Practical considerations for clinicians for transitioning patients on maintenance therapy with olaparib capsules to the tablet formulation of olaparib

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Abstract
Purpose: Olaparib was originally formulated as 50 mg capsules with a recommended dose of 400 mg twice daily which requires patients to take 16 capsules a day. More recently, a tablet formulation with equivalent efficacy has become available and reduces the pill burden for patients to two tablets twice daily which is more convenient for patients. However, it is important to understand the key differences between the olaparib capsule and tablet formulations as they are not bioequivalent, and the doses are not interchangeable. Educating patients when transitioning from capsules to tablets is critical to avoid dosing errors and maintain both safety and efficacy of olaparib maintenance therapy.

Main recommendations: There are no established guidelines on transitioning patients from capsules to tablets. Patients taking 400 mg of the capsules twice daily should be switched to 300 mg of the tablets twice daily. In patients on a reduced dose of 200 mg capsules twice daily, consider switching to 250 mg twice daily of the tablet formulation. In patients on 100 mg capsules twice daily, consider 200 mg tablets twice daily. Particular care should be taken in transitioning patients who are on a reduced dose due to anemia and who have a low hemoglobin (9 g/dL) where a lower dose of the tablets should be considered initially. Close monitoring of patients for the first 3 months with further dose reductions based on tolerability is recommended. The tablet dose can be escalated or de-escalated depending on tolerance.

KEYWORDS
formulation, maintenance olaparib, ovarian cancer, pharmacokinetics

1 | INTRODUCTION

Olaparib is an oral small molecule inhibitor of the nuclear enzymes poly(adenosine diphosphate ribose) polymerase 1 and 2. In Australia, olaparib capsules are approved as maintenance therapy in women with BRCA-mutations and platinum-sensitive recurrent high-grade serous epithelial ovarian, fallopian tube or primary peritoneal carcinoma after complete or partial response to platinum-based chemotherapy. The approval was based on the results from Study 19 which demonstrated a significant increase in progression-free survival (PFS) associated with maintenance olaparib compared to placebo.1 In Study 19, patients were prescribed eight 50 mg olaparib capsules (400 mg) twice daily. Olaparib is poorly soluble and patients need to take 16 capsules a day to achieve adequate bioavailability.

The initial clinical trials of olaparib all used the capsule formulation, but it has been possible to develop a well-absorbed tablet formulation of olaparib that significantly reduces the pill burden for patients to two tablets twice a day which should improve patient adherence with ongoing treatment. This has been welcomed by patients as many will continue on maintenance olaparib for a long duration, with 13%
of patients in Study 19 still on treatment with olaparib capsules beyond 5 years. Study 24 was an adaptive study designed to help establish the optimal dose of the tablet formulation by comparing the bioavailability, efficacy and safety of tablets to the 400 mg capsule formulation twice daily. The recommended dose of the tablets was 300 mg twice daily (two 150 mg tablets twice a day), as the tablets have a higher bioavailability and different pharmacokinetic profile to the capsules. The recent phase 3, SOL02 trial (ENGOT Ov-21) confirmed that maintenance therapy with the olaparib tablet formulation significantly prolonged PFS in patients with platinum-sensitive relapsed ovarian cancer and a germline BRCA1/2 mutation.4 In SOLO2, median investigator-assessed PFS was 19.1 months with olaparib versus 5.5 months with placebo (hazard ratio 0.30, 95% confidence interval [CI] 0.22–0.41; P < 0.0001).4 In the SOLO2 trial, 40% of patients continued to take olaparib tablets at 2 years.4

The dosing of the tablet and capsule formulations are not equivalent. Therefore, it is important for clinicians to understand the differences between the two formulations, as well as how to transition patients safely from the capsule to the tablet formulation. The aim of this publication is to outline the key differences between olaparib capsules and tablets, including the differences in pharmacokinetics, pharmacodynamics and adverse effects. Not all physicians and patients will choose to transition from capsules to tablets, but will have the option to do so in the near future. We provide recommendations on how to transition patients from olaparib capsules to the tablet formulation as well as the suggested dosing and the dose reductions where required. The primary objective is to help clinicians manage the transition to olaparib tablets from olaparib capsules and in particular what doses to use in patients who have had dose reductions of olaparib capsules for adverse effects.

