Weekly single-agent carboplatin in heavily pretreated patients with recurrent ovarian, peritoneal and fallopian tube carcinoma

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Summary

Purpose of investigation: To report the experience of a single institution in the south of Israel with weekly carboplatin in heavily pretreated patients with platinum-sensitive recurrent ovarian, peritoneal and fallopian tube carcinoma.

Methods: The hospital records of ten patients with platinum-sensitive recurrent ovarian, peritoneal and fallopian tube carcinoma who had 2nd-line or later chemotherapy with weekly carboplatin between January 2003 and December 2004 were retrospectively reviewed. Weekly carboplatin, at a dose calculated with use of the Hilary Calvert's formula at AUC = 2, was given intravenously in 500 ml dextrose 5% over 30 minutes on day 1 of every seven days. Response was determined using clinical evaluation, radiological reports and CA-125 level. Toxicity was graded using the National Cancer Institute (NCI) criteria.

Results: Overall, 155 courses of weekly carboplatin were given. The median number of courses per patient was 14 (range, 2-37) and median duration of treatment was 22.5 (range, 2-40) weeks. Four patients (40%) had complete response lasting for 8-20 (median, 12) weeks, two (20%) had partial response lasting for five and 14 weeks, respectively, one (10%) had stable disease lasting for 23 weeks and three (30%) had progressive disease. Toxicity was mainly hematological with only grade 1-2 hematological toxicity as follows: anemia – four patients (40%), leukopenia – three (30%), neutropenia – three (30%) and thrombocytopenia – two (20%).

Conclusion: Weekly carboplatin has considerable activity and low and well tolerated toxicity in heavily pretreated patients with platinum-sensitive recurrent ovarian, peritoneal and fallopian tube carcinoma.

Key words: Ovarian carcinoma; Chemotherapy; Carboplatin; Disease response; Toxicity.

Introduction

Despite cytoreductive surgery and postoperative adjuvant 1st-line chemotherapy with a platinum and paclitaxel combination, the majority (70% - 80%) of ovarian carcinoma patients will relapse within two years and die of disease within five years of initial diagnosis. The management of recurrent ovarian carcinoma has been a challenge, since 2nd-line or later chemotherapy is less effective than 1st-line chemotherapy and is associated with high and most often unacceptable toxicity [1]. The main intent of therapy in patients with recurrent ovarian carcinoma is not cure, but prolongation of survival and maintenance of quality of life [2]. Clearly, there is a constant need for improving 2nd-line and later chemotherapy by either optimizing the use of existing agents and/or developing regimens incorporating new agents.

According to the response to 1st-line platinum-containing chemotherapy, recurrent ovarian carcinomas are classified as platinum-sensitive – tumor relapsed or progressed > 6 months of the end of 1st-line platinum-containing chemotherapy, platinum-resistant – tumor relapsed or progressed ≤ 6 months of the end of 1st-line platinum-containing chemotherapy, and platinum-refractory – tumor relapsed or progressed during 1st-line platinum-containing chemotherapy. Patients with platinum-sensitive recurrent ovarian carcinoma are more responsive to 2nd-line and later chemotherapy and have a better prognosis than patients with platinum-refractory/resistant recurrent disease [3]. Patients with platinum-sensitive recurrent ovarian carcinoma will sensibly benefit from further platinum-based chemotherapy. The likelihood of responding again to platinum-based chemotherapy in these patients ranges from 25% to 60%, depending on the disease-free interval and the interval from the last course of 1st-line platinum-containing chemotherapy [4]. Prolongation of the platinum-free interval is associated with increased probability of response to 2nd-line and later platinum-containing chemotherapy [3].

