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# Phase II evaluation of topotecan and navelbine in patients with recurrent ovarian, fallopian tube or primary peritoneal cancer

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**Abstract**

*Objective.* To assess the efficacy and toxicity profile in patients with recurrent ovarian or primary peritoneal cancer treated with topotecan at 2.5 mg/m$^2$ days 1 and 8 plus vinorelbine at 25 mg/m$^2$ days 1 and 8 every 3 weeks.

*Materials and methods.* Eligibility criteria included patients with recurrent primary peritoneal or epithelial ovarian cancer with either platinum-resistant or platinum-sensitive disease. Patients were required to have a performance status of ≤2 and normal hepatic and renal function. Response to therapy and toxicity were assessed using standard criteria. Chi square and Student's *t*-tests were used as appropriate. Survival was assessed with Kaplan–Meier method.

*Results.* All 40 patients enrolled were assessable for response. The median age of the patients was 58 years (range 30–82). Median treatment-free interval was 4.0 months. A total of 216 cycles of chemotherapy were administered with a median of 5.0 cycles per patient. Overall median TTP with this treatment regimen was 19 weeks (range 2–136 weeks). The response rate was 30% overall, and the response for platinum-sensitive and platinum-resistant patients was 44% (95% CI:22–69%) and 18% (95% CI:5–40%) respectively. Median progression-free survival was 3.0 months (range 1–9 months). Median overall survival was 16.4 months (range 1.5–51.7 months). Assessment of toxicity by patient showed 58% demonstrating grade 3/4 neutropenia with the vast majority being uncomplicated. No severe non-hematological toxicity was observed.

*Conclusion.* Administration of topotecan and navelbine is feasible with demonstrable activity and tolerable toxicity. This regimen may be considered especially in platinum-sensitive patients if a non-platinum based doublet is desired.


*Keywords:* Recurrent ovarian cancer; Topotecan; Navelbine

## Introduction

Optimizing ovarian cancer outcomes remains a clinical challenge, especially in the setting of recurrent disease. Despite modest gains in 5-year outcomes over the last 3 decades, ovarian cancer continues to be the leading cause of death in women with a gynecologic malignancy and nearly all women developing recurrence ultimately succumb to their disease [1,2]. This observation has driven the search for novel therapies and strategies.

Topotecan (Hycamtin, GSK) is a semi-synthetic derivative of camptothecin that functionally inhibits topoisomerase I, resulting in failure to repair single and double strand DNA breaks leading to apoptotic cell death. It has been the subject of two large phase III trials in mixed (platinum-resistant and platinum-sensitive) populations demonstrating response rates from 11–29% and is FDA-approved for use in recurrent ovarian cancer [3,4]. Administration originally consisted of a 5-day schedule with 30-minute, intravenous (IV) bolus infusions of 1.5 mg/m$^2$ repeated every 21 days. The dose-limiting toxicity was neutropenia, but was commonly non-cumulative and uncomplicated in terms of febrile sequelae. Nevertheless, alternative doses and schedules have been investigated, generally producing reduced toxicity [5–9]. Efficacy evaluation is more problematic across these studies given the heterogeneous treated population, however, responses are clearly documented. Vinorelbine (Navelbine,

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GSK) is a semi-synthetic vinca alkaloid which functions as an anti-mitotic agent and has demonstrated clinical activity in the treatment of ovarian cancer (response rate: 21–30%) [10–12]. Its dose-limiting toxicity is neutropenia, but it has been utilized as a single agent and in combination with other chemotherapeutics.

Our interest in combining these agents stemmed from the clinical efficacy of each single agent in ovarian cancer, their preclinical synergistic cytotoxicity, and their alternative mechanisms of action. [13–16] Herein we report our phase II experience with this novel combination in patients with recurrent ovarian, primary peritoneal and fallopian tube cancer.