### 2 | PHARMACOKINETICS

Study 24 was an adaptive trial designed to compare the bioavailability, efficacy and safety of the tablet formulation of olaparib, with the 400 mg capsule formulation administered twice daily.3 The 300 mg twice daily dose of the tablet formulation was recommended for phase III clinical trials. Although pharmacokinetic modeling predicted that a 200 mg twice daily tablet dose would deliver similar dose exposure to that observed with 400 mg twice daily of the capsule, direct intrasubject comparison of steady-state exposure showed that while the $C_{max}$ achieved was similar, the geometric mean area under the curve (AUC) and $C_{min}$ were lower. The 400 mg twice daily tablet dose was not well tolerated and showed similar antitumor efficacy to the 300 mg twice daily tablet dose, and therefore development of the 400 mg twice daily dose was not pursued further.

There are important differences in the pharmacokinetics between the capsule and tablet formulations of olaparib, particularly with respect to bioavailability, absorption and dose exposure (summarized in Table 1). Based on Bayesian estimates, the population pharmacokinetic model predicted the geometric mean steady-state exposure of the 300 mg twice daily tablet was 13% higher compared to that following 400 mg twice daily capsule doses.5

Following multiple dosing, steady-state exposure for the 300 mg twice daily dosing of the tablet formulation is 1.2 to 1.4 times that of the capsule formulation dosed at 400 mg twice daily.3 Exposure increased dose proportionally with the maximum concentration ($C_{max}$) increasing 1.9- to 7.5-fold and the geometric mean AUC increasing 1.6- to 12-fold for between a 2- and 10-fold increase in dose (Figure 1).3,10

#### 2.1 | Absorption

Olaparib tablets are rapidly absorbed with a maximum concentration observed between 0.5 and 2 h after tablet dosing compared to between 1 and 3 h for the capsules. Plasma concentration-time profiles decline biphasically with a half-life ($t_{1/2}$) of between 5 and 9 h for tablets compared with 12 h for the capsules.3,10 A high-fat meal does not increase the exposure of olaparib tablets significantly and tablets can be taken without regard to food.11 The relative bioavailability of olaparib 250 mg tablets compared to 400 mg capsules is 1.74 (90% CI 1.36–2.23; AUC ratio).3

#### 2.2 | Metabolism

Olaparib (both capsules and tablets) is primarily metabolized by CYP3A. Concomitant administration with a strong CYP3A inhibitor increases the AUC of olaparib by 2.7-fold. Concomitant administration with a moderate CYP3A inhibitor increases olaparib AUC by twofold.12 Therefore, concomitant use of a strong or moderate CYP3A inhibitor should be avoided. However, if this is unavoidable, the product information recommends a dose reduction for olaparib to 100 mg tablets.
2.3 | Excretion

Following a single dose of $^{14}$C-olaparib, 86% of the dosed radioactivity was recovered within a 7-day collection period, 44% via the urine and 42% via the feces. The majority of the material was excreted as metabolites.\(^{10}\)

3 | SELECTING THE DOSE

The efficacy in relation to tumor shrinkage was similar between olaparib 300 and 400 mg tablets and 400 mg capsules twice daily in Study 24, but tolerability was better with olaparib 300 mg twice daily tablet formulation and this is the recommended dose.\(^3\)

For patients currently on maintenance treatment with the capsule formulation at the recommended initial dose of 400 mg capsules twice daily and who have had no significant adverse effects, the starting dose of olaparib tablets should be the standard recommended dose of 300 mg twice daily. However, for those patients who have required a dose reduction of olaparib capsules due to adverse effects, selecting the equivalent olaparib tablet dose to transition to, is not as straightforward.