Carboplatin has recently replaced cisplatin in the routine treatment of ovarian carcinoma patients because of its equivalent activity to that of cisplatin, its easy administration and its tolerance [5-7]. In contrast to cisplatin, the administration of carboplatin is associated with negligible neurotoxicity, ototoxicity and nephrotoxicity. Nevertheless, the treatment with carboplatin is associated with a higher rate of thrombocytopenia and, in fact, severe thrombocytopeina is the dose-limiting toxicity of carboplatin [5-7]. Previous studies have investigated the efficacy of single-agent carboplatin every three or four weeks versus carboplatin-containing combination chemotherapy every three or four weeks [4-8] and the efficacy of weekly carboplatin combined with a weekly

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non-platinum agent [9-12] as 2nd-line and later chemotherapy in recurrent ovarian carcinoma patients. We are not aware of previous studies investigating the efficacy of weekly carboplatin alone as 2nd-line and later chemotherapy in recurrent ovarian carcinoma patients. The aim of this study is to report the experience of a single institution in the south of Israel with weekly single-agent carboplatin in heavily pretreated patients with platinum-sensitive recurrent ovarian, peritoneal and fallopian tube carcinoma.

Patients and methods

The hospital records of ten patients with platinum-sensitive ovarian, peritoneal and fallopian tube carcinoma who had 2nd-line and later chemotherapy with weekly single-agent carboplatin between January 2003 and December 2004 at the Unit of Gynecologic Oncology, Soroka Medical Center, Beer-Sheva, Israel were retrospectively reviewed. The following data were retrieved from the files: primary site of malignancy, histologic type, stage at diagnosis, type of initial surgery, type and number of previous chemotherapy regimens, details of weekly carboplatin treatment, disease and CA-125 response to weekly carboplatin and toxicity of weekly carboplatin. Initial surgery included total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, retroperitoneal lymph node sampling and maximal debulking of tumor masses. Surgery was defined as optimal debulking when the largest tumor left in the abdomen measured ≤ 1.5 cm and non-optimal debulking when it measured > 1.5 cm. Standard postoperative adjuvant 1st-line chemotherapy usually included a combination of platinum (cisplatin 75 mg/m^2 or carboplatin [AUC = 6]) with paclitaxel (175 mg/m^2) administered intravenously on day 1, every 21 days, for a total of six courses.

Weekly carboplatin, at a dose calculated with the use of Hilary Calvert's formula at AUC = 2 [13, 14], was given intravenously in 500 ml dextrose 5% over 30 minutes on day 1 of every seven days. Every 7-day cycle was accepted as one course. Antiemetic premedication consisted of 20 mg dexamethasone and 8 mg ondansetrone given intravenously 30 minutes prior to carboplatin infusion. Courses were repeated until disease progression and sometimes were stopped after complete response was achieved.

Disease status was determined using clinical evaluation, imaging studies and serum CA-125. The following criteria were used for disease response: 1) Complete response – disappearance of all lesions, without evidence of any new lesions, for ≥ 4 weeks; 2) Partial response – a ≥ 50%-reduction in the size of the lesions, without evidence of any new lesions, for ≥ 4 weeks; 3) Stable disease – a < 50%-reduction or a ≤ 25%-increase in the size of the lesions, without evidence of any new lesions; 4) Progressive disease – a > 25%-increase in the size of the lesions, or evidence of any new lesions. The following criteria were used for CA-125 response: 1) Complete response – returning of CA-125 levels to normal range (0 - 35 U/ml) for ≥ 4 weeks; 2) Partial response – a ≥ 50%-reduction in CA-125 levels, as compared to pretreatment levels, for ≥ 4 weeks; 3) Stable response – a < 50%-reduction or ≤ 25% increase in CA-125 levels as compared to pretreatment levels; 4) Progressive response – a > 25%-increase in CA-125 levels as compared to pretreatment levels.

Hematological and non-hematological toxicities were graded using the common terminology criteria for adverse events of the National Cancer Institute (NCI) [15].

Results

The median age of the patients was 69.5 (range, 52-81) years. Patient characteristics are summarized in Table 1. Type of previous chemotherapy regimens is detailed in Table 2. Number of previous chemotherapy regimens per patient is displayed in Table 3. All ten patients were previously treated with at least one platinum-containing combination chemotherapy regimen, most often paclitaxel and platinum combination chemotherapy, and all of them were sensitive to 1st-line platinum-containing combination chemotherapy.

