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Pazopanib (GW786034) and cyclophosphamide in patients with platinum-resistant, recurrent, pre-treated ovarian cancer - Results of the PACOVAR-trial

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HIGHLIGHTS

- Pazopanib with cyclophosphamide had a MTD of 600 mg per day.
- Main side effects were elevation of the liver enzymes, diarrhea, leukopenia.
- Quality of life was not reduced during treatment.
- One patient experienced durable benefit from therapy for more than two years.

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ABSTRACT

Purpose. The prognosis is poor for patients with recurrent, platinum-resistant epithelial ovarian cancer (EOC). Evidence suggests that antiangiogenic treatment modalities could play a major role in EOC. A combined therapy consisting of the investigational oral antiangiogenic agent pazopanib and metronomic oral cyclophosphamide may offer a well-tolerable treatment option to patients with recurrent, previously treated EOC.

Patients and methods. This study was designed as a multicenter phase I trial evaluating the optimal dose as well as activity and tolerability of pazopanib with metronomic cyclophosphamide in the treatment of patients with recurrent, platinum-resistant, previously treated ovarian, peritoneal, or fallopian tube cancer. Here, 50 mg cyclophosphamide were combined with 400 to 800 mg pazopanib daily.

Results. Sixteen patients were treated; mean age was 66 years. At dose levels (DL) I and II, one instance of dose-limiting toxicity (DLT) was seen in one of 6 patients. At DL III, two of four patients showed a DLT, leading to a maximum tolerated dose (MTD) of 600 mg pazopanib daily. Median number of administered cycles was 6 (2 − 13), with three patients being treated for at least 13 months. Median progression-free survival (PFS) and overall survival (OS) were 8.35 months and 24.95 months, respectively. 155 adverse events (AE) occurred, most frequently elevation of liver enzymes, leukopenia, diarrhea and fatigue. Altogether, five serious adverse events (SAE) developed in four patients.

Conclusion. Pazopanib 600 mg daily p.o. and metronomic cyclophosphamide 50 mg daily p.o. is a feasible regimen for patients with recurrent platinum-resistant EOC and showed promising activity in this previously treated patient population.

Trial registration. Clin.trial.gov registry no.: NCT01238770.

1. Background/purpose

About 22,800 women per year in the USA develop a malignant tumor of the ovary and the incidence of ovarian carcinoma has

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remained unchanged in the last few decades [1]. With >14,000 deaths, it is the fifth highest cause of cancer-related mortality in women [1]. Symptoms of the disease usually develop at a very late stage. For this reason, in about 70% of patients the tumor is already in an advanced stage at the time of diagnosis (FIGO III or IV). In most cases, surgical tumor removal constitutes the primary treatment. After surgery, chemotherapy with carboplatin and paclitaxel is indicated for treating an initially advanced tumor stage [2,3]. Despite improved surgical procedures and a high primary response to chemotherapy, however, about 75% of patients with advanced ovarian carcinoma develop a tumor recurrence and die from the disease [4]. In particular, patients with platinum-resistant disease have a poor prognosis.

Data from numerous preclinical and clinical trials support the assumption that vascular endothelial growth factor/-receptor (VEGF/VEGFR) and platelet derived growth factor (PDGFR) are target molecules for the treatment of ovarian cancer. Angiogenesis is a critical pathway in the development and progression of cancer. Therefore, identifying and developing novel agents with limited toxicity that target mechanisms of tumor progression such as angiogenesis represent high-priority goals.

Metronomic chemotherapy suppresses tumor growth in experimental models, possibly by inhibiting angiogenesis and stimulating the release of thrombospondin [5–7]. These experimental findings are supported by a clinical trial in which encouraging activity with minimal toxicity was observed in patients with breast cancer [8]. In 2007, Samaritani and coworkers investigated cyclophosphamide "metronomic" chemotherapy for the palliative treatment of a young patient with advanced epithelial ovarian cancer. They reported that the progression-free survival time associated with daily low-dose oral cyclophosphamide treatment was 65 months without relevant side effects [9]. Furthermore, in experimental models, the combined use of metronomic chemotherapy with antiangiogenic therapies demonstrated marked inhibition of tumor growth [10–13].

Recent data showed that the combination of bevacizumab and metronomic oral cyclophosphamide was encouraging in treating recurrent ovarian cancer [14–16]. Further studies of potential synergistic effects of antiangiogenic agents and metronomic chemotherapy are warranted.

