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Randomized phase II trial of carboplatin and paclitaxel with or without lonafarnib in first-line treatment of epithelial ovarian cancer stage IIB–IV

Werner Meier [a,*], Andreas du Bois [b], Jörn Rau [c], Martina Gropp-Meier [d], Klaus Baumann [e], Jens Huober [f], Kerstin Wollschlaeger [g], Rolf Kreienberg [h], Ulrich Canzler [i], Barbara Schmalfeldt [j], Pauline Wimberger [k], Barbara Richter [l], Willibald Schröder [m], Antje Belau [n], Anne Stähle [o], Alexander Burges [p], Jalid Sehouli [q]

[a] Department of Gynecology and Obstetrics, Evangelisches Krankenhaus Duesseldorf, Germany
[b] Department of Gynecology & Gynecologic Oncology, Klinikum Essen Mitte, Germany
[c] Coordinating Center for Clinical Trials, University of Marburg, Germany
[d] Department of Gynecology and Obstetrics, Elisabethkrankenhaus Ravensburg, Germany
[e] Department of Gynecology and Obstetrics, University of Marburg, Germany
[f] Department of Gynecology and Obstetrics, University of Tübingen, Germany
[g] Department of Gynecology and Obstetrics, University of Magdeburg, Germany
[h] Department of Gynecology and Obstetrics, University of Ulm, Germany
[i] Department of Gynecology and Obstetrics, University of Dresden, Germany
[j] Department of Gynecology and Obstetrics, TU München, Germany
[k] Department of Gynecology and Obstetrics, University of Duisburg-Essen, Germany
[l] Department of Gynecology and Obstetrics, Radebeul, Germany
[m] Gynaecologicum, Bremen, Germany
[n] Department of Gynecology and Obstetrics, University of Greifswald, Germany
[o] Department of Gynecology and Obstetrics, Vincentius Kliniken Karlsruhe, Germany
[p] Department of Gynecology and Obstetrics, Klinikum Großhadern, München, Germany
[q] Department of Gynecology, Charité Campus Virchow-Klinikum, Berlin, Germany

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ABSTRACT

Objectives. This study evaluates whether a molecular targeted therapy with the farnesyltransferase inhibitor lonafarnib added to standard chemotherapy in first-line treatment of advanced ovarian cancer (OC) could improve progression-free (PFS) and overall survival (OS).

Patients and Methods. We performed a prospective randomized phase II study to compare standard therapy carboplatin (C; AUC 5) and paclitaxel (T; 175 mg/m^2) in primary advanced OC with or without lonafarnib (L). Lonafarnib was given in a dose of 100 mg orally twice a day during chemotherapy and was increased afterwards to 200 mg up to six months as a maintenance therapy.

Results. 105 patients were recruited (53 patients were randomized to receive LTC, 52 to TC). Hematologic toxicity was similar in both arms. Grade 3 and 4 non-hematological toxicity, occurred significantly more often with LTC (23% versus 4%, $p = 0.005$) and was associated with a higher dropout rate. PFS and OS were not significantly different among both arms. The LTC arm showed inferiority in the stratum with residual tumor of more than 1 cm: median PFS was 11.5 months (95% CI: 7.4–14.2) compared with 16.4 (95% CI: 10.3–40.4) for TC ($p = 0.0141$; HR = 0.36 (95% CI: 0.15–0.84)) with median OS 20.6 months (95% CI: 13.1–31.0) and 43.4 months (95% CI: 15.7–) for the TC arm ($p = 0.012$; HR = 0.32 (95% CI: 0.13–0.8)).

Conclusion. The addition of lonafarnib did not improve PFS or OS. Patients with a residual tumor of more than 1 cm had significantly shorter PFS and OS. Incorporation of lonafarnib into future studies for primary therapy of OC is not recommended.