Table 1. — *Patient characteristics.*

Characteristic	No. of patients	%
Primary site of malignancy		
Ovary	4	40.0
Peritoneum	4	40.0
Fallopian tube	2	20.0
Histologic subtype		
Papillary serous	10	100.0
Histologic grade		
G1	1	10.0
G3	9	90.0
Stage at initial diagnosis		
IIa	1	10.0
IIIa	1	10.0
IIIc	6	60.0
IV	2	20.0
Surgery before 1st-line chemotherapy		
Optimal debulking	8	80.0
Non-optimal debulking	2	20.0

Table 2. — *Type of previous chemotherapy.*

Type of chemotherapy	No. of patients
1st-line chemotherapy (n = 10)	
Paclitaxel 175 mg/m^2 + Carboplatin (AUC = 6) on day 1 every 21 days	6
Paclitaxel 175 mg/m^2 + Cisplatin 75 mg/m^2 on day 1 every 21 days	3
Docetaxel 80 mg/m^2 + Carboplatin (AUC = 6) on day 1 every 21 days	1
2nd-line chemotherapy (n = 4)	
Paclitaxel 175 mg/m^2 + Carboplatin (AUC = 6) on day 1 every 21 days	2
Carboplatin (AUC = 6) on day 1 every 21 days	1
Gemcitabine 1000 mg/m^2 on day 1, 8 and 15 every 28 days	1
3rd-line chemotherapy (n = 2)	
Topotecan 1.5 mg/m^2 on days 1-5 every 21 days	1
Weekly docetaxel 35 mg/m^2	1
4th-line chemotherapy (n = 1)	
Weekly docetaxel 35 mg/m^2	1

Weekly carboplatin was 2nd-line chemotherapy in six patients (60%), 3rd-line – two (20%), 4th-line – one (10%) and 5th-line – one (10%). The median interval between the last course of any prior chemotherapy and the beginning of weekly carboplatin was 48 (range, 2-235; mean, 73.2) weeks. The median interval between the last course of platinum-containing chemotherapy and the beginning of weekly carboplatin was 55.5 (range, 4-235; mean, 85.8)

Table 3. — *Number of previous chemotherapy regimens.*

No. of regimens per patient	No. of patients	%
Any regimen		
1	6	60.0
2	2	20.0
3	1	10.0
4	1	10.0
Platinum-containing chemotherapy		
1	7	70.0
2	3	30.0
Paclitaxel + platinum combination chemotherapy		
0	1	10.0
1	7	70.0
2	2	20.0

weeks. The reason for starting weekly carboplatin after previous chemotherapy was recurrent disease and rising levels of CA-125 in nine patients (90%) and rising levels of CA-125 without evidence of recurrent disease in one patient (10%).

The details of weekly carboplatin treatment are displayed in Table 4. Overall, ten patients received 155 courses of weekly carboplatin. The median number of weekly carboplatin courses per patient was 14 (range, 2-37, mean, 15.5). The median duration of weekly carboplatin treatment was 22.5 (range, 2-40; mean, 20.4) weeks. The median average dose per course was 147.5 (range, 90-209; mean, 153.2) mg/course. The median average dose per week was 122 (range, 72-161; mean, 115.6) mg/week. The median cumulative absolute dose per patient was 2,287.5 (range, 220-6,120; mean 2552.5) mg.

Disease and CA-125 responses to weekly carboplatin are summarized in Table 5. Of the ten patients, four (40%) had a disease complete response lasting for 8-20 (median, 12) weeks and two (20%) had a disease partial response lasting for five and 14 weeks, respectively. Overall, six patients (60%) had an objective disease response lasting for 5-20 (median, 12) weeks. One patient (10%) had stabilization of disease lasting for 23 weeks and three (30%) had progressive disease. Thus, seven patients (70%) had either an objective response or stabilization of disease during weekly carboplatin treatment with a progression-free interval ranging from 5-23 (median, 14) weeks. Four patients (40%) had a CA-125 complete response, two (20%) – CA-125 partial response, one (10%) – stable CA-125 levels and three (30%) – progressive CA-125 levels. In all ten patients, the median CA-125 level before and after weekly carboplatin treatment was 529.5 (range, 47-2,169; mean, 792.4) U/ml and 286.5 (range, 6-3,441; mean, 1007.2) U/ml, respectively. All patients had sometimes experienced a nadir of reduction in CA-125 level during weekly carboplatin treatment. The median level of the nadir of the reduction was 68 (range, 3-1,420; mean, 378.5) U/ml; it represented a median of 77.7%-reduction (range, 7.2%-96.8%; mean, 63.1%) of the pretreatment CA-125 level, and it occurred after a median of 6.5 (range, 1-27; mean, 9.8) courses of weekly carboplatin.

