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A phase II trial of pemetrexed in combination with carboplatin in patients with recurrent ovarian or primary peritoneal cancer ☆

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ABSTRACT

Objective. Carboplatin-based combinations are commonly used in platinum-sensitive ovarian cancer (PSOC). Pemetrexed in combination with carboplatin has been shown to be feasible in a phase I study in PSOC. The primary objective of this subsequent phase II study was to determine the overall response rate (ORR; defined by Response Evaluation Criteria in Solid Tumors) of this combination in patients with recurrent PSOC. Secondary objectives included progression-free survival (PFS), overall survival (OS), and toxicity.

Methods. Patients with PSOC (defined by recurrence ≥6 months after completion of up to two lines of prior platinum-based therapy), measurable disease, Eastern Cooperative Oncology Group performance status of 0 to 2, and adequate organ function were eligible. Pemetrexed 500 mg/m^2 was administered as a 10-minute infusion followed by carboplatin AUC 6 as a 30-minute infusion on day 1 of a 21-day cycle.

Results. Sixty-six patients were treated. Of the 61 patients evaluable for response, there were 20 responders (one complete response and 19 partial responses), for an ORR of 32.8% (95% CI: 21.3%, 46.0%). For the intent-to-treat population (all 66 patients), the median PFS was 9.4 months (95% CI: 8.3, 11.1), with 22.7% censoring. Median OS was not reached due to the high censoring rate. There was one drug-related death (multi-organ failure). The most common drug-related grade 3/4 toxicities were neutropenia (39.4%), thrombocytopenia (24.2%), carboplatin hypersensitivity (9.1%), nausea (6.1%), and vomiting (6.1%).

Conclusions. Carboplatin AUC 6 and pemetrexed 500 mg/m^2 has a low incidence of serious toxicities. Defining the platinum-based combination with the best therapeutic index would require a prospective phase III study.

Introduction

More than 230,000 cases of ovarian cancer are diagnosed worldwide each year [1]. Newly diagnosed patients generally respond well to platinum agents, but most patients experience recurrent disease that often becomes refractory to further treatment [2]. For patients with recurrent platinum-sensitive ovarian cancer (defined as disease recurring ≥6 months), platinum-based combination therapy is considered standard [3]. However, the improvement in clinical outcome with combination therapy is associated with an increase in hematologic and/or nonhematologic toxicity compared with single-agent platinum therapy [3,4]. Development of alternative platinum-based combinations that are more efficacious with less toxicity would support treatment optimization for patients with platinum-sensitive recurrent ovarian cancer.

Pemetrexed is a multitargeted antifolate that is active in combination with cisplatin in nonsquamous non-small cell lung cancer in both the first- and second-line settings [5] as well as in mesothelioma [6]. Preclinical and clinical data suggest that pemetrexed may have activity in ovarian cancer [7–10]. Carboplatin is an analog of cisplatin with a more favorable toxicity profile [11] that has been developed and studied in numerous tumor types [12,13], including ovarian cancer [14]. In preclinical studies, the combination of pemetrexed and

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carboplatin was shown to have additive growth-inhibitory effects in tumor cell lines (Eli Lilly, data on file). In a clinical study, the combination of the two compounds was well tolerated in patients with malignant pleural mesothelioma [15]. These data suggest that a combination of pemetrexed and carboplatin may be a less toxic but efficacious novel platinum-based therapy for patients with recurrent ovarian cancer.

To further investigate this treatment, a phase I/II study was developed. Phase I was a three-patient cohort, dose-escalation study [16] that evaluated the dose-related toxicity profile of the combination of pemetrexed and carboplatin in patients with advanced ovarian cancer. Based on the results of that study, a dose of 500 mg/m^2 for pemetrexed in combination with carboplatin AUC 6 was selected for the phase II study reported here.

The primary objective of this multicenter, open-label, phase II study was to determine the overall tumor response rate of the combination of pemetrexed and carboplatin in patients with platinum-sensitive recurrent ovarian cancer. Secondary objectives included time-to-event efficacy parameters, and quantitative and qualitative toxicities.