Therefore, we suggest following the dose modifications based on the SOL02 clinical trial, to determine the starting dose of olaparib tablets in patients who have required a dose reduction of olaparib capsules (summarized in Figure 2). If the patient is currently taking 200 mg capsules twice daily (dose level 1), then consider switching the dose to 250 mg twice daily of the tablet formulation which is the initial recommended dose reduction for adverse effects. If the patient is taking 100 mg capsules twice daily (dose level 2), then switch to 200 mg tablets twice daily (dose level 2). It is important to note that no study has been conducted to investigate switching patients from olaparib capsules to the tablet formulation and these recommendations are based on opinion rather than direct evidence from trials. Clinicians should exercise judgment and monitor their patients closely particularly in the first 3 months when transitioning from the capsule to the tablet formulation and further dose modifications may be required depending on tolerability.\(^6\)

The half-life of the capsule formulation is slightly longer than for the tablet formulation (Table 1) and the dose exposure less predictable and is only linear up to doses of 100 mg, whereas dose exposure is more linear for the tablets up to 450 mg (Figure 1). This means that it is not possible to simply calculate the proportional dose of the tablets based on the capsule dose when transitioning patients. In addition, we cannot assume that the maximum dose of the tablet formulation will be as well tolerated in all patients stable on the maximum dose of the capsule formulation. This is the reason why patients should be monitored closely, particularly in the first 3 months, and reminded about the potential toxicities and how they can be managed, as we have previously described in detail.\(^13\)

Patients can switch from capsules to tablets consecutively, or alternatively they could cease olaparib capsules for 2–3 days (3–5 half-lives) prior to starting the tablets. We suggest monitoring hematology (FBC) and biochemistry (UEC) weekly for the first month, then monthly during the first year and then periodically thereafter.\(^7\) This may appear onerous but should be considered given the absence of data on transitioning from capsules to tablets and how this may impact on patients.

There is the potential for dose escalation, based on the original reason for the prior dose reduction of olaparib capsules. For example, it would be reasonable to dose escalate if the patient was dose reduced because of gastrointestinal symptoms such as nausea and is tolerating the reduced dose of olaparib tablets well, as in many patients, nausea is self-limiting and improves over time. Whereas, we would be more cautious about dose escalation in the setting where the dose of olaparib was reduced due to anemia requiring transfusions.

3.1 | Pharmacokinetics and dosing in specific populations

3.1.1 | Hepatic impairment

In a hepatic impairment trial, the mean AUC increased by 15% and the mean $C_{\text{max}}$ by 13% when olaparib was dosed in patients with mild hepatic impairment (Child–Pugh classification A) compared with patients with normal hepatic function.\(^7\) Mild hepatic impairment had no effect on the protein binding of olaparib and therefore total plasma exposure was representative of free drug. Olaparib can be administered to
patients with mild hepatic impairment with no dose adjustment; however, these patients should be monitored closely for hepatic function and adverse events.7 There are no data in patients with moderate or severe hepatic impairment, and therefore olaparib is not currently recommended in this setting.7,10

3.1.2 Renal impairment

In a renal impairment trial, the mean AUC increased by 24% and C\text{max} by 15%, when olaparib was dosed in patients with mild renal impairment (creatinine clearance [CrCL] between 51 and 80 mL/min defined by the Cockcroft–Gault equation; \( n = 13 \)) and by 44% and 26%, respectively, when olaparib was dosed in patients with moderate renal impairment (CrCL between 31 and 50 mL/min; \( n = 13 \)), compared to those with normal renal function (CrCL 81 mL/min or more; \( n = 12 \)).9 There was no evidence of a relationship between the extent of plasma protein binding of olaparib and creatinine clearance. For patients with moderate renal impairment (CrCL between 31 and 50 mL/min), the recommended dose is 200 mg tablets twice daily.7 No dose adjustment is required in mild renal impairment. There are no data in patients with severe renal impairment or end-stage renal disease (CrCL 30 mL/min or less).7,10 Olaparib is not recommended in these patients.

