The role of topotecan as second-line therapy in patients with recurrent ovarian cancer

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Summary

Introduction: Up to 80% of patients with advanced ovarian cancer will recur following first-line platinum containing chemotherapy. Topotecan has recently been used as a second-line agent in treatment of advanced ovarian disease. The aim of the study was to evaluate the effect of topotecan on response rate and progression-free interval on patients with recurrent ovarian cancer who had been treated with platinum-containing first-line chemotherapy.

Methods: A retrospective review of all cases of recurrent ovarian cancer treated with topotecan was done. Response was determined using radiologic reports (CT scans, ultrasound scans), CA-125 level and the clinical evaluation. Response type was determined using World Health Organization (WHO) criteria.

Results: Between 1998-2000, a total of 43 patients were treated with topotecan. Median age was 57 (range 41-80), 40/43 patients had stage III and IV, 37/43 patients had Grade 3 tumors. Seventeen of 43 patients (39.5%) demonstrated stable disease and 9/43 (21%) patients demonstrated partial response. Median time to response was eight weeks, median progression-free interval was 31 weeks and median time of follow-up and survival was 48 weeks.

Conclusion: Topotecan is considered a reasonable option for treatment of patients with recurrent ovarian cancer that have failed previous treatment with platinum-containing chemotherapy.

Key words: Topotecan; Recurrent ovarian cancer and response.

Introduction

Ovarian cancer is the fourth most common cancer among women and the leading cause of death from gynecologic malignancy in North America [1]. The absence of symptoms in early stage ovarian cancer results in the majority of patients presenting with advanced disease. Standard first-line chemotherapy for women with advanced ovarian cancer is currently a platinum analog and paclitaxel [2-4]. Although 70-80% of patients have an initial clinical response, most patients with advanced disease will recur following first-line platinum-containing chemotherapy [5, 6]. Because patients who relapse have a poor prognosis, treatment options are limited. Therapeutic options include retreatment with platinum and/or paclitaxel, employing a non cross-resistant agent or use of investigational agents [7-10]. Poor prognostic factors in relapsing or recurrent ovarian cancer include: disease-free interval <6 months, poor performance status, serum CA-125 level >35 U/ml, multiple disease sites, large tumor volume and mucinous or clear cell tumor histology [6, 11-13].

The primary goal of second-line therapy includes control of disease to maintain quality of life and extend survival [14]. Paclitaxel was initially used to treat recurrent disease with response rates from 14% to 24% in small non-randomized studies. Topotecan has recently been introduced as a second-line agent in the treatment of advanced ovarian cancer [15-20]. Topotecan is a water-soluble alkaloid anti-tumor agent which inhibits topoisomerase I antinuclear enzyme [21]. Topotecan inhibits DNA breakage and resealing resulting in DNA breaking, fragmentation and cell death [22]. Topotecan has been shown to have significant anti-tumor activity in vivo and in vitro [23-25].

A recent large randomized study comparing topotecan versus paclitaxel showed a response rate of 20.5% and 13.2% for topotecan and paclitaxel, respectively [15].

The objective of the study was to evaluate the effect of topotecan on response rate and progression-free interval in patients with recurrent ovarian cancer who had initially been treated with platinum-based chemotherapy.

Methods

A retrospective study was conducted on all patient records with recurrent ovarian cancer treated with topotecan between 1998-2000. A total of 43 patients were treated with topotecan in the Division of Gynecology Oncology at the University of Ottawa. All patients had demonstrated progressive/recurrent disease after completing primary cisplatinum-based chemotherapy.

Response was determined using radiologic reports (CT scans, ultrasound scans), CA-125 level and clinical evaluation. Response type was determined using the World Health Organization (WHO) criteria. Complete response was defined as complete disappearance of all known measurable and assessable disease on two separate measurements at least four weeks apart. Partial response was defined as 50% reduction in the all-measurable lesions for at least four weeks, and with no new lesion or progression of assessable disease. Progressive disease was defined as a 25% increase in a single measurable lesion, reappearance of measurable disease or the development of a new

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metastatic lesion. Stable disease was any measurement not fulfilling the criteria for response or progression and lasting at least eight weeks.

