TITLE PAGE

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

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ABSTRACT

PURPOSE

The PARP inhibitor olaparib (Lynparza™) has shown an acceptable toxicity profile as monotherapy at doses up to 400 mg twice daily with encouraging signs of anti-tumor activity, especially in BRCA mutation carriers. Based on its mode of action, olaparib could also sensitize tumor cells to DNA-damaging agents, particularly platinum compounds. In the first parts of this phase I trial (ClinicalTrials.gov identifier NCT00516724; AstraZeneca study code D0810C0004), continuous olaparib (in capsule formulation) was combined with carboplatin and/or paclitaxel.

PATIENTS AND METHODS

This paper describes the first three parts (P) of the study: continuous olaparib with carboplatin alone (PI), paclitaxel alone (PIIb) or with carboplatin and paclitaxel (PIIa) . Safety assessments included physical examinations, vital signs and blood sampling for hematology and clinical chemistry. Pharmacokinetic (PK) sampling was conducted for olaparib, carboplatin and paclitaxel. Tumor responses were assessed every 2 cycles.

RESULTS

In total, 57 patients (46% female; 54% male) were included. Most common tumor types were breast (21%) and melanoma (9%). BRCA mutations were identified in 14% of patients. Non-hematological adverse events were predominantly mild (grade 1-2) and included fatigue (70%), nausea (40%) and alopecia (30%). Bone marrow suppression,

mainly neutropenia (51%) and thrombocytopenia (25%), which were often ≥ grade 3 and frequently led to dose modifications was the main toxicity encountered. Paclitaxel reduced systemic exposure to olaparib. Anti-tumor activity was observed with an objective response rate of 11% in the total population and …% in BRCA mutation carriers.

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CONCLUSION

The combination of continuous olaparib with carboplatin and/or paclitaxel resulted in an increased level of bone marrow suppression which made it challenging to establish a dosing regimen that could be tolerated for multiple cycles without the need for dose modifications.

INTRODUCTION

Development of new anti-cancer drugs is focusing ever more on targeted therapies which, in contrast to classic chemotherapy, can discriminate between the tumor and healthy tissues by targeting specific abnormalities that are only present in tumor cells.

One of the most promising targeted therapies is the class of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors. PARP is a DNA-damage recognition protein that is involved in the repair of single strand DNA breaks (SSBs). Inhibition of PARP eventually leads to accumulation of SSBs, resulting in double strand DNA break (DSB) formation during replication. Homologous recombination (HR) is responsible for adequate repair of DSBs. If cells are HR-deficient, DSBs will not be repaired properly, most likely resulting in apoptosis of these cells. Therefore, PARP inhibition is expected to be especially effective in tumors harbouring a BRCA mutation, since these tumors lack the ability to repair DSBs through HR.[1–5] This concept of so-called 'synthetic lethality' has been proven to be effective and is currently being exploited in a variety of clinical trials with PARP inhibitors.

Olaparib (Lynparza™) is a potent, selective PARP inhibitor. Clinical studies with this drug have shown a favourable safety profile at doses up to 400 mg twice daily in capsule formulation as single agent with main toxicities being nausea, fatigue and vomiting. More importantly, olaparib has shown impressive anti-tumor activity in BRCA mutation carriers, in both phase I and II studies.[6–9]

In addition to its anti-tumor activity as monotherapy in patients with BRCA-mutated tumors, olaparib could sensitize tumor cells to the DNA-damaging effects of cytotoxic

anti-cancer agents based on its mode of action. Accordingly, preclinical research has already established the role of PARP in the repair of DNA-damage caused by platinum adducts.[10] Moreover, inhibiting PARP has been shown to increase the sensitivity of tumor cells to platinum agents in preclinical models.[11–14]

Olaparib has already been shown to be active and well-tolerated when combined with either paclitaxel[15] or carboplatin[16] alone in patients with metastatic breast and ovarian cancer. The combination of carboplatin with paclitaxel has also been shown to be an effective treatment modality in the same patient groups and possesses a more favourable toxicity profile than cisplatin with paclitaxel.[17–21] Additionally, paclitaxel has been demonstrated to show activity as monotherapy against various types of cancer, especially breast and ovarian cancer, but even more so in combination with carboplatin.[22,23]

The main aims of this phase I study (ClinicalTrials.gov identifier NCT00516724; AstraZeneca study code D0810C0004) were to establish the safety and tolerability and maximum tolerated dose (MTD) of olaparib in combination with carboplatin and/or paclitaxel in patients with advanced solid tumors, to facilitate future clinical development of these combinations.

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.

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

Study design

First, 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. At the same time, the safety profile and pharmacokinetics (PK) of paclitaxel in combination with olaparib were established in part IIb. An overview of the dose-levels is given in table 1.
For each new cohort, the duration and timing of the dosing were decided by the investigators and sponsor upon review of the safety, tolerability and operational feasibility of the regimen adopted in previous cohorts.
For all drug combinations, the MTD was 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 given as Gelucire® capsules that contained up to 50 mg of drug. In part I and IIa, olaparib was given twice daily (BID) together with 3-weekly carboplatin or paclitaxel/carboplatin, respectively. In part IIb, olaparib was given continuously with weekly paclitaxel.
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 200 mg BID, AUC5 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.[24] 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

Pharmacokinetic sampling to determine the influence of carboplatin, paclitaxel and the combination on the steady state PK of olaparib was performed.

