The addition of topotecan to carboplatin and paclitaxel as first-line therapy for advanced ovarian cancer; is it possible only with peripheral blood stem cell support?

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Summary

A phase I study was performed in order to evaluate the tolerability of the combination of fixed doses of carboplatin and paclitaxel and escalated doses of topotecan as first line chemotherapy for advanced epithelial ovarian cancer. Three stage III and one stage IV patients entered the study. The dose limiting toxicity (neutropenia and thrombocytopenia) was reached at the first dose level: paclitaxel 175 mg/m2 on day 1, carboplatin AUC 5 on day 1 and topotecan 0.5 mg/m2 daily from day 1 to day 3. We conclude that it is not possible to add topotecan to standard regimens of carboplatin and paclitaxel without bone marrow support.

Key words: Topotecan; Paclitaxel; Carboplatin; Polychemotherapy; Ovarian cancer.

Introduction

The combination of paclitaxel and platinum compounds is now considered the standard treatment in first-line chemotherapy for stage III suboptimally debulked and stage IV ovarian cancer. Topotecan, a semi-synthetic analog of camptothecin, is a topoisomerase I inhibitor. Its activity as a single agent at the dosage of 1.5 mg/m^2 by 30 minute intravenous infusion for five consecutive days in ovarian cancer is not inferior to paclitaxel [1]. Particular interest is focused on the possibility of combining platinum compounds (cisplatin or carboplatin), paclitaxel and topotecan in order to improve the results in the treatment of advanced ovarian cancer.

Therefore, we carried out a phase I study to evaluate the tolerability and the maximum tolerated dose (MTD) of the combination of carboplatin, paclitaxel and topotecan as first-line chemotherapy of stage III-IV epithelial ovarian cancer patients.

In a phase I-II study [2] on the combination of paclitaxel and carboplatin conducted in our Institution, the dose limiting toxicities were febrile neutropenia and fatigue, the MTD was paclitaxel 200 mg/m^2 and carboplatin 400 mg/m^2 (AUC 5 to 6) and the overall response rate was 74% (26% complete remissions and 48% partial remissions). No grade 3-4 thrombocytopenia occurred.

Even though we did not observe a clear dose-response relationship in that study, a trend of higher complete remission rates (35% vs 17%) exists in favour of higher dose levels (paclitaxel 175 to 225 mg/m2 and carboplatin 350 to 400 g/m2) as compared to paclitaxel 125 to 175 mg/m2 and carboplatin 250 to 300 mg/m2.

Patients and Methods

Based on this experience we started the present study with a fixed dose level of paclitaxel (175 mg/m2 3-hour infusion on day 1) and carboplatin (AUC 5 on day 1, as a 30-minute infusion after paclitaxel) and escalated doses of topotecan starting at 0.5 mg/m2/day as a 30-minute infusion daily from day 1 (after carboplatin) to day 3 (dose level I). Further dose-level progressions were planned by increasing topotecan to 0.125 mg/m2/day intervals and at least three patients were required at each dose-level.

Cycles were repeated every 3 weeks. The dose limiting toxicities were defined as follows: grade 4 netropenia (ANC < 0.5 x 10^9/I) lasting more than 7 days or associated with fever ≥ 38.2°C or ANC < 0.1 x 10^9/I lasting more than 3 days; WHO grade ≥ 3 non-hematological toxicity excluding alopecia and vomiting; absence of ANC recovery (≥ 1.5 x 10^9/I) and/or absence of platelets recovery (≥ 100 x 10^9/I) at day 28.

Chemotherapy-naive patients with FIGO stage III suboptimally debulked or stage IV epithelial ovarian cancer, aged less than 65 years, with an ECOG performance status ≤ 2 and with normal renal, hepatic, cardiac and bone marrow functions were eligible for the study. A written informed consent was required.

Four patients entered the study and were treated with dose level I. The median ECOG performance status was 1; in all the cases a bulky residual tumor was present at study entry. The FIGO stage at diagnosis was IIIC in 3 cases and IV in one case.

Results

Up to now 19 courses have been evaluated for toxicity. Grade 3 hypersensitivity reaction to paclitaxel occurred at the 1st cycle in one patient. Dose limiting toxicities (grade 4 thrombocytopenia in one patient and grade 4 neutropenia lasting more than 7 days in another one) were observed after the first cycle of chemotherapy. No other grade 3-4 toxicities were observed. One complete remission and one partial response were observed after

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the first cycle of chemotherapy. No other grade 3-4 toxicities were observed. One complete remission and one partial response were observed.

Discussion and conclusions

Similarly to other authors [3, 4] who investigated the combination of cisplatin, paclitaxel and topotecan, we conclude that it is not possible to add topotecan to standard regimens of carboplatin and paclitaxel because of the bone marrow toxicity – the MTD of a dose of topotecan was found to be only 20% of the standard dose of the drug when used as single agent.

Furthermore, also considering the occurrence of grade IV thrombocytopenia, it is improbable that the addition of G-CSF could allow us to administer a dose of topotecan of clinical usefulness.

Initial experience of this 3-drug combination therapy with peripheral blood stem cell support, as suggested by Schilder and coworkers [5], appears interesting.

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