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Introduction

The combination of platinum and paclitaxel is accepted worldwide as a standard treatment in advanced ovarian cancer after primary debulking surgery [1,6,18,19,22,25]. One option to optimize therapy could be the addition of a third cytotoxic drug [8,9]. However, the addition of conventional cytotoxics as third drugs as evaluated in several prospective randomized trials failed to show any benefit [2,7,8,11,24]. As an important result the addition of the third cytotoxic drug caused more toxicities and a higher treatment burden [2,8,24]. The addition of targeted drugs to standard chemotherapy could be another option. Epidermal growth factor inhibitors, antiangiogenetic

* Corresponding author at: Department of Obstetrics and Gynecology, Evangelisches Krankenhaus, Kirchfeldstr.40, 40217 Duesseldorf, Germany.
E-mail address: wmeier1620@aol.com (W. Meier).

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drugs, or farnesyltransferase inhibitors might be among the candidates for such an approach [20,27].

Lonafarnib is a farnesyltransferase inhibitor that is active against a broad spectrum of tumor cell lines in vitro and tumor xenografts in nude mice [20,21,27]. It inhibits the post-translational lipid modification of H-Ras and other farnesylated proteins [1]. In addition, lonafarnib has single-agent antitumor activity as well as enhanced activity in combination with taxanes in a number of tumor cell lines and mice models [1,5,10,14,15,26,27]. Based upon positive results from clinical studies demonstrating enhanced activity when combining taxanes with lonafarnib [1,13,15] combination therapy with carboplatin, paclitaxel, and lonafarnib was expected to have greater efficacy than standard therapy alone in primary ovarian cancer patients.

We report on a randomized phase II trial in which we compared the effects of paclitaxel, carboplatin, and lonafarnib to those of paclitaxel and carboplatin in the first-line treatment of patients with epithelial ovarian cancer and FIGO stage IIB–IV. The study was performed by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR).

Patients and methods

The study was performed in accordance with good clinical practice guidelines, national laws, and the Declaration of Helsinki. It was approved by the ethic committees of all sites. Patients were enrolled only having given their written informed consent. Study procedures followed the AGO-OVAR Standard Operating Procedures including central randomization, regular on-site monitoring, and double data entry.

Patients above 18 years with histologically confirmed International Federation of Gynecology and Obstetrics (FIGO) stages IIB to IV ovarian cancer who had undergone previous debulking surgery within six weeks before random assignment were eligible. Further inclusion criteria were an Eastern Collaborative Oncology Group (ECOG) performance status <2, adequate bone marrow function (absolute neutrophil count $\geq 1.5\times10^9$ cells/L, platelets $\geq 100\times10^9$ cells/L), renal function (estimated glomerular filtration rate ≥50 mL/min according to Jelliffe [12]), and liver function (bilirubin within the normal range, AST and ALT ≤ 1.5 × upper limit of normal range). Exclusion criteria were ovarian tumors with low malignant potential or non-epithelial tumors; patients with other malignancies except carcinoma in situ of the cervix and basal cell carcinoma of the skin; previous chemotherapy, radiotherapy or immunotherapy; severe neuropathy; congestive heart failure, myocardial infarction within the last six months, cardiac arrhythmias and significant Fridericia QTc prolongation of more than 470 ms.

Patients were stratified according to residual tumor size and FIGO stage. Stratum 1 contained patients with FIGO IIB to IIIC and a residual tumor up to 1 cm, stratum 2 contained patients with FIGO stage IV and a residual tumor of more than 1 cm. Patients were centrally randomized by an independent institution. All centers were regularly monitored by trained field monitors. These checks included reviews of the surgeons' and pathologists' reports and data-source verification.

