily for a total daily dose of 400 mg. A further final reduction to 100 mg (two 50 mg capsules) twice daily for a total daily dose of 200 mg can also be considered if required.

The specific management of important toxicities observed with olaparib is summarized in Table 2. In particular, patients should be made aware that nausea and/or vomiting and fatigue are very common side effects of

olaparib, particularly when commencing treatment, and that patients should be monitored during the treatment (see recommendations below). As nausea is often experienced repeatedly in some patients, a proactive approach

whereby antiemetics are prescribed preemptively for nausea and vomiting can be effective in combating these symptoms.

It should be explained to the patient that dose reductions are generally implemented as a secondary approach to toxicity management when other methods have not been successful. If a dose reduction is required, the recommended reduction is 200 mg (four 50 mg capsules) twice daily for a total daily dose of 400 mg. A further final reduction to 100 mg (two 50 mg capsules) twice daily for a total daily dose of 200 mg can also be considered if needed.

Patients should also be made aware that myelodysplastic syndrome (MDS), acute myeloid leukemia (AML) and pneumonitis have been reported in a small number (<1%) of patients. While these conditions are serious, they have not been directly associated with olaparib use. Nevertheless, patients should be monitored during the treatment.

Nausea and vomiting

Nausea and vomiting are common side effects that represent the main toxicities of olaparib maintenance therapy.

In Study 19, 71% and 34% of patients reported nausea and vomiting, respectively.⁷ Most of these events were mild or moderate in nature, with grade ≥ 3 events occurring in only 2% of patients for each symptom. Recent analyses of these events showed that nausea and vomiting were generally reported early in Study 19, with events occurring most frequently in the first month of treatment.^{15,16} The majority of cases were grade 1 and were tolerated without the need for treatment. Patients experiencing grade ≥ 2 events benefited from symptomatic treatment, in most cases responding to standard oral antiemetics, and rarely required olaparib dose adjustments or treatment discontinuation.¹⁵

In the clinical practice setting, nausea or vomiting events should be effectively managed by using an aggressive and proactive approach in order to allow patients to adhere to treatment and maximize treatment outcomes. This can be achieved by prescribing appropriate preemptive, standard antiemetic therapy such as metoclopramide or prochlorperazine. Typically, metoclopramide taken prior to olaparib is effective in most patients, combined with patient education, clear communication and management of patient expectations regarding these symptoms. Patients should understand that prophylaxis of nausea and/or vomiting is not required prior to first starting olaparib. If patients experience nausea or vomiting after taking olaparib, they should be advised to

take an antiemetic such as metoclopramide prior to subsequent doses, at least for the first month of treatment. Such an approach should minimize the need for olaparib dose adjustments or discontinuations, enabling patients to receive uninterrupted olaparib treatment. Although a need for the substance P/neurokinin 1 receptor antagonist aprepitant is highly unlikely, this antiemetic should be avoided with olaparib therapy as it is a CYP3A inhibitor and may impact olaparib plasma concentrations.²⁰

In cases where standard antiemetic therapies are not sufficient, temporary treatment interruption and restarting at the same or a lower dose of olaparib can be used. In order to optimize treatment benefits, dose interruption followed by resumption at the same dose should be considered as a first approach prior to reducing the dose, because nausea usually improves and resolves over 4–8 weeks.

Fatigue

Fatigue is also a common symptom; it may be related to prior chemotherapy but can be increased with olaparib.

In the pivotal phase II olaparib study, fatigue was reported in 52% of patients receiving olaparib versus 39% of patients receiving placebo.⁷ As with nausea and vomiting, most cases were mild to moderate and transient in nature,¹⁶ with events of grade ≥ 3 reported in 7% of patients.⁷ Patients receiving olaparib should be regularly questioned about fatigue and reassured that it is common when first starting olaparib and will usually improve over time. Patients should be evaluated for other possible underlying causes or contributors to fatigue as an initial management step.²¹ For example, fatigue may be associated with other conditions such as anemia, insomnia, depression, anxiety or hypothyroidism, which may then require specific treatment.