Platinum-resistant was defined as an incomplete response to treatment with a platinum compound, progression of disease while on treatment with a platinum compound, or relapse within six months of treatment. Platinum-sensitive was defined as complete response to treatment with a platinum compound for more than six months [6, 26, 27].

The duration of response was measured from the time of initial documented response to the first sign of disease progression. The time to progression was measured from the time the drug was administrated to documented progressive disease or initiation of third or fourth-line therapy. The time to response and survival were measured from the time of initial drug administration to initial response and death, respectively.

Topotecan was administered intravenously at a dose of 1.5 mg/m^2/day for five consecutive days every 21 days. Dose reduction either to 1.25mg/m^2/day for five days or 1.5mg/m^2/day for four days was done for documented myelotoxicity. A planned fourth cycle of therapy was prescribed followed by clinical and radiologic assessment. Stable disease or documented response was followed by an additional four cycles of therapy.

Results

Between 1998-2000, a total of 43 patients were treated with topotecan. Median age was 57 (range 41-80). Tables 1 and 2 outline the grade and histology distribution of the study population. Noteworthy and expected is that the majority of patients had grade 3 and serous tumors. (Tables 1, 2)

Thirty-three of 43 patients were treated with cisplatinum/taxol while 10/43 patients were treated with carboplatinum/taxol. Thirty-three patients were treated previously with a single line of platinum chemotherapy, while ten patients were treated with multiple lines of chemotherapy (2 lines and/or more). The median number of treatment cycles with cisplatinum/taxol was six cycles.

Five patients withdrew from treatment; three patients secondary to ongoing neutropenia, one patient had severe thrombocytopenia and one patient had intolerance to topotecan.

Seventeen of 43 patients (39.5%) demonstrated stable disease, and 9/43 (20.9%) patients had a partial response.

Table 1. — *Tumor grade in patients receiving topotecan*

Tumor Grade	Number of Patients
I	2
II	4
III	37

Table 2. — *Tumor histology in patients receiving topotecan*

Tumor Histology	Number of Patients
Serous	33
Mucinous	1
Clear cell	4
Endometriod	3
Undifferentiated	2

Table 3. — *Responses to topotecan chemotherapy*

	Platinum-sensitive* Patient Number 26 (100%)	Platinum-resistant** Patient Number 17 (100%)	Total Patient Number 43 (100%)
Withdrawal	3 (11.5%)	2 (11.8%)	5 (11.6%)
Progressive Disease	4 (15.4%)	8 (47.1%)	12 (27.9%)
Stable Disease	12 (46.1%)	5 (29.4%)	17 (39.5%)
Partial Response	7 (26.9%)	2 (11.8%)	9 (20.9%)
Complete Response	0 (0%)	0 (0%)	0 (0%)

**Platinum-resistant was defined as an incomplete response to treatment with a platinum compound, progression of disease while on treatment with a platinum compound, or relapse within 6 months of treatment.
*Platinum-sensitive was defined as complete response to treatment with a platinum compound for more than 6 months.

No patient demonstrated complete response, 12/43 (27.9%) patients demonstrated progressive disease and 5/43 (11.6%) patients withdrew from treatment. Median time to response was eight weeks. Median progressive-free interval was 31 weeks and median time of follow-up and survival was 48 weeks (Table 3).

Twenty-six of 43 patients (60.5%) were considered platinum-sensitive. Twelve out of 26 platinum-sensitive patients (46.1%) demonstrated stable disease while seven patients (26.9%) demonstrated partial response. Therefore, 19/26 platinum-sensitive patients (73%) demonstrated a clinical benefit from topotecan therapy.