Olaparib

Plasma samples were taken for olaparib alone and when administered in combination with carboplatin and/or paclitaxel both separately and in combination at the following time-points:

Cycle 1 day 4 (alone at steady state) and 8 (combination) → predose, 30 min, 1, 2, 3, 4 6, 8 hours post-dose.

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.

Carboplatin

From the first 10 patients only a single PK sample was drawn 24 hours after the cycle 1 day 8 administration. The free platinum area under the plasma concentration-time curve (AUC) was then estimated using the Ghazal-Aswad method.[25]

From the following patients, PK samples were taken for platinum with olaparib alone and in combination with paclitaxel at the following time-points:

Part I (combination with olaparib alone) and IIa (combination with olaparib and paclitaxel): Cycle 1 day 8, 9 and 10 → predose, end of infusion (EOI), EOI + 0.25, 0.5, 1, 2, 4, 8, 12, 24 and 48 hours.

The samples were not processed to determine free (unbound) platinum, thus only total platinum concentrations were analyzed and used to generate the AUC for total carboplatin. These AUCs were then corrected for plasma protein binding using the protein data in section 5.2 of the carboplatin SPC.[26]

Paclitaxel

Lastly, sampling was performed to estimate the exposure to paclitaxel with olaparib alone and in combination with carboplatin at the following time-points:

Part IIa (combination with olaparib and carboplatin) and IIb (combination with olaparib alone): Cycle 1 day 8 and 9 → predose, 1 hour after start infusion, EOI, EOI + 6 and 24 hours.

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.[27] 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.

RESULTS

Patients

A total of 57 patients was included in the first two parts (10 cohorts) of this study. Baseline patient characteristics are summarized in table 2. Roughly half of patients was male (54%); the most common tumor types were breast cancer (21%), melanoma (9%) and lung/bronchus (9%). Most patients were heavily pre-treated with surgery, radiotherapy and several lines of chemotherapy.

Dose Limiting Toxicities (DLTs)

Two patients experienced DLTs, both in cohort 2: a grade 1 thrombocytopenia together with grade 2 neutropenia lasting for 16 days and leading to discontinuation of study drug and grade 2 neutropenia lasting for 7 days resulting in dose interruption, both in cohort 2.

Safety

Of the 57 patients that were evaluable for safety, the majority (97%) experienced a treatment-emergent adverse event (TEAE). The most frequently occurring adverse events are summarized in table 3. These encompassed fatigue (70% of patients), gastrointestinal disorders, including nausea (40%), constipation (28%) and diarrhea (26%) and alopecia (30%).

In total, 32 patients experienced a TEAE of grade 3 or higher in severity. These toxicities

almost universally consisted of hematological toxicities, mostly neutropenia (35%). Thrombocytopenia was only grade ≥ 3 in patients who also received carboplatin.
Most striking in this study was the relatively high incidence of bone marrow suppression, most prominently neutropenia (51%). As it could be expected, the frequency of thrombocytopenia and anemia were lower in the cohorts where olaparib was only combined with paclitaxel. Despite the fact that these toxicities did not lead to any clinical adverse events, many cohorts were declared intolerable due to the prolonged bone marrow suppression. Often dose interruptions, delays and/or reductions 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. Overall, dose adjustments of olaparib, carboplatin or paclitaxel were needed in more than half of the patients. While the bone marrow suppression frequently led to interruptions and reductions of study dosing, it led to discontinuation of treatment in only three patients (5.3%).
When looking into the dose adjustments in more detail, it became clear that some regimens appeared tolerable for up to 3 cycles, while later cycles did show an increase in toxicity. Interestingly, in two dose-levels (cohorts 3 and 4) that both contained 50 mg BID continuous olaparib, hardly any dose adjustments were needed and these dose-levels appeared fully tolerable for up to at least 3 cycles. In another dose-level (cohort 8) that also explored 50 mg BID continuous olaparib one patient required a treatment interruption due to neutropenia, but did not show any other dose adjustment up to 7 cycles of therapy.

Pharmacokinetics

PK parameters for olaparib, carboplatin and paclitaxel are summarized in tables 4a-4c. Additionally, figure 1 shows the plasma concentration-time curves of olaparib alone and in combination with carboplatin and/or paclitaxel.

Olaparib

Part I, IIa and IIb (continuous)

Whole blood samples were taken and plasma was analysed from 50 patients. Geometric mean plasma concentration-time profiles were similar for olaparib alone and in the presence of carboplatin in part I; exposure to olaparib (AUC_{0-8}) was, however, reduced when co-administered with paclitaxel alone (part IIb) and in combination with carboplatin and paclitaxel (part IIa), with a mean reduction of 40-43% and 22-45%.

Carboplatin

24-hour estimation

A single PK sample was collected from 10 patients 24 hours after administration of the cycle 1 day 8 carboplatin infusion. When used to estimate free AUC, this turned out to be approximately 25% (range 9-57%) higher than the target of 4 mg*min/mL.

