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Title: Phase I and pharmacological study of discontinuous olaparib tablets in combination with carboplatin, paclitaxel, or a carboplatin/paclitaxel doublet (part 2)

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ABSTRACT

PURPOSE

In the first part of this extensive phase I study (ClinicalTrials.gov identifier NCT00516724; AstraZeneca study code D0810C0004), it was attempted to combine continuous olaparib (Lynparza™) with carboplatin and/or paclitaxel. This resulted in increased myelosuppression, leading to many dose modifications. In the last parts, the safety, tolerability and preliminary anti-tumor activity of *dis*continuous olaparib (both as capsules and a new tablet formulation) combined with carboplatin and paclitaxel was evaluated.

PATIENTS AND METHODS

This paper describes the last parts (P) of this study: *dis*continuous olaparib (both as capsules and the new tablet formulation) schedules with carboplatin/paclitaxel (PIII and PIV). Safety assessments included physical examinations, vital signs and blood sampling for clinical chemistry and hematology. In PIII, only single-dose pharmacokinetic (PK) sampling was conducted for olaparib. Tumor evaluations were done every 2 cycles.

RESULTS

In total, 132 heavily pre-treated patients (88% female; 12% male) were included. Most common tumor types were breast (49%) and ovarian cancer (29%). BRCA mutations were identified in 33% of patients. As previously observed, most common haematological toxicities were mainly neutropenia (47%) and thrombocytopenia (39%),

which were often severe and frequently led to dose modifications. Both Cmax and AUC0-8 were higher with the tablet formulation when compared to the olaparib capsules, following a 200 mg dose. Anti-tumor activity was observed with an objective response rate of 46%.

CONCLUSION

Discontinuous dosing of olaparib did not result in less myelosuppression. Many cycles had to be interrupted and/or delayed. Olaparib tablets showed a higher bioavailability. Anti-tumor activity was encouraging in this cohort of patients enriched with tumor type and BRCA mutation in these parts of the study. Overall, this study supports that a low dose of olaparib can be given in combination with carboplatin and paclitaxel for a limited number of cycles.

TEXT

INTRODUCTION

This is the second part of an extensive Phase I study (ClinicalTrials.gov identifier NCT00516724; AstraZeneca study code D0810C0004) that aimed to combine the PARP inhibitor olaparib (Lynparza™) with the cytotoxic anti-cancer agents carboplatin and paclitaxel, since it was shown in preclinical experiments that PARP inhibitors, such as olaparib, could increase the sensitivity of tumor cells to DNA-damaging agents.[1, 2] Monotherapy studies of olaparib showed that this novel anti-cancer drug has a relatively mild toxicity profile. Moreover, in the early clinical studies olaparib already demonstrated very encouraging signs of anti-tumor activity in patients whose tumors harboured a BRCA mutation.[3–5]

However, as shown in the first part of this study, the combination of olaparib with carboplatin resulted in an increased frequency and severity of myelosuppression, especially thrombocytopenia. The addition of paclitaxel, which was thought to reduce the rate of thrombocytopenia, still resulted in increased myelosuppression, especially neutropenia. While this myelosuppression rarely lead to clinical consequences, it did lead to extensive dose modifications, such as dose interruptions, dose reductions and cycle delays.[6]

Since up to this point in the study, olaparib had been continuously administered, it was thought that perhaps switching to a discontinuous schedule of olaparib could reduce the frequency and severity of myelosuppression. Furthermore, in the monotherapy studies,

the olaparib formulation had been switched from a capsule to a tablet, since this would reduce capsule burden (16 capsules 25 mg equals 4 tablets of 50 mg in bioavailability).[7] Thus, it was decided to also switch the formulation in this part of the study.

In summary, due to tolerability issues with a continuous dosing regimen in combination with carboplatin and paclitaxel, these last two parts of this Phase I study incorporated discontinuous dosing schedules of olaparib to establish whether a tolerable regimen could be found, while also using the olaparib tablet formulation.

PATIENTS AND METHODS

All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki, local institutional review board ethical approval, Good Clinical Practice and applicable regulatory requirements.

Patient selection

Male or female patients with histologically or cytologically diagnosed malignant solid tumors were recruited. In the dose expansion phase of the study, female patients with histologically or cytologically diagnosed metastatic triple-negative breast cancer (platinum-naïve) or advanced ovarian cancer (where further treatment with platinum-based chemotherapy was indicated) were eligible for participation.