3.1.3 Body weight, age, race and sex

There are limited data available on the impact of body weight, sex or race on the pharmacokinetics of olaparib tablets. Olaparib tablet doses of 200 and 300 mg twice daily were considered tolerable in Japanese patients and the 300 mg twice daily dose was selected as the recommended tablet dose for future studies.14 There are no apparent differences in the safety or effectiveness in patients older than 65 years, but there are limited clinical data in patients over 75 years old.7,10

4 TOXICITY

A comparison of the adverse effects reported with the capsule and tablet formulations of olaparib is outlined in Table 2 and includes the pivotal trials in patients with ovarian as well as breast cancer.

The most common adverse events observed in the SOLO2 trial, that compared 300 mg olaparib tablets twice daily to placebo, are reported in Table 2 and discussed in greater detail below.4 The overall incidence of grade 3–4 adverse events was low in both groups, and similar to that previously reported for olaparib capsules.4 The most common adverse event of grade 3 or worse severity in the olaparib group was anemia.4 One in five patients in the olaparib group required a blood transfusion compared with only one in 100 in the placebo group.4 The incidence of neutropenia and thrombocytopenia of grade 3 or worse severity did not differ between the groups.4

Serious adverse events were experienced by 35 (18%) patients in the olaparib group and eight (8%) patients in the placebo group.4 The most common serious adverse events in the olaparib group were anemia (4%), abdominal pain (2%) and intestinal obstruction (2%). The most common in the placebo group were constipation (2%) and intestinal obstruction (2%).4

One (1%) patient in the olaparib group had a treatment-related adverse event (acute myeloid leukemia) with an outcome of death.4 No other deaths were considered to be related to study treatment.4 The incidence in the safety population of acute myeloid leukemia, myelodysplastic syndrome and chronic myelomonocytic leukemia on long-term follow-up was 2% in the olaparib group and 4% in the placebo group in SOLO 2.4 This is most likely attributed to the effects of multiple prior lines of systemic chemotherapy and/or genetic predisposition.4
TABLE 2  Comparison of adverse events between capsule and tablet formulations of olaparib in ovarian cancer (and comparison to breast cancer)

|                  | Capsules² | Tablets⁴ | Breast⁵ |
|------------------|-----------|----------|---------|
|                  | All grades (%) | Grade ≥ 3 (%) | All grades (%) | Grade ≥ 3 (%) | All grades (%) | Grade ≥ 3 (%) |
| Olaparib         | (n = 136)  | (n = 136) | Olaparib| (n = 196)  | (n = 196)  | Olaparib| (n = 205)  | (n = 205)  |
| Olaparib         | Placebo   | Placebo   | Olaparib| Placebo   | Placebo   | Olaparib| Placebo   | Placebo   |
| Any adverse event| 97.1      | 93.0      | 43.4    | 21.9      | 98.5      | 94.9    | 36.4    | 18.2      | 97.1      | 36.6      |
| Nausea           | 70.6      | 35.9      | 2.2     | 0         | 75.9      | 33.3    | 2.6     | 0         | 40.0      | 0.0       |
| Fatigue/asthenia | 63.2      | 46.1      | 8.8     | 3.1       | 65.6      | 39.4    | 4.1     | 2.0       | 28.8      | 2.9       |
| Vomiting         | 35.3      | 14.1      | 2.2     | 0.8       | 37.4      | 19.2    | 2.6     | 1.0       | 29.8      | 0.0       |
| Diarrhea         | 27.2      | 24.2      | 2.2     | 2.3       | 32.8      | 20.2    | 1.0     | 0.0       | 20.5      | 0.5       |
| Anemia           | 21.3      | 5.5       | 5.9     | 0.8       | 43.6      | 8.1     | 19.5    | 2.0       | 40.0      | 16.1      |
| Neutropenia      | 5.1       | 3.9       | 3.7     | 0.8       | 19.5      | 6.1     | 5.1     | 4.0       | 27.3      | 9.3       |
| Thrombocytopenia | 3.7       | 2.3       | 0.7     | 0         | 8.2       | 3.0     | 0.5     | 1.0       | -         | -         |

Note: Grade refers to NCI CTCAE criteria.