PK profiles

Subsequently, carboplatin PK samples were evaluated in 24 patients over a 48-hour period following 0.5-hour carboplatin infusion. The mean free $AUC_{0-48.5}$ was determined to be lower than the target of AUC 4 mg*min/mL (range 48-10% lower).

Paclitaxel

Whole blood samples for paclitaxel concentrations were taken from patients in parts IIa and IIb up to 24 hours after a 3-hour infusion. In total, 20 patients had calculable AUC_{0-27} parameters.

Anti-tumor activity

The anti-tumor activity results are summarized in table 5. In total 44 patients were evaluable for at least 1 response assessment. Two patients achieved CR and three patients PR, resulting in an ORR of 11% for the total evaluable population. Additionally, there was 1 unconfirmed PR. 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. A number of patients switched to olaparib monotherapy after 6 cycles due to tolerability issues (predominantly prolonged/increased bone marrow suppression, but also allergic reactions to the chemotherapies) with the combination therapy.

DISCUSSION

This phase I study was originally designed to determine the safety and tolerability of combining olaparib with carboplatin alone. While the frequency of non-hematological toxicities was in line with what is seen when giving carboplatin with paclitaxel, the frequency, severity and duration of myelosuppression (neutropenia 51%; thrombocytopenia 25%) was higher than previously reported for carboplatin alone in patients with advanced ovarian cancer. [21, 28, 29] A protocol amendment then added paclitaxel to the regimen with the aim of reducing the incidence of thrombocytopenia.[30] The combination of olaparib with paclitaxel alone did not result in thrombocytopenia, but an increased incidence of neutropenia (50%; of which 42% grade ≥ 3) was observed when compared with paclitaxel monotherapy (12% grade 2, no grade ≥ 3).[31] Unfortunately, the addition of paclitaxel to olaparib and carboplatin did not significantly reduce the rate of myelosuppression, which remained the cause of many dose modifications. Analyses of all dose-levels revealed that at least two dose-levels (3 and 4) with 50 mg olaparib BID continuously did not cause dose modifications for up to 3 cycles.

The enhancement of myelosuppression by olaparib has also been seen in other phase I trials in which olaparib was added to other chemotherapeutics, such as dacarbazine[32], topotecan[33] and cisplatin/gemcitabine[34]. A possible explanation is that olaparib, in addition to its effect in tumor cells, also enhances the toxic effects of chemotherapeutics on bone marrow cells. Accordingly, when exposed to ionizing radiation, bone marrow

cells in PARP-null mice were shown to have an increased rate of chromatid breaks, suggesting a serious DNA-repair deficiency.[35]

Whilst numbers of patients were small and variability within treatment groups was high, there was no evidence that carboplatin had a marked effect on exposure to olaparib at steady state. However, when co-administered with paclitaxel alone or in combination with both paclitaxel and carboplatin, the steady state exposure to olaparib was markedly reduced, by up to 45%. While paclitaxel is also metabolized by CYP3A4, the enzyme primarily involved in the oxidative metabolism of olaparib, it is not a known inducer of this CYP enzyme. The possibility of a plasma protein binding based interaction and an interaction between olaparib, the drug excipient Cremorphor EL (CrEL) or a mix of CrEL with paclitaxel has been investigated in vitro in plasma from healthy volunteers. Results actually suggested a slight increase in the free fraction of olaparib (10-23% for olaparib alone vs 16-26% with CrEL and 15-28% with CrEL/paclitaxel). Therefore, it seems that the possible observed interaction might not be caused by paclitaxel itself.

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When 24-hour platinum PK samples were used, the estimated free carboplatin AUC appeared to be approximately 25% higher than based on the calculated AUCs employing Calvert's formula.[36] When samples were collected across the whole PK profile, the estimated free $AUC_{0\text{-}48.5}$ was determined to be lower than the target AUC across all cohorts. However, it is important to note that these observations have to be viewed with caution. Numbers of patients were small, the free AUC values were not determined directly and the carboplatin AUC values in the absence of olaparib were not determined. It appeared that paclitaxel exposure was higher in the presence of olaparib in this study when compared to published data.[28, 37] However, this implication should also be

considered with caution; patient numbers were small, variability was high and paclitaxel concentrations alone were not determined, making it difficult to make intra- and interpatient comparisons.

The overall ORR seen in this study was 11%. This is relatively low when compared with other phase I studies in which olaparib is combined with chemotherapeutic agents. However, it is important to note that at the start of this study, the population was not yet enriched with patients carrying BRCA mutations, in whom responses are most likely to be observed.

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. However, certain dosing regimens could be given up to at least 3 cycles without the need for any dose modifications for myelosuppression. These revealed a relatively low dose of olaparib (50 mg BID) continuously. However, pharmacodynamic data from the phase I study with olaparib monotherapy have shown that the AUCs at 100 mg were already sufficient to inhibit PARP in peripheral blood mononuclear cells.[6] Further studies are needed to elucidate how to optimally combine olaparib with these chemotherapeutics without decreasing its potentiating anti-tumor effects.

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