Inclusion criteria were as follows: age $\geq$ 18 years; performance status $\leq$ 2 (ECOG scale); adequate bone marrow, hepatic and renal function as defined by hemoglobin $\geq$ 10.0 g/dl (6.2 mmol/L), absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L; total bilirubin : $\leq$ 1.25 x upper normal limit (ULN); serum aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT): $\leq$ 2.5 x ULN; creatinine: $\leq$ 1.5 x ULN; and a minimum washout period of 4 weeks after any previous anti-cancer therapy. Patients were not allowed to have had more than two previous courses of platinum-containing chemotherapy; additionally, in the dose expansion phase triple-negative breast cancer patients were not allowed to have had any previous platinum-containing chemotherapy.

Study design

In the earlier two parts of the study, the highest safe doses of continuous olaparib with carboplatin (part I) was investigated. Because of an increased frequency/severity of thrombocytopenia, it was decided to add paclitaxel to the regimen and thus olaparib in combination with a paclitaxel/carboplatin doublet was explored in part IIa. As described separately, since a clinically acceptable dose of the combination regimen could not be achieved in part IIa due to an increased toxicity profile consisting mostly of bone marrow suppression (mainly neutro- and thrombocytopenia), part III was opened in which olaparib was given *dis*continuously. Towards the end of part III, a formulation switch to olaparib tablets (all previous parts had been dosed with the capsule formulation) was performed. One dose-level in part III that was deemed tolerable was expanded, but the expansion part unfortunately showed a less favourable toxicity profile and this dose-level was judged not to be appropriate for further phase II/III studies. Thus, the last part of this study (part IV) was started which explored other discontinuous dosing schedules of olaparib, including off-setting of the starting day (from day 1 to day 3). An overview of the dose-levels is given in table 1.

The dosing schedule for each new cohort was determined by investigators and sponsor after reviewing of the safety, tolerability and operational feasibility of the regimen adopted in previous cohorts.

MTD was again defined as the prior or intermediate dose-level below the combination that caused a dose-limiting toxicity (DLT) in 2 patients in a cohort of at least 3 patients.

Drug administration and dosing schedule

Olaparib was first given as Gelucire® capsules that contained up to 50 mg. Towards the end of part III there was a formulation switch to a Melt-Extrusion tablet that contained up to 100 mg olaparib and was expected to show a higher bioavailability.
In part III, olaparib was administered from day 1 to 10 together with a paclitaxel/carboplatin doublet in a 3-weekly cycle. In part IV other discontinuous schedules, consisting of administration of olaparib for any pre-defined number of days (up to 20 days) in combination with a paclitaxel/carboplatin doublet, were given including off-setting the start dose of olaparib to day 2 or later.
Lowest doses of olaparib, carboplatin and paclitaxel doses were 50 mg once daily (QD), AUC4 and 80/90 mg/m^2 (weekly/3-weekly) or above 400 mg BID, AUC6 and 175 mg/m^2 (3-weekly), respectively.

Toxicity criteria

All adverse events were monitored and graded according to the National Cancer Institute Common Terminology Toxicity Criteria for Adverse Events (NCI-CTCAE) version 3.0.[8]
A DLT was defined as the following study drug-related events experienced during the first treatment cycle: thrombocytopenia with platelets < 25 x10^9/L or grade 4 neutropenia lasting ≥ 7 days; grade 3 or 4 febrile neutropenia; grade 3 or greater non-hematological toxicities (excluding grade 3 diarrhea, nausea or vomiting despite adequate treatment and

grade 3 fatigue, lethargy and gamma-glutamyltransferase (GGT) elevation); Delay of > 2 weeks for next scheduled carboplatin or paclitaxel due to toxicity.

Pharmacokinetic sampling

Extensive PK sampling for the combination and olaparib capsule monotherapy were completed in part I, IIa and IIb, therefore only the single dose PK of the olaparib capsules was compared with olaparib tablets in part III.

Olaparib

Plasma samples were taken for olaparib at the following time-points:

Olaparib given day 1-7: Cycle 1 day 1, 2 and 8 → predose, 30 min, 1, 2, 3, 4 6, 8 hours post-dose.