Seventeen out of 43 patients (39.5%) were defined as platinum-resistant. Eight of 17 platinum-resistant patients (47.1%) demonstrated progressive disease. Five of 17 patients (29.4%) demonstrated stable disease, while 2/17 patients (11.8%) had partial response. Therefore, 7/17 platinum-resistant patients (41.2%) demonstrated a clinical benefit from topotecan therapy.

The response of platinum-sensitive patients (73%) was compared with platinum-resistant patients (41.2 %) using the Chi Square test. There was a statistically significant difference between both groups with p *value = 0.036.*

The major toxicity with topotecan was myelosuppression. Hematological toxicity is summarized in Table 4. Thirteen of 43 patients developed type III neutropenia (30.2%) and 21/43 patients developed type IV neutropenia (48.8%). Six of 43 patients developed neutropenic fever or sepsis (13.9%).

Thirty-three of 43 patients had normal platelet counts (76.7%), 4/43 patients developed type II thrombocytopenia (9.3%). One patient developed type III thrombocytopenia (2.3%) and one patient developed type IV thrombocytopenia (2.3%).

Two of 43 patients had developed type I anemia (4.6%), 24/43 patients developed type II anemia (55.8%), and 14/43 patients developed type III anemia (32.5 %%). There was no patient who developed type IV anemia (Table 4).

Table 4. — *Hematological toxicity of topotecan*

	Grade I	Grade II	Grade III	Grade IV
Anemia	2/43 (4.6%)	24/43 (55.8%)	14/43 (32.5%)	0/43 (0%)
Neutro-penia	0/43 (0%)	7/43 (16.2)	13/43 (30.2)	21/43 (48.8)
Thrombo-cytopenia	1/43 (2.3%)	4/43 (9.3%)	1/43 (2.3%)	1/43 (2.3%)

Discussion

Despite high clinical response rates achieved with primary platinum/taxol chemotherapy (up to 80%), most patients subsequently relapse, develop drug-resistant disease and progressive disease [5, 6, 11]. Thus, the primary goal of therapy in relapsed or recurrent ovarian cancer is to extend survival while minimizing side-effects and preserving quality of life [14].

However, the treatment of recurrent disease is challenging, especially if recurrence is less than six months after first-line platinum-based chemotherapy. Treatment recommendations if disease progresses greater than six months after first-line therapy may include retreating with a platinum agent. If disease progresses less than 6 months following initial therapy, treatment is often an investigational agent [7-10].

As Paclitaxel has moved into first-line therapy, there is a need for alternative treatment of recurrent ovarian cancer. Topotecan has a novel mechanism of action and has been shown to be effective with an acceptable toxicity profile, for treatment of patients with advanced or recurrent metastatic carcinoma of the ovary after failure of the first-line therapy [15-20, 28]. Topotecan is active in patients who are platinum-sensitive or platinum- resistant [29-31].

A recent large randomized study, comparing the efficacy and safety of topotecan versus paclitaxel, was completed by Gore, *et al.* [32]. The study demonstrated that topotecan and paclitaxel have similar activity as second-line therapies with regard to response rates, progression-free interval and overall survival. The study also demonstrated that the two drugs have a degree of non cross-resistance. Thus, there may be a rational for incorporating these drugs into future first-line regimens.

In our study we had very good response to topotecan with 39.5% of the patient population demonstrating stable disease and 21% of the patient population demonstrating a partial response. The therapeutic response in the platinum-sensitive and platinum-resistant patients was 73% and 41%, respectively.

The median time to response was eight weeks, median progressive interval was 31 weeks and median time of follow-up and patient survival was more than 48 weeks (11 months).

Therefore, topotecan is considered a reasonable option for treatment of patients with recurrent and advanced metastatic ovarian cancer that have failed previous treatment with platinum-containing chemotherapy.