When there is no clear cause of fatigue that can be treated, patients should receive guidance on conserving energy, timing activities when energy is highest, undertaking moderate exercise and ensuring adequate nutrition. Patients can be referred to several self-management resources about fatigue. In addition, referral to an exercise physiologist may be of benefit for some patients. In the authors' experience, many patients receiving olaparib have found that a brief nap or rest in the afternoon for the first 4–6 weeks of treatment helps combat fatigue, following which the symptom improves.

If fatigue persists despite supportive measures, the olaparib dose can be interrupted and restarted either at the same or at a lower dose. For mild-to-moderate fatigue, a short-dose interruption followed by resumption at the

same dose may be sufficient to alleviate this symptom. For more severe fatigue, or fatigue that persists despite dose interruptions, a reduction in dose may be beneficial.

Dysgeusia

Dysgeusia is an alteration in taste; it is a common complaint following treatment with olaparib, as well as with other PARP inhibitors and many cytotoxic agents, and may impact negatively on quality of life.²² The CTCAE grading for dysgeusia is either grade 1, corresponding to altered taste without a change in diet, or grade 2, corresponding to altered taste with a change in diet (e.g. oral supplements). This symptom can impact on a patient's ability to eat, potentially leading to weight loss.²³

In the phase II olaparib study, dysgeusia was observed in 16% of patients receiving olaparib versus 6% of patients receiving placebo.⁷ Although not directly related, decreased appetite was reported in 21% of patients receiving olaparib and 13% of patients receiving placebo.⁷

Although dysgeusia can be disturbing to patients, it is often overlooked in initial discussions of treatment side effects.²⁴ Prior to commencing olaparib therapy, this symptom should be discussed with patients so that they know what to expect; additionally, it is helpful for patients to have an awareness of the self-management strategies that they can employ if they do experience this symptom. Some patients will have already experienced this with prior chemotherapy.

Taste alterations vary with each patient and nonpharmacological strategies involving modification of food preparation to improve the flavor of foods have been suggested.^{25,26} These include changing food temperatures, adding flavorings, choosing frozen fruits, avoiding foods the patient has noticed that exacerbate the symptom, adding fats and sauces, and drinking more water. Good oral hygiene may also help alleviate some taste alterations. At present, there is no evidence-based pharmacological treatment for dysgeusia.

Hematological toxicity

Hematological toxicity occurs commonly in patients treated with olaparib, including clinical diagnoses and/or laboratory findings of anemia, neutropenia, thrombocytopenia and lymphopenia. Although the majority of anemia events in Study 19 were generally mild or moderate, grade ≥ 3 events of anemia (based on laboratory values of hemoglobin levels) occurred in 7.4% of patients, and anemia reported as a grade ≥ 3 AE occurred in 5.1% of patients.⁷

Prior to commencing the treatment, patients need to be aware of the potential for hematological side effects and the possibility that a blood transfusion may be required. Patients should not start treatment with olaparib until they have recovered from any hematological toxicity caused by previous anticancer therapy (hemoglobin, platelet and neutrophil levels should be within normal range or CTCAE grade 1). In order to monitor for clinically significant changes in any parameter during the treatment, baseline testing followed by monthly assessment of complete blood counts (including a blood film) is recommended for the first 12 months of olaparib treatment and then periodically (if counts remain in the normal range, assessment every 3 months would be appropriate) after this time.

Toxicities can be managed by dose interruptions. If required, dose interruptions can be repeated for a maximum of 4 weeks on each occasion to allow events to resolve to grade ≤ 1 . It is possible that in the case of treatment-related anemia, events may be managed by transfusions without interruption of study drug. If events are grade 3 or 4 and toxicity resolves to grade ≤ 1 within a maximum of 28 days following dose interruption, patients should restart treatment at a lower dose (dose reduction to 200 mg twice daily for a total daily dose of 400 mg). For grade 3 or 4 events that do not resolve within a maximum of 28 days and whereby the patient has already undergone two dose reductions (to a minimum of 100 mg twice daily for a total daily dose of 200 mg), treatment should be discontinued. If a patient develops severe hematological toxicity or still requires blood transfusion after dose reductions, treatment with olaparib should be interrupted and appropriate hematological investigations undertaken. Referral to a hematologist should also be considered. Assessment of reticulocyte counts and other markers of blood cell production may be used to provide a clinical picture of bone marrow response. Additionally, deficiency in vitamin B12, folate and iron needs to be ruled out. If blood parameters remain clinically abnormal after 4 weeks of olaparib dose interruption, bone marrow biopsy and cytogenetic analysis are recommended.