Olaparib given ≥ 8 days: Cycle 1 day 1 and 18 → predose, 30 min, 1, 2, 3, 4, 6, 8 hours post-dose; day 18 anytime.

A validated high performance liquid chromatography method with tandem mass spectrometric detection (HPLC/MS/MS) was used to analyze the olaparib plasma samples. PK parameters for olaparib were calculated using non-compartmental analyses.

Response measurements

Tumor assessments by CT or MRI scans were performed at baseline and at the end of

every two cycles. Patients with measurable disease had objective response assessments determined according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 guidelines.[9] Responses were assigned as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) at each scheduled imaging visit by the investigator.

Clinical endpoint for response was objective response rate (ORR), defined as CR+PR.

RESULTS

Patients

A total of 132 patients was included in the last two parts of this study. Baseline patient characteristics are summarized in table 2. The majority of patients was female (88%); most common tumor types were breast (49%) and ovarian (29%) cancer. Most patients were heavily pre-treated with surgery, radiotherapy and several lines of chemotherapy. Although the study originally started in an unselected patient population, part III and IV were enriched with BRCA mutation carriers and triple negative breast and ovarian cancer patients since emerging evidence suggested that these patients were expected to benefit most from the treatment.

Dose Limiting Toxicities (DLTs) and Maximum Tolerated Dose (MTD)

One DLT was observed: a grade 3 elevated ALT lasting for 8 days and leading to olaparib dose interruption (cohort 20; olaparib 100 mg BID day 3-12; carboplatin AUC4; paclitaxel 175 mg/m^2).

Despite two dose-levels being expanded (cohort 17 and 21, table 1), a MTD was not attained in this study due to extensive dose modifications needed due to increased bone marrow toxicity (described in further detail below).

Safety

Most frequently observed adverse events (table 3) were alopecia (89%), fatigue (84%) and gastrointestinal disorders, including nausea (71%), constipation (50%) and diarrhea (45%).

In total, 99 patients experienced a TEAE of grade 3 or higher in severity. As previously observed in the first two parts of this study, these consisted of mostly hematological toxicities, mainly neutropenia (39%). Nearly all non-hematological toxicities were mild (grade 1-2); only fatigue reached grade ≥3 in 9% of patients.

Despite the intermittent dosing of olaparib and formulation switch, bone marrow suppression incidence remained high, most prominently neutropenia (43%) and thrombocytopenia (41%). Neutropenia and leucocytopenia were most abundant throughout all dosing cohorts, whereby the frequency and severity increased after the formulation switch to tablets, despite discontinuous dosing. As was the case with continuous dosing, the prolonged bone marrow suppression often led to dose interruptions, delays and/or reductions which were needed for the laboratory values to recover back to grade 1 and some patients required frequent doses of the granulocyte colony-stimulating factor pegfilgrastim. Therefore, most cohorts were declared intolerable for multiple cycles. An overview of olaparib dose modifications in all dose levels of this phase I study is given in table 4. It shows that dose-levels with a relatively low dose of olaparib (50 mg) combined with carboplatin and paclitaxel were best tolerated, having to apply the least dose modifications.

Pharmacokinetics

Olaparib

Part III (discontinuous)

A total of 38 patients was sampled and analyzed for olaparib PK in part III. The geometric mean single dose exposure to olaparib (maximum plasma concentration (C_{max}) and AUC_{0-8}) following administration of a 200 mg tablet dose (6.16 ug/mL (CV% 19.3) and 16.7 ug*h/mL (CV% 18.6) respectively) was higher than after the same dose given in capsule formulation (2.08 ug/mL (CV% 40.9) and 8.60 ug*hr/mL (CV% 36.0) respectively). C_{max} was also higher with 200 mg tablets than after administration of the 400 mg capsule formulation (4.35 ug/mL (CV% 28.5)); however, AUC_{0-8} (17.4 ug*hr/mL (CV% 36.2)) was similar.

Figure 1 shows the plasma concentration-time curves of 200 mg olaparib doses for both the capsules and the tablets when combined with carboplatin AUC4 and paclitaxel 175 mg/m^2.