Only grade 1 or 2 hematological toxicity was observed (Table 6). Anemia was observed in four patients (40%), leukopenia – three (30%), neutropenia – three (30%) and thrombocytopenia – two (20%). Granulocyte colony-stimulating factor (G-CSF) and erythropoietin support were not needed. Blood or platelet transfusions were not used. Nevertheless, weekly carboplatin dose reduction by 25% was required for the last eight of 37 courses in one patient and for the last six of 13 courses in another patient because of thrombocytopenia. Non-hematological toxicity, apart from fatigue in one patient, was negligible. None of the patients experienced allergic reactions to carboplatin.

Table 4. — *Treatment with weekly carboplatin.*

Weekly carboplatin	No. of patients	%
Number of courses		
2	1	10.0
4	1	10.0
6	1	10.0
13	2	20.0
15	1	10.0
17	2	20.0
31	1	10.0
37	1	10.0
Average dose per course		
< 100 mg	1	10.0
100 - 149 mg	4	40.0
150 - 199 mg	4	40.0
≥ 200 mg	1	10.0
Average dose per week		
< 100 mg	3	30.0
100 - 149 mg	5	50.0
150 - 199 mg	2	20.0
≥ 200 mg	–	–
Cumulative absolute dose per patient		
< 1,000 mg	3	30.0
1,000 - 2,999 mg	4	40.0
3,000 - 4,999 mg	1	10.0
≥ 5,000 mg	2	20.0

Table 5. — *Response to weekly carboplatin.*

Response	No. of patients	%
Disease response		
Complete	4	40.0
Partial	2	20.0
Stable	1	10.0
Progressive	3	30.0
CA-125 response		
Complete	4	40.0
Partial	2	20.0
Stable	1	10.0
Progressive	3	30.0

Table 6. — *Hematologic toxicity associated with weekly carboplatin.*

Toxicity	Anemia	Leukopenia	Neutropenia	Thrombocytopenia
None	6 (60.0%)	7 (70.0%)	7 (70.0%)	8 (80.0%)
Grade 1	3 (30.0%)	2 (20.0%)	2 (20.0%)	1 (10.0%)
Grade 2	1 (10.0%)	1 (10.0%)	1 (10.0%)	1 (10.0%)
Grade 3	–	–	–	–
Grade 4	–	–	–	–

Discussion

With respect to single agent carboplatin as 2nd-line and later chemotherapy in recurrent ovarian carcinoma patients, we have found two studies in the literature that investigated the efficacy of single-agent carboplatin every three or four weeks versus carboplatin-containing combination chemotherapy every three or four weeks [4, 8]. Bolis *et al.* [4] compared a group of 95 platinum-sensitive recurrent ovarian carcinoma patients who had 2nd-line chemotherapy with single-agent carboplatin 300 mg/m^2 every four weeks for five cycles with a group of 95 platinum-sensitive recurrent ovarian carcinoma patients who had 2nd-line chemotherapy with the combination of carboplatin 300 mg/m^2 and epidoxorubicin 120 mg/m^2 every four weeks for five cycles. No significant differences in objective response rate (55% and 58.1%, respectively), median duration of response (16 and 20 months, respectively) and 3-year survival (29% and 42%, respectively) were noticed between the two groups. As expected, the toxicity (grade 3-4 leucopenia, anemia, thrombocytopenia, and alopecia) was significantly higher in the combination chemotherapy group. Gonzalez-Martin *et al.* [8] compared single-agent carboplatin (AUC = 5) every three weeks with the combination of carboplatin (AUC = 5) and paclitaxel 175 mg/m^2 every three weeks. The combination of carboplatin and paclitaxel was found to be superior to single-agent carboplatin in terms of response rate (74.4% vs 52.6%, p = 0.047), with acceptable toxicity profile.