7 | DISCUSSION

The development of the olaparib tablet formulation has simplified the management of patients who now require a significantly lower pill burden compared to the capsule formulation. Maintenance olaparib following response to platinum-based chemotherapy in patients newly diagnosed with platinum-sensitive recurrent ovarian cancer is now considered standard of care, and every effort should be made to ensure patients are not restarted on the capsule formulation. The treatment because of toxicity is now rare compared to the capsule formulation.

Educating patients about the change in formulation and the number of tablets to be taken per day is critical as it is important to explain that the 100 mg twice daily tablet dose is equally effective as the 400 mg twice daily capsule dose. It is also important to explain that the 100 mg twice daily tablet dose is equally effective as the 400 mg twice daily capsule dose, as some patients may equate receiving fewer pills with a reduction in efficacy. It may also be useful to relay that the experience of women in the United States transitioning from the capsule to the tablet formulation has been positive. Written information should be provided to patients transitioning to the tablet formulation clearly explaining the number of tablets that should be taken.

6 | AVOIDING MEDICATION ERRORS

A greater proportion of patients in the placebo group discontinued treatment because of toxicity compared to the oblaparib group (11% vs 2%). The most common adverse events leading to discontinuation in the placebo group were anemia (3%) and neutropenia (1%).

Dose reductions (25% vs 3%) and dose interruptions (45% vs 18%) following adverse events were more common in the olaparib group than in the placebo group. Despite the above, there were no appreciable differences in quality of life reported by patients receiving olaparib compared with those receiving placebo. In the SOLO2 trial, patients who switched from capsules to tablets experienced more discontinuations on olaparib (11% vs 6%) and more dose interruptions (44% vs 30%). This could be because of the greater bioavailability of the tablet versus the capsule formulation which underscores the need for initial close monitoring of the adverse events.

Nausea, vomiting, diarrhea, and anemia were the most commonly reported adverse events in the SOLO2 trial, but most were grade 2 or lower (Table 2). In keeping with the trial protocol, our recommendation is for dose interruptions only in patients with grade 3 or higher toxicities. If a dose interruption is insufficient to manage the adverse event, then dose reductions initially to 250 mg twice daily olaparib tablets and then subsequently to 200 mg twice daily are recommended (Figure 2). Patients with grade 1 or 2 nausea should be prescribed appropriate antiemetic therapy. Likewise, patients who experience grade 1 or 2 diarrhea should be given maximal supportive therapy as these symptoms are usually self-limiting.

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that patients are well managed and that they are aware of the potential adverse effects associated with treatment. The adverse effects can, for the most part, be managed with supportive care and dose interruptions/dose reductions and we have provided guidance on this previously.13 There are many patients currently taking olaparib capsules who may choose to be transitioned to tablets and we expect that the majority will welcome the reduced pill burden. Given that there have not been any studies on switching formulations, we have provided an overview of olaparib tablets and suggestions regarding appropriate dosing, particularly in patients who are taking a reduced dose of the olaparib capsules due to toxicity. We accept that these recommendations are not based on strong evidence, but they are intended to serve as a guide for clinicians and pharmacists. The ultimate decision regarding olaparib dosing must lie with the clinician managing the patient and be based on tolerability and ongoing benefit.

Not all physicians and patients will choose to transition from capsules to tablets but, as the tablets become available, they will have the option to do so in the near future. Where capsules are currently available, existing patients will be able to have continued access to the capsule dose form; however, once tablets become available, new patients are expected to initiate olaparib therapy with the tablets.

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