Myelodysplastic syndrome/acute myeloid leukemia

Treatment-related MDS/AML is a well-known but rare complication of chemotherapy. MDS/AML in olaparib-treated patients has a current incidence rate of $<1\%$, which is in line with the expected rate in a heavily pretreated cancer population. Reports of MDS/AML

in olaparib-treated patients were typical of secondary MDS/cancer therapy-related AML. The duration of therapy with olaparib in patients who developed secondary MDS/AML varied from <6 months to >2 years. All patients had potential contributing factors for the development of MDS/AML, having received multiple lines of chemotherapy with platinum agents. Many had also received other DNA-damaging agents.

Patients should be made aware of the potential risks of MDS/AML with an understanding that, because of its serious consequences, monitoring is important. At the same time, patients should be advised that a direct link between olaparib use and MDS/AML has not been demonstrated. The patient must decide whether the potential benefits of olaparib maintenance therapy outweigh the potential risk of MDS/AML. Patients should be advised to contact their health care provider if they experience weakness, tiredness, fever, weight loss, frequent infections, bruising, easy bleeding, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts or a need for blood transfusions, as these may be signs of hematological toxicity or MDS/AML.

In the event that MDS and/or AML are confirmed while on treatment with olaparib, it is recommended that the patient is referred to a hematologist for appropriate management. Olaparib therapy must be ceased and the AE reported to AstraZeneca, which will also inform the health authorities.

Pneumonitis

Pneumonitis has been reported in a small number of patients receiving olaparib (<1%), and some cases have been fatal. The reports of pneumonitis had no consistent clinical pattern and were confounded by a number of predisposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history and/or previous chemotherapy and radiotherapy).⁸ In the phase II olaparib study, grade 1 pneumonitis was reported by one patient each in the olaparib (0.7%) and placebo (0.8%) groups.

Patients need to be aware of the potential risks of pneumonitis and should be advised to contact their health care provider if they experience any new or worsening respiratory symptoms, including shortness of breath, fever, cough or wheezing. If a patient presents with new or worsening respiratory symptoms such as dyspnea, cough and fever, or a radiological abnormality occurs, olaparib therapy should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, olaparib treatment should be discontinued and the patient treated

appropriately (e.g. with steroids) through consultation with a respiratory physician.

CONCLUSIONS

Olaparib has a safety and tolerability profile that supports its long-term administration as maintenance monotherapy. It is important that health care providers effectively communicate not only the potential benefits of maintenance therapy but also the potential side effects, as well as give an overview of the management strategies to control side effects, prior to treatment initiation. Management strategies should be tailored to the individual patient's symptoms. Appropriate and timely management of common AEs, which are generally predictable, mild to moderate, and self-limiting in nature, enables patients to continue with olaparib therapy and potentially derive maximum treatment benefit.

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REFERENCES

- 1 Press JZ, De Luca A, Boyd N *et al.* Ovarian carcinomas with genetic and epigenetic BRCA1 loss have distinct molecular abnormalities. *BMC Cancer* 2008; 8: 17.
- 2 Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature* 2011; 474: 609–15.
- 3 Daniels MS, Babb SA, King RH *et al.* Underestimation of risk of a BRCA1 or BRCA2 mutation in women with high-grade serous ovarian cancer by BRCAPRO: a multi-institution study. *J Clin Oncol* 2014; 32: 1249–55.
- 4 Patel AG, Sarkaria JN, Kaufmann SH. Nonhomologous end joining drives poly(ADP-ribose) polymerase (PARP) inhibitor lethality in homologous recombination-deficient cells. *Proc Natl Acad Sci U S A* 2011; 108: 3406–11.