With respect to weekly carboplatin as 2nd-line and later chemotherapy in recurrent ovarian carcinoma patients, we have found in the literature only studies that investigated the efficacy of weekly carboplatin combined with a weekly non-platinum agent [9-12]. Van der Burg *et al.* [9] treated patients with recurrent ovarian carcinoma with induction chemotherapy comprised of six cycles of the combination of carboplatin (AUC = 4) and paclitaxel 90 mg/m^2 on day 1, 8, and 15 every 28 days, followed by six cycles of standard combination chemotherapy comprised of carboplatin and paclitaxel every three weeks. In platinum-sensitive and platinum-resistant recurrent carcinoma patients, the response rate was 80% and 53%, respectively. It has been concluded that induction chemotherapy with weekly carboplatin combined with weekly paclitaxel is highly active in both platinum-sensitive and platinum-resistant recurrent ovarian carcinoma patients and is well tolerated. Dunton [10] treated 20 platinum-sensitive recurrent ovarian carcinoma patients with weekly combination of carboplatin (AUC = 2) and paclitaxel 80 mg/m^2 and achieved a disease response rate of 82% and CA-125 response rate of 100%. Havrilesky *et al.* [11] treated 29 recurrent ovarian and peritoneal carcinoma patients with the combination of carboplatin (AUC = 2) and paclitaxel 80 mg/m^2 on days 1, 8, and 15 on a 28-day cycle. The overall response rate was 82.8% (37.5% and 100% in platinum-refractory and platinum-sensitive patients, respectively) and median time to progression was 11.5 months (3.2 and 13.7 months in platinum-refractory and platinum-sensitive patients, respectively). Hematological toxicity was common (32% grade 3 neutropenia, 14.2% grade 3 or 4 thrombocytopenia) and managed by treatment delay, dose reduction of paclitaxel, or discontinuation of carboplatin. In a series of 27 platinum-sensitive recurrent ovarian carcinoma patients treated with weekly combination of carboplatin (AUC = 2) and paclitaxel 80 mg/m^2 on day 1 every seven days, Kikuchi *et al.* [12] achieved a response rate of 81.4% and median survival time of 48.3 months. The toxicity profile and therapeutic index associated with weekly carboplatin combined with weekly paclitaxel were better than those associated with monthly platinum-containing combination chemotherapy [12].

We are not aware of previous studies investigating the efficacy of weekly single-agent carboplatin alone as 2nd-line and later chemotherapy in patients with recurrent ovarian carcinoma. Thus, this is the first study in the literature investigating the efficacy of weekly carboplatin alone as 2nd-line and later chemotherapy in platinum-sensitive recurrent ovarian, peritoneal and fallopian tube carcinoma. In this small series of patients with platinum-sensitive recurrent ovarian, peritoneal and fallopian tube carcinoma, treatment with weekly carboplatin alone achieved a considerable objective response rate of 60%, albeit the duration of response lasted for only a median of 12 weeks. The toxicity was mainly hematological, low and well tolerated. Dose reduction by 25% because of thrombocytopenia was required for part of the courses in two patients. Noteworthy, although the planned standard schedule was carboplatin at AUC = 2 on day 1 every seven days and every seven day-cycle was accepted as one course, the median duration of weekly carboplatin treatment expressed in weeks (22.5 weeks) was greater than the median number of weekly carboplatin courses per patient (14 courses). This is because some patients were not always compliant and occasionally delayed treatments.

Conclusion

Weekly single-agent carboplatin has considerable activity and low and well tolerated toxicity in heavily pretreated patients with platinum-sensitive recurrent ovarian, peritoneal and fallopian tube carcinoma. Because of the ease of administration and low and well tolerated toxicity, weekly carboplatin alone as 2nd-line or later chemotherapy seems to be a very attractive regimen especially for frail patients who are not expected to tolerate the toxicity associated with combination chemotherapy. Nevertheless, there is a need for further evaluation of the role of weekly carboplatin alone in the treatment of recurrent ovarian, peritoneal and fallopian tube carcinoma.

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