Patients were randomly assigned to receive six cycles of carboplatin plus paclitaxel (TC) or the same combination supplemented by lonafarnib (LTC). The TC arm consisted of paclitaxel 175 mg/m^2 administered intravenously over 3 h followed by carboplatin AUC 5 administered intravenously over 30 to 60 min, both on day 1 of a three-week schedule. The carboplatin dose was calculated according to the Calvert formula [4]. In the LTC arm lonafarnib was given in a dose of 100 mg orally twice a day during chemotherapy; after completion of chemotherapy the lonafarnib dose was increased to 200 mg twice a day for a maximum of a further six months. The study was not placebo controlled and not blinded. Treatment was discontinued in the case of progressive disease, unacceptable toxicity, or at the patient's wish. Dose reductions were allowed depending on hematologic or non-hematologic toxicity. In the case of grade 3 or 4 vomiting, nausea, or diarrhea on non-chemotherapy days despite the use of optimal antiemetic and antidiarrheal therapy, lonafarnib was withheld until the symptoms improved to grade 1 or baseline. The lonafarnib dose was then restarted at 75 mg twice a day. If grade 3 or 4 toxicity reappeared at this dose level, the patient was discontinued from study treatment. During lonafarnib monotherapy therapy was discontinued until symptoms improved to grade 1 or baseline. Lonafarnib was restarted with a dose of 150 mg twice a day. Dose reduction was possible down to 100 mg twice a day if diarrhea increased again up to grade 3 or 4 toxicity. The maximum delay for lonafarnib was two weeks.

Bayesian methodology was used to provide guidance as to whether the effect of lonafarnib would be sufficient to conduct *further* phase III trials: A Bayesian prior distribution centered around a hazard ratio (HR) of 1.25 with a standard deviation of 0.2 was assumed to reflect that lonafarnib in addition to chemotherapy would provide a clinical benefit for PFS as compared to chemotherapy alone (with HR > 1 indicating that TC + lonafarnib is superior to TC alone). The amount of information provided by this prior distribution was approximately equal to 100 events. On the base of this prior distribution and an assumed potential outcome in favor of additional lonafarnib with HR ≥ 1.3, a posterior distribution was generated to determine the Bayesian predictive probability for a (potential) following standard frequentist significant pivotal phase III trial — this predictive probability was calculated as $p = 0.68$.

With $n = 100$ and 70 events and under the assumption of a true HR = 1.5 the probability of observing an HR ≥ 1.3 in this phase II trial was $p = 0.73$. Therefore, the total sample size for this study was planned as $N = 100$ patients (50 patients per treatment group).

Results

Between February 2006 and September 2006, 105 patients were randomly assigned from among 23 institutions in Germany. 75 patients fulfilled the criteria for stratum 1 and 32 for stratum 2. 53 patients were randomly assigned to receive LTC, and 52 patients to receive TC. The treatment arms were well balanced for baseline patient characteristics such as age, ECOG performance status, FIGO stage, histological subtype, and histological grading (Table 1). Two patients (one in either arm) did not receive the study drugs, so that 103 patients received at least one course of chemotherapy. The reason for not receiving the study drugs was in both cases the withdrawal of informed consent.

Overall 503 cycles were administered: 230 in the LTC and 273 in the TC arm. 73 patients received at least six cycles of chemotherapy, 32 (62%) in the LTC arm and 41 (80%) in the TC arm. Thus 20 patients (38%) in the LTC arm and ten (20%) in the TC arm received fewer than six cycles; this difference was statistically significant ($p = 0.033$). Treatment delays of more than seven days occurred in 15 cycles (7%) in the LTC and in 17 cycles (6%) in the TC arm. More than one dose reduction was necessary in 28 (12%) cycles in the LTC arm and in three (1%) in the TC arm with a statistical significance of $p < 0.0001$. Dose reduction due to lonafarnib was seen in 25 of 28 cycles in the LTC arm.

Hematological toxicity findings grade 3 and 4 were consistent with those in patients within other carboplatin/paclitaxel studies into ovarian cancer (Table 2). There was no significant difference between the treatment arms, in particular febrile neutropenia occurred only in one patient of either arm. Supportive hematological treatment as antibiotics, G-CSF/GM-CSF, erythropoietin, and blood products were also similar in both arms. With respect to grade 3 and 4 non-hematological toxicity, diarrhea occurred significantly more frequently in the LTC arm (23% versus 4%, $p = 0.005$). The occurrence of all other toxicities did not show any difference.

Only 16 patients (eleven LTC, five TC) had measurable disease at study entry. Because of this small number, tumor response could not be reliably assessed.

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