

Prolonged stabilization of platinum/paclitaxel-refractory ovarian cancer with topotecan: A case report and review of the literature

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Summary

A combination of a paclitaxel and platinum analog is currently the standard first-line chemotherapy for women with ovarian cancer, with response rates of 20-37%. As patients who relapse have a poor prognosis and treatment options are limited, there is an urgent need to develop new agents with novel mechanisms of action for use as a second-line, non-cross-resistant chemotherapy in ovarian cancer.

In this report, we describe a patient with platinum/paclitaxel-refractory ovarian cancer who received topotecan and reached long-term stabilization of her disease. The patient was administered 1.5 mg/m² topotecan for five days in 17 cycles. She was also given granulocyte colony-stimulating factor (G-CSF) support to prevent severe granulocytopenia; no hematologic toxic effect was experienced. Her quality of life was good throughout the treatment, and also her daily activities were unaffected.

Key words: Ovarian cancer; Topotecan; Prolonged stabilization.

Introduction

Among gynecologic malignancies ovarian cancer is the leading cause of death in the United States, with a mortality rate that surpasses those for cervical and endometrial cancers combined.

An estimated 25,200 new cases of ovarian cancer were predicted in 1999, and about 14,500 deaths expected [1]. Approximately 85% of patients receive some form of systemic therapy [2]. Platinum-based chemotherapy is the traditional treatment, with response rates of 70-80% and pathologic complete remissions in 20-25% of patients [3].

However, a combination of a paclitaxel and platinum analog is currently the standard first-line chemotherapy for women with ovarian cancer with response rates of 20-37% [4]. Since patients who relapse have a poor prognosis and treatment options are limited, there is an urgent need to develop new agents with novel mechanisms of action for use as a second-line, non-cross-resistant chemotherapy in ovarian cancer. Topotecan (Hycamtin; Smith Kline Beecham Pharmaceuticals, Philadelphia, PA) is a water-soluble, semisynthetic analog of camptothecin; an alkaloid antitumor agent isolated from *Camptotheca acuminata*, a tree native to South China. Topotecan (TPT) and other camptothecin analogs bind with the DNA-topoisomerase I complex and interfere with the process of DNA breakage and resealing [5]. This stabilized cleavable complex blocks the replication fork, resulting in DNA breaks, fragmentation, and cell death [5]. Results of phase II studies suggest considerable anti-tumor activity of single-agent topotecan in ovarian cancer

patients who had progressed after one or more platinum-based regimens. Response rates ranged from 14% to 25% [6, 7]. Topotecan was shown to be active (21% response rate) in a randomized trial that compared paclitaxel and topotecan as first-line salvage therapy in ovarian cancer patients pretreated with cisplatin/cyclophosphamide [8]. Prolonged use of topotecan in patients with ovarian cancer is uncommon. In this report, we present a patient with platinum/paclitaxel-refractory ovarian cancer who received topotecan and reached long-term stabilization of her disease. The patient was administered 1.5 mg/m² topotecan for five days in 17 cycles. The patient also received granulocyte colony-stimulating factor (G-CSF) support, and no hematologic toxic effect was experienced.

Case Report

In our case we present a 54-year-old woman who underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and suboptimal debulking surgery for advanced ovarian cancer in October 1999. The pathology report revealed papillary serous cyst adenocarcinoma of the ovary with omental metastases (Stage IIIC, grade 3). Following surgery, the patient received six courses of combination chemotherapy with cyclophosphamide and carboplatin. After six cycles of chemotherapy, her serum CA 125 level was 2434 U/ml. A computed tomography (CT) scan of her pelvis and abdomen revealed a pelvic mass 4 x 5 cm in diameter. Explorative laparotomy with secondary optimal tumor reductive surgery was performed in April 2000. The pathologic report was consistent with papillary serous carcinoma of the ovary. She was then administered paclitaxel, 200 mg/m² over three hours every three weeks in six cycles. Also G-CSF support of 300 µg/day for five to seven days, and leuprolide acetate depot, 7.5 mg per month, by intramuscular injection was given. A control CT scan of her pelvis and abdomen

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revealed no mass, but her serum CA 125 level was 532 U/ml after six cycles of paclitaxel therapy. The patient was finally given 1.5 mg/m² topotecan for five days every three weeks. She was also administered G-CSF support of 300 µg/day 24 hours after chemotherapy for five to seven days. She received 17 cycles of TPT therapy without any major toxic effects. During treatment, serum CA 125 levels were stabilized at 300-400 U/ml. Unfortunately, after the 17 cycles of topotecan therapy the patient developed dyspnea and vomiting. Her serum CA 125 level was 2747 U/ml. The chest X-ray showed a new pulmonary metastasis, and pelvic and abdominal ultrasound examination revealed ascites and a new mass 2 x 3 cm in diameter. Topotecan therefore was stopped. The patient died of disease 22 months after starting topotecan therapy.

Discussion

In patients with ovarian cancer who had failed standard therapy, topotecan demonstrated response rates of 13% to 25%, with median times to progression of 12 to 19 weeks [9]. Compared with paclitaxel, the response rates were similar, 20.5% and 14.0%, respectively, as were median times to progression (19 weeks for topotecan vs 15 weeks for paclitaxel) [9, 10]. The common side-effects in all studies included neutropenia, thrombocytopenia, alopecia, rash, vomiting, nausea, and diarrhea [5]. The dose-limiting toxicity of topotecan is neutropenia in all phase I clinical trials [5]. Profound neutropenia is more frequently observed after intermittent and continuous infusions than after single bolus schedules. Because of the profound neutropenia seen in some phase I studies, G-CSF has been tested in more recent phase I studies [11, 12]. The severity and duration of neutropenia may be related to schedules of G-CSF and TPT. Concurrent administration of TPT and G-CSF increases the severity of myelosuppression caused by TPT [5, 11, 12]. In contrast, sequential administration of TPT and G-CSF, with G-CSF treatment starting after completion of TPT, induced only a modest and transient myelosuppression [12]. The patient whose case report is presented herein tolerated topotecan very well and achieved an excellent quality of life without major reactions to TPT for 17 cycles. Interestingly, there was no hematopoietic toxicity. Alopecia was the only toxicity to be cumulative. Accord-

ingly, an occasional patient with platinum and paclitaxel-refractory ovarian cancer may achieve a prolonged stabilization of the progressive disease with an excellent quality of life and no significant cumulative toxicity.

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