Patients and methods

Eligibility criteria

For inclusion in the study, women had to be 18 years or older, have had a histologic diagnosis of ovarian or primary peritoneal cancer as per the International Federation of Gynecology and Obstetrics (FIGO) criteria not amenable to curative therapy, and had recurrent, platinum-sensitive disease (defined as disease that recurred ≥6 months after completion of prior platinum-based therapy). Patients could have received up to two lines of prior platinum-based therapy resulting in a best response of complete response (CR), partial response (PR), stable disease (SD), or not evaluable because of optimal debulking surgery. Patients must have had measurable disease as defined by Response Evaluation Criteria In Solid Tumors (RECIST) guidelines. Additional requirements included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, adequate organ function, and life expectancy of at least 24 weeks. Patients were excluded from the study for: clinically significant third-space fluid that could not be managed with drainage; peripheral neuropathy ≥ grade 2 per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0; an inability to interrupt the use of aspirin and/or other nonsteroidal anti-inflammatory agents for 2 days before, the day of, and 2 days after the dose of pemetrexed (5 days before for long-acting agents); and an inability or unwillingness to take folic acid and vitamin B_{12} supplementation, and corticosteroids. Exclusion criteria also included abdominal–pelvic procedure before enrollment in this study, murine antibody-based therapy within 28 days of enrollment, pemetrexed for any indication, high-dose therapy, consolidation or maintenance therapy, or any therapy with noncytotoxic targeted agents.

Written informed consent was obtained before study participation. The study was approved by the ethical review board(s) and was conducted in accordance with the Declaration of Helsinki, good clinical practice guidelines, and applicable laws and regulations. The study was additionally approved by the North-Eastern German Society of Gynaecological Oncology (NOGGO).

Treatment plan

Treatment was administered on day 1 of a 21-day cycle. Pemetrexed 500 mg/m^2 was administered intravenously over approximately 10 min with carboplatin at an AUC 6 administered intravenously over approximately 30 min, beginning 30 min after completion of the pemetrexed infusion. In the absence of progressive disease (PD) or unacceptable toxicity, patients received at least six cycles of therapy (with the possibility of two additional cycles at the physician's discretion). Patients were also required to take 350–1000 μg of oral folic acid daily, at least 1 to 2 weeks before cycle 1 until 3 weeks after the last pemetrexed dose, and 1000 μg vitamin B_{12} intramuscularly every 9 weeks, at least 1 to 2 weeks before cycle 1 until 3 weeks after the last pemetrexed dose. To prevent skin rash, dexamethasone 4 mg orally (or equivalent) was given twice daily for 3 days, starting 1 day before pemetrexed administration.

The absolute neutrophil count (ANC) had to be $\geq 1.5\times10^9$/L, platelets $\geq 100\times10^9$/L, and creatine clearance ≥45 mL/min before the start of any cycle. For nonhematologic toxicity ≥ grade 3, treatment was delayed until resolution to less than or equal to the patient's baseline value. Any cycle delay of more than 3 weeks because of unresolved grade 3 or greater toxicity or a toxicity that required a third dose reduction was cause for study discontinuation. Doses of both drugs were reduced by 25% for an ANC $<0.5\times10^9$/L and/or platelets $\geq 50\times10^9$/L, any ANC and platelets <50, or any grade 3/4 nonhematologic toxicity (except grade 3 transaminase elevations that returned to baseline by day 1 of the next cycle). For diarrhea requiring hospitalization, pemetrexed was reduced by 25% and for grade 3/4 mucositis, pemetrexed was reduced by 50%. Patients requiring a dose reduction continued to receive the reduced dose for the duration of the study.

Baseline and treatment assessments

Before starting treatment and at each cycle, patients underwent a medical history and physical examination, determination of ECOG performance status, complete blood count (including ANC, platelets, white blood cells, and hemoglobin), creatinine clearance, and chemistry panel. Toxicity was assessed before each cycle for all patients who received at least one dose of either drug using the CTCAE version 3.0. Efficacy was assessed with computed tomography or magnetic resonance imaging scan before every other cycle for evaluable patients who received at least one dose of either drug per RECIST, which includes confirmation of response. For CR or PR, response was to be confirmed by a second assessment approximately 6 weeks (no sooner than 4 weeks) after the first documentation of response.

Progression-free survival time (PFS) was defined as the time from the date of study enrollment to the date of objectively determined PD or death from any cause, whichever occurred first. For patients who were still alive at the time of analysis and who did not have objective PD, PFS was censored at the date of the last objective progression-free disease assessment. Time to response was defined as the time from study enrollment to the first observation of CR or PR. Duration of response (DOR) was defined as the time from first observation of CR or PR to the first observation of PD or death from any cause. For patients who were still alive at the time of analysis and who did not have objective PD, DOR was censored at the date of the last objective progression-free disease assessment. Time to treatment failure (TTF) was defined as the time from the date of study enrollment to the date of the first observation of PD, death from any cause, or early discontinuation of treatment (any reason). For patients who were alive, progression-free, and had not discontinued early at the time of analysis, TTF was censored at the date of the last objective progression-free disease assessment. Overall survival time (OS) was defined as the time from the date of study enrollment to the date of death from any cause. For patients who were still alive at the time of analysis, OS was censored at the last contact date.

Statistical considerations

Using a normal approximation to the binomial distribution, it was determined that 64 qualified patients were required for the phase II portion. This one-stage design tested the null hypothesis that the true response rate for this population was equal to 40% compared