A study by McGuire et al, examined 48 platinum-sensitive patients with recurrent ovarian cancer after one or two prior chemotherapy regimes [29]. The study demonstrated that topotecan achieved an impressive 33% response rate, with stable disease in another 48% of patients, confirming the activity of topotecan as salvage therapy in recurrent ovarian cancer in platinum sensitive patients. These results are similar to the results seen by Markman *et al.* (33%), and close to the results we have seen in our platinum-sensitive patients [27].

There is also speculation that platinum-sensitive patients responding to topotecan might respond to further platinum therapy after the failure of topotecan but this possibility warrants further investigation [29].

At present topotecan is not recommended to be part of initial therapy for patients with advanced ovarian cancer. However, its role in conjunction with platinum/paclitaxel as initial therapy is currently undergoing clinical evaluation. It is possible that in the near future it may become a component of primary chemotherapy.

References

[1] Landis S. H., Murray T., Bolden S. *et al.*: "Cancer Statistics, 1999". *CA Cancer J. Clin.*, 1999, *49*, 8.

[2] Mcguire W. P., Hoskins W. H.: "Cyclophosphamide and Cisplatin compared with Paclitaxel and Cisplatin in patients with stage III and stage IV ovarian cancer". *NEJM*, 1996, *334 (1)*, 1.

[3] McGuire W. P., Rowisky E. K., Rosenshein N. B. *et al.*: "Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasm". *Ann. Intern. Med.*, 1989, *111*, 273.

[4] Thigpen J. T., Blessing J. A., Ball H. *et al.*: "Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy: a GOG study". *J. Clin. Oncol.*, 1994, *12*, 1748.

[5] Christian M. C., Trimble E. L.: "Salvage therapy for epithelial ovarian carcinoma". *Gynecol. Oncol.*, 1994, *55 (suppl)*, 143.

[6] Mcguire W. P., Ozols R. F.: "Chemotherapy of advanced ovarian cancer". *Semin. Oncol.*, 1998, *25*, 340.

[7] Markman M., Rothman R. *et al.*: "Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatinum". *J. Clin. Oncl.*, 1991, *9*, 389.

[8] Blackledge G., Lawton F., Redman C. *et al.*: "Response of patients in phase II studies of chemotherapy in ovarian cancer: implications for patient treatment and design of phase II trails". *Br. J. Cancer*, 1989, *59*, 650.

[9] Gore M. E., Fryatt I., Wiltshaw E. *et al.*: "Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compound". *Gynecol. Oncol.*, 1990, *36*, 207.

[10] Kavanagh H., Tresukosol D., Edwards C. *et al.*: "Carboplatin reinduction after taxane in patients with platinum-refractory epithelial ovarian cancer". *J. Clin. Oncol.*, 1995, *13*, 1584.

[11] Omura G. A., Brady M. F., Homesly H. D. *et al.*: "Long-term follow-up and prognostic factor analysis in advanced ovarian carcinoma: the Gynecologic Oncology Group experience". *J. Clin. Oncol.*, 1991, *9*, 1138.

[12] NIH Consensus Development Panel on Ovarian Cancer: "Ovarian cancer: screening, treatment and follow-up". *JAMA*, 1995, *273*, 491.

[13] Eisenhauer E. A., Vermorken J. B., Van Glabbeke M.: "Predictors of response to subsequent chemotherapy in platinum pretreated ovarian cancer: a multivariate analysis of 704 patients". *Ann. Oncol.*, 1997, *8*, 963.

[14] Bookman M. A.: "Extending the platinum-free interval in recurrent ovarian cancer: the role of Topotecan in second-line chemotherapy". *The Oncologist*, 1999, *4*, 87.