## Materials and methods

Institutional review board approval was obtained from Washington University, and all patients underwent informed consent prior to enrollment. Patients were required to have documented epithelial ovarian, primary peritoneal or fallopian tube cancer. All patients had a Gynecologic Oncology Group (GOG) performance status $\leq 2$. No restriction was made on the basis of potential sensitivity to platinum or taxane re-treatment; however, eligible patients could not have been previously treated with four or more regimens. Treatment with the same drugs was considered two different regimens if there was a treatment-free interval of >8 weeks. All patients had adequate liver and renal function. Patients were required to have measurable disease on radiographic studies or to have a cancer antigen 125 (CA-125) value >100 U/ml that had risen from a previous value of <35 U/ml, with a second measured level >100 U/ml at least 1 week later. Rustin criteria was used for evaluable disease [17]. Measurable disease was defined as at least one "target" lesion that could be accurately measured in at least one dimension (longest dimension to be recorded). Each target lesion had to be $\geq 20$ mm when measured by conventional techniques, including palpation, plain X-ray, CT or MRI or $\geq 10$ mm when measured by spiral CT.

### *Dose and administration*

Study drug was supplied by study sponsor GSK (Glaxo SmithKline). Topotecan was administered at a dose of 2.5 mg/m$^2$ IV day 1 that was repeated day 8 of a 21-day cycle. This was followed by navelbine administered at a dose of 25 mg/m$^2$ IV day 1 and repeated day 8 of a 21-day cycle. Dosing was based on previous Phase I/II trials that combined these agents [13,14]. Maximum BSA of 2.0 for all dosing was utilized. All patients were treated until there was progression of disease or their physician opted to discontinue therapy due to toxicity or patient request.

### *Primary endpoints*

The principal study measures were time to progression (TTP) and clinical response. Clinical responses were defined as:

- *Complete Response* (CR) was defined by disappearance of all *target* and *non-target* lesions and no evidence of a new lesion documented by two disease assessments at least 4 weeks apart. Normalization of CA-125, if elevated at baseline, was required.
- *Partial Response* (PR) was defined by at least a 30% decrease in the sum of the longest dimensions (LD) of all *target* measurable lesions taking as reference the baseline sum LD. There could be no unequivocal progression of *non-target* lesions and no new lesions. Documentation by two disease assessments at least 4 weeks apart was required. In the cases where the ONLY target lesion was a solitary pelvic mass measured by physical exam that was not radiographically measurable, a 50% decrease in the LD was required.
- *Progression of Disease* was defined by the occurrence of ANY of the following:
  - At least a 20% increase in the sum of LD of *target* lesions taking as reference the smallest sum LD.
  - The appearance of one or more new lesions.
  - Unequivocal progression of existing *non-target* lesions, other than pleural effusion without cytological proof of neoplastic origin, in the opinion of the treating physician, within 8 weeks of study entry was also considered increasing disease.
  - In the case where the ONLY target lesion was a solitary pelvic mass measured by physical exam, which was not radiographically measurable, a 50% increase in the LD was required.
  - Death due to disease without prior objective documentation of progression.
  - Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression.
- *Stable Disease* was defined as any condition not meeting the above criteria.

Where possible, tumor size was measured directly. Otherwise, CA-125 criteria were used as follows:

- CR: CA-125 normalizes to <34 U/ml for at least 4 weeks on two separate occasions, 4 weeks apart.
- PR: >50% decrease in CA-125 level for at least 4 weeks on two separate occasions, 4 weeks apart.
- PD: >50% increase in CA-125 level
- SD: disease not meeting any of the above criteria

### *Toxicity*

Hematologic and non-hematologic toxicity was assessed and categorized using revised National Cancer Institute Common Toxicity Criteria (CTC)-Version 3.0.

### *Statistical analysis*

Sample size determination was based upon Simon's two-stage design. A total of 40 patients provided a power of approximately 0.80 to detect a difference in response rate between <10% (ineffective) and 28% (effective therapy), which are