Anti-tumor activity

Anti-tumor activity is summarized in table 5. In total, 109 patients were evaluable for at

least 1 response assessment. Four patients achieved CR and 46 patients PR, resulting in an ORR of 46% for the total evaluable population. Additionally, there was one unconfirmed CR and seven unconfirmed PRs. Although this ORR is much greater than the ORR of 11% found in the first two parts of this study, it should be noted that by this time in the study there was a selection bias, as sites included more patients with breast and ovarian cancer with known BRCA mutations, since these patients were expected to gain more benefit from PARP inhibition.

Again, duration of response was not calculated for the majority of patients with a confirmed PR or CR because per protocol only 6 cycles of study data were collected, with a number of patients switching to olaparib monotherapy after 6 cycles due to tolerability issues with the combination therapy.

DISCUSSION

Due to the extensive nature of this Phase I study, it was decided to publish the data over two separate papers. In the first two parts of this study, it became clear that combining continuous olaparib with carboplatin led to a significant increase in bone marrow suppression. Adding paclitaxel to this combination did not reduce the incidence and severity of the hematological toxicities.

In the last two parts of this study, it was therefore decided to administer olaparib discontinuously.However, the incidence and duration of myelosuppression remained high (neutropenia around 47% and thrombocytopenia 39%), resulting in dose modifications in approximately 75% of patients. Two dosing cohorts with acceptable toxicity profiles (17 and 21) were chosen for expansion, both comprising discontinuous olaparib tablet dosing (100 mg BID day 1-10 and 50 mg BID day 1-5) with paclitaxel 175 mg/m^2 and carboplatin AUC4 and AUC5, respectively, in a 21-day cycle. However, the observed related adverse events (especially myelosuppression) in the expansion of these dose-levels suggested that a MTD was not attained in this study.

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Recently published results of clinical trials in which olaparib was combined with chemotherapeutic agents have also shown increased myelosuppression, hampering the development of these combinations.[10, 11] Interestingly, two recent Phase I studies, in which olaparib was combined with either gemcitabine or cisplatin, both found a tolerable dosing regimen when olaparib was given intermittently, while continuous dosing of olaparib resulted in unacceptable hematological toxicities.[11, 12] As previously reported[7], the switch to the tablet formulation showed higher olaparib exposures than seen with the

capsule formulation, which might also account for the increased incidence of adverse events observed with the tablet formulation.

The ORR seen in these parts of the study was 46%. The observed response rates were higher in the tablet than in the capsule cohorts. However, by the time of the formulation switch in the study, more stringent patient selection had resulted in a population enriched with breast and ovarian cancer patients with a BRCA mutation. Response rates are difficult to compare to published data on carboplatin/paclitaxel treatment, since this phase I study included a heavily pre-treated patient population with various tumor types. The duration of response was not calculated due to the fact that data were not collected for more than 6 cycles. Patients who showed a response in this study but did not tolerate the combination of olaparib with carboplatin and/or paclitaxel switched to olaparib monotherapy after 6 cycles, as it was believed they would experience further clinical benefit from continued PARP inhibition. Interestingly, a recent publication has strengthened this hypothesis in a phase II study, in which platinum-sensitive ovarian cancer patients were first given a lower dose of olaparib in combination with carboplatin and paclitaxel, followed by a higher dose of olaparib as monotherapy. Progression-free survival was shown to be significantly improved (12.2 vs 9.6 months) when compared to carboplatin/paclitaxel alone, especially in patients carrying a BRCA mutation.[13]

Responses were mostly seen in BRCA mutation carriers. Data on the identified BRCA mutations were not available. It is known from previous research that not all BRCA mutations are clinically relevant[14], which might explain why not all patients who had a BRCA mutation showed a response. Furthermore, there are several known and unknown

mechanisms that could infer resistance to PARP inhibition, such as the restoration of BRCA function.[15]

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Due to the increased frequency, severity and duration of myelosuppression seen when adding olaparib to carboplatin and/or paclitaxel it was difficult to find a tolerable dosing regimen for combination therapy. None of the regimens explored could be given for multiple cycles without the need for dose modifications within 6 cycles. When looking at the totality of this Phase I study, it appears that a only a low dose of olaparib (50 mg BID in capsules) could be given continuously in combination with carboplatin/paclitaxel. Perhaps a low daily dose of olaparib would be sufficient to fully inhibit PARP and still enhance the effects of chemotherapy.

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