[15] Ten Bokkel Huinink W., Gore M., Carmichael J. *et al.*: "Topotecan versus paclitaxel for treatment of recurrent epithelial ovarian cancer". *J. Clin. Oncol.*, 1997, *15*, 2183.
[16] Cremers G. J., Bolis G., Gore M. *et al.*: "Topotecan, an active drug in the second-line treatment of epithelial ovarian cancer: results of a large European phase II study". *J. Clin. Oncol.*, 1996, *14*, 3056.
[17] Kudelka A. P., Treskosol D., Edwards C. L. *et al.*: "Phase II study of intravenous Topotecan as a 5-day infusion for refractory epithelial ovarian carcinoma". *J. Clin. Oncol.*, 1996, *14*, 1552.
[18] Swisher E. M., Mutch D. G., Rader J. S. *et al.*: "Topotecan in Platinum- and Paclitaxel-resistant ovarian cancer". *Gyncol. Oncol.*, 1997, *66*, 480.
[19] Bookman M. A., Malmstrom H., Bolis G. *et al.*: "Topotecan for the treatment of advanced epithelial ovarian cancer: an open-label phase II study in patients treated after prior chemotherapy that contained Cisplatin or Carboplatin and Paclitaxel". *J. Clin. Oncol.*, 1998, *16*, 3345.
[20] Armstrong D., Rowinsky E., Donehower R. *et al.*: "A phase II trial of Topotecan as salvage therapy in epithelial ovarian cancer". *Proc. Am. Soc. Clin. Oncol.*, 1995, *12*, 275.
[21] Burris H. A. III, Fields S. M.: "Topoisomerase I inhibitors: an overview of the camptothecin analogs". *Hematol. Oncol. Clin. North Am.*, 1994, *15*, 987.
[22] Katz E. J., Vick J. S., Kling K. M. *et al.*: "Effect of Topoisomerase modulators on cisplatin cytotoxicity in human ovarian carcinoma cells". *Euro J. Cancer*, 1990, *26*, 724.
[23] Saltz L., Sirott M., Young C. *et al.*: "Phase I clinical and pharmacologic study of Topotecan given daily for 5 consecutive days to patients with advanced solid tumors". *J. Natl. Cancer Inst.*, 1993, *85*, 1499.
[24] Verweij J., Lund B., Beijnen J. *et al.*: "Phase I and pharmacokinetic study of Topotecan, a new topoisomerase I inhibitor". *Ann. Oncol.*, 1993, *4*, 673.
[25] Rowinsky E. K., Grochow L. B., Hendricks C. B. *et al.*: "Phase I and pharmacologic study of Topotecan: a novel topoisomerase I inhibitor". *J. Clin. Oncol.*, 1992, *10*, 647.
[26] Thigpen J. T., Vance R. B., Khansur T. *et al.*: "Second-line chemotherapy for recurrent carcinoma of the ovary". *Cancer*, 1993, *71*, 1559.
[27] Markman M., Rothman R., Hates T. *et al.*: "Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin". *J. Clin. Oncol.*, 1996, *14*, 1877.
[28] O'Reilly S., Armstrong D.: "Clinical guidelines for managing Topotecan-related Hematologic toxicity". *The Oncologist*, 1998, *4*, 4.
[29] McGuire W. P, Blessing J. A., Bookman M. A. *et al.*: "Topotecan has substantial anti-tumor activity as first-line salvage therapy in platinum-sensitive epithelial ovarian carcinoma: a GOG Study". *J. Clin. Oncol.*, 2000, *18*, 62.
[30] Malik I. A. *et al.*: "An open label evaluation of Topotecan in patients with relapse or refractory epithelial ovarian cancer, single institution experience in a developing country". *Int. Gynecol. Cancer*, 2000, *10 (6)*, 433.
[31] Rose P. G., Gordon N. H., Fusco N. *et al.*: "A phase II and pharmacokinetic study of weekly 72-hrs Topotecan infusion in patients with platinum-resistant and paclitaxel-resistant ovarian carcinoma". *Gynecol. Oncol.*, 2000, *78 (2)*, 228.
[32] Gore M., ten Bokkel huinink W., Carmichael J. *et al.*: "Clinical evidence for Topotecan-Paclitaxel non-cross-resistance in ovarian cancer". *J. Clin. Oncol.*, 2001, *19 (7)*, 1893.

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