- 5 Scott CL, Swisher EM, Kaufmann SH. Poly (ADP-ribose) polymerase inhibitors: recent advances and future development. *J Clin Oncol* 2015; **33**: 1397–406.
- 6 Ledermann J, Harter P, Gourley C *et al*. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med* 2012; **366**: 1382–92.
- 7 Ledermann J, Harter P, Gourley C *et al*. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol* 2014; **15**: 852–61.
- 8 AstraZeneca. LYNPARZA. Australian prescribing information. 2016.
- 9 Audeh MW, Carmichael J, Penson RT *et al*. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet* 2010; **376**: 245–51.
- 10 Tutt A, Robson M, Garber JE *et al*. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. *Lancet* 2010; **376**: 235–44.
- 11 Gelmon KA, Tischkowitz M, Mackay H *et al*. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol* 2011; **12**: 852–61.
- 12 Ledermann JA, Harter P, Gourley C *et al*. Overall survival (OS) in patients (pts) with platinum-sensitive relapsed serous ovarian cancer (PSR SOC) receiving olaparib maintenance monotherapy: an interim analysis. *J Clin Oncol* 2016; **34**(15 Suppl): abst 5501.
- 13 Matulonis U, Harter P, Gourley C *et al*. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer and a BRCA mutation: overall survival adjusted for post-progression PARP inhibitor therapy. *Cancer* 2016; **122**: 1844–52.
- 14 Ledermann J, Harter P, Gourley C *et al*. Health-related quality of life (HRQoL) during olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer (PSR SOC) and a BRCA mutation (BRCAm). *European Society for Medical Oncology Congress*; 26–30 September 2014, Madrid, Spain; poster 885PD.
- 15 Banerjee S, Ledermann J, Matulonis U *et al*. Management of nausea and vomiting during treatment with the capsule (CAP) and tablet (TAB) formulations of the PARP inhibitor olaparib. *European Cancer Congress*; 25–29 September 2015, Vienna, Austria; abst 2759.
- 16 Matulonis U, Friedlander M, du Bois A *et al*. Frequency, severity and timing of common adverse events (AEs) with maintenance olaparib in patients (pts) with platinum-sensitive relapsed serous ovarian cancer (PSR SOC). *J Clin Oncol* 2015; **33**(15 Suppl): abst 5550.
- 17 AstraZeneca. LYNPARZA. EU label. 2016.
- 18 AstraZeneca. LYNPARZA. US label. 2016.
- 19 Rolfo C, Swaisland H, Leunen K *et al*. Effect of food on the pharmacokinetics of olaparib after oral dosing of the capsule formulation in patients with advanced solid tumors. *Adv Ther* 2015; **32**: 510–22.
- 20 Sanchez RI, Wang RW, Newton DJ *et al*. Cytochrome P450 3A4 is the major enzyme involved in the metabolism of the substance P receptor antagonist aprepitant. *Drug Metab Dispos* 2004; **32**: 1287–92.
- 21 Bower JE. Cancer-related fatigue—mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol* 2014; **11**: 597–609.
- 22 Hovan AJ, Williams PM, Stevenson-Moore P *et al*. A systematic review of dysgeusia induced by cancer therapies. *Support Care Cancer* 2010; **18**: 1081–7.
- 23 Berteretche MV, Dalix AM, d'Ornano AM, Bellisle F, Khayat D, Faurion A. Decreased taste sensitivity in cancer patients under chemotherapy. *Support Care Cancer* 2004; **12**: 571–6.
- 24 Wilson J, Rees JS. The dental treatment needs and oral side effects of patients undergoing outpatient cancer chemotherapy. *Eur J Prosthodont Restor Dent* 2005; **13**: 129–34.
- 25 Hong JH, Omur-Ozbek P, Stanek BT *et al*. Taste and odor abnormalities in cancer patients. *J Support Oncol* 2009; **7**: 58–65.
- 26 Rehwaldt M, Wickham R, Purl S *et al*. Self-care strategies to cope with taste changes after chemotherapy. *Oncol Nurs Forum* 2009; **36**: E47–56.