Pazopanib (Votrient®, Novartis Pharma) is an oral, angiogenesis inhibitor targeting VEGFR, PDGFR, and c-kit. VEGF and PDGF are critical for the development and growth of blood vessels. By inhibiting VEGFR, PDGFR, and c-kit pazopanib may stop or slow the rate of tumor growth and development. Pazopanib is licensed for the treatment of renal cell carcinoma and soft-tissue sarcoma. Indeed, the drug showed clinical efficacy in several phase II studies, including in renal cell cancer [17], soft-tissue sarcoma [18], vascular sarcoma [19], breast, and non-small-cell lung cancer [20]. Study VEG104450 provided proof-of-concept data for pazopanib as monotherapy in ovarian cancer: 28% of 36 treated patients showed response to pazopanib therapy in decreasing CA 125 levels [21]. In the AGO-OVAR 16 trial, pazopanib maintenance treatment after first-line chemotherapy improved progression-free survival by 5.6 months compared to placebo treatment [22].

The aim of the current trial was to clarify the potential of the multitargeting antiangiogenic tyrosine kinase inhibitor GW 786034 (pazopanib) in combination with metronomic oral cyclophosphamide as salvage treatment in patients with recurrent platinum-resistant and previously treated ovarian cancer.

2. Patients and methods

This study was designed as a multicenter phase I trial evaluating both the optimal dose for pazopanib and the activity and tolerability of a combination regimen consisting of pazopanib and metronomic cyclophosphamide in the palliative treatment of patients with recurrent, platinum-resistant, previously treated ovarian cancer.

The primary objective was to determine the maximum tolerable dose (MTD) for pazopanib; secondary objectives included time-to-progression (TTP) according to RECIST criteria, overall survival, evaluation of CA125 tumor response, safety and tolerability, and assessment of quality of life over time as defined by EORTC-QLQ C 30 and Ovar-28 questionnaire. Changes in the quality of life were evaluated by these standardized quality of life questionnaires, which were given to the patients before treatment and after every three cycles as well as during follow-up.

The PACOVAR trial was initiated at the Department of Gynecology and Obstetrics at the University of Heidelberg Medical School. Other centers participating in this multicenter trial were: (a) Department of Gynecology and Obstetrics of the University of Tuebingen Medical School, (b) Department of Gynecology and Gynecologic Oncology of Marienkrankenhaus Hamburg, (c) Department of Gynecology and Obstetrics, Klinikum Hetzelstift Neustadt, (d) Department of Gynecology and Obstetrics, Klinikum Konstanz, and (e) the Department of Gynecology and Obstetrics of the University of Mainz Medical School.

The final protocol was approved by the ethics committee of the University of Heidelberg, Germany (AFmu-241/2010). A data and safety monitoring board (DSMB) was established.

The patient population in this trial included patients with histologically or cytologically confirmed diagnosis of recurrent platinum-resistant or -refractory EOC, cancer of the fallopian tube, or peritoneal cancer. Patients had measurable disease according to RECIST criteria and the available standard chemotherapies must have failed. The study medication consisted of cyclophosphamide 50 mg p.o. daily and pazopanib 400/600/800 mg p.o. daily. Six patients were meant to be treated at each dose level or less if 2 dose-limiting toxicities (DLTs) developed at one dose level. DLTs were defined as grade 3 or 4 nonhematological toxicity other than nausea or vomiting. Hypertension and elevated liver enzymes were only considered as DLT if they resulted in a dose reduction or a treatment interruption for more than two weeks. Grade 4 thrombocytopenia (platelet count <25,000/μl) or grade 3/grade 4 thrombocytopenia associated with bleeding, grade 4 neutropenia lasting >4 days, or febrile neutropenia defined as ANC < 1000/μl concurrent with fever or any toxicity requiring dose interruption for >14 days were considered as DLT.

A treatment cycle consisted of 4 weeks. Patients received up to 13 cycles (52 weeks) of cyclophosphamide with pazopanib in the study. Treatment was continued until disease progressed or the study drug regimen was no longer tolerated.

The tumor response was investigated every 12 weeks during the treatment phase and every three months during follow-up or upon signs of tumor progression by CT scan and CA 125 levels.

Study monitoring was undertaken by ALCEDIS GmbH, Giessen, Germany.

3. Results

In all, 16 patients were treated in this trial; mean age was 66 years. The median age was 68.5 years, with seven patients younger than 65 years (43.8%). Furthermore, the median body height amounted to 161.5 cm, the median bodyweight to 68.3 kg, and the median body surface area to 1.7 m^2. In addition, ECOG at pre-examination was either 0 (68.8%) or 1 (25%) and unknown for one patient (6.3%). Detailed patients' characteristics are shown in Table 1.

At dose level I (400 mg pazopanib daily) 6 patients were treated and another 6 patients were treated at dose level II (600 mg pazopanib daily). At DL I and II one DLT was seen in one patient of six (AST elevation, hypertension). Four patients were treated at dose level III (800 mg pazopanib daily). In the DL III group, two patients out of four showed a DLT (AST elevation), leading to a MTD of 600 mg pazopanib daily. At dose level II one patient suffered from AST and ALT elevation, which would have required a dose interruption (protocol violation). By the time we had realized this, AST and ALT had already decreased again without therapy and the patient continued study treatment without any problems.

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