Gemcitabine in heavily pretreated patients with recurrent ovarian, peritoneal and fallopian tube carcinoma

B. Piura, *M.D., F.R.C.O.G.*; **A. Rabinovich,** *M.D.*

Unit of Gynecologic Oncology, Department of Obstetrics and Gynecology, Soroka Medical Center and Faculty of Health Sciences, Cancer Research Center, Ben-Gurion University of the Negev, Beer-Sheva (Israel)

Summary

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

Methods: The hospital records of 21 patients with ovarian, peritoneal and fallopian tube carcinoma who had salvage chemotherapy with gemcitabine between October 1998 and November 2003 were retrospectively reviewed. Gemcitabine, 1000 mg/m^2, was given on days 1, 8, and 15 of every 28 days. Dose intensity and relative dose intensity of gemcitabine were calculated. Response was determined using clinical evaluation, radiological reports and CA-125 level. Toxicity was graded using the National Cancer Institute (NCI) criteria.

Results: The median relative dose intensity of gemcitabine received by the patients was 0.91, with 17 (81%) patients receiving more than 80% of the planned standard dose intensity. Two (9.5%) patients had complete response of disease lasting for ten and 33 months, respectively, eight (38.1%) had stable disease and 11 (52.4%) had progressive disease. Three (14.3%) patients had CA-125 complete response, five (23.8%) had CA-125 partial response, six (28.5%) had CA-125 stable levels and seven (33.3%) had CA-125 progressive levels. Toxicity was mainly hematological with grade 3-4 toxicity as follows: leukopenia – two (9.5%) patients, neutropenia – four (19%), thrombocytopenia – three (14.3%) and anemia – one (4.7%).

Conclusion: Gemcitabine has some activity and low and well tolerated toxicity in heavily pretreated patients with platinum-resistant recurrent ovarian, peritoneal and fallopian tube carcinoma.

Key words: Ovarian carcinoma; Chemotherapy; Gemcitabine; CA-125; Toxicity.

Introduction

Despite cytoreductive surgery and postoperative adjuvant first-line chemotherapy with a combination of platinum and paclitaxel, the majority of ovarian carcinoma patients will relapse within two years and die of disease within five years of initial diagnosis. The management of carboplatin- and paclitaxel-resistant recurrent ovarian carcinoma has been a challenge, since second-line or later chemotherapy with other drugs and regimens has achieved a response rate of < 20% and has been associated with high and most often unacceptable toxicity [1]. There is a need for investigating new drugs whose profiles match ease of administration and low toxicity, to warrant the probability of improving the response rate, progression-free and overall survival with minor impact on quality of life of patients with heavily pretreated ovarian, peritoneal and fallopian tube carcinoma.

Several studies have indicated that gemcitabine (2',2'-difluorodeoxycytidine), a novel nucleoside analogue that replaces natural deoxycytidine in the DNA strand and blocks DNA synthesis, seems to have a reasonable activity and low and well-tolerated toxicity in platinum- and paclitaxel-resistant ovarian carcinoma [2-10]. The aim of this study is to report our experience with gemcitabine in heavily pretreated patients with paltinum-resistant recurrent ovarian, peritoneum and fallopian tube carcinoma.

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Material and Methods

The hospital records of 21 patients with platinum-resistant ovarian, peritoneal and fallopian tube carcinoma who had salvage chemotherapy with gemcitabine between October 1998 and November 2003 in the Unit of Gynecologic Oncology at the 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 gemcitabine treatment, disease and CA-125 response to gemcitabine and toxicity of gemcitabine. Initial 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. Refractory disease was defined as relapse or progression during chemotherapy, resistant disease – relapse or progression within six months of the end of chemotherapy and sensitive disease – relapse or progression occurring > 6 months of the end of chemotherapy.

The planned standard dosage and schedule of salvage chemotherapy with gemcitabine was 1,000 mg/m^2 in 150 ml saline given by a 30-minute intravenous infusion on days 1, 8, and 15 of every 28 days. Every 28-day cycle was accepted as one course. The method of dose intensity calculations suggested by Levin and Hryniuk [11, 12] was adopted for gemcitabine as follows: 1) The planned standard length of a gemcitabine course was four weeks, the planned standard dose per course was 3,000 mg/m^2/course and the planned standard dose intensity was 750 mg/m^2/week; 2) The actual dose intensity of gemcitabine received by the patient (expressed in mg/m^2/week) was calculated by dividing the cumulative absolute dose of gemcitabine (expressed in mg/m^2) by the total number of weeks encompassing the treatment period; 3). The relative dose intensity (RDI) is the actual dose intensity received by the patient calculated as a decimal fraction of the planned standard dose intensity.

Disease status was determined using clinical evaluation, imaging studies and serum CA-125. The following criteria were used for disease response [8, 13]: 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 [8, 13]: 1) Complete response – return 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) [14].

Results

The median age of the patients was 58 (range, 33-76) 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 21 patients were previously treated with at least one platinum-containing combination chemotherapy regimen, most often platinum/paclitaxel combination chemotherapy, and eventually developed platinum-refractory or platinum-resistant disease. Prior to gemcitabine several patients received other chemotherapeutic regimens such as weekly carboplatin, weekly paclitaxel, weekly docetaxel, single agent paclitaxel every three weeks, single agent docetaxel every three weeks, and topotecan. These drugs and regimens proved to be ineffective.

The details of gemcitabine treatment are displayed in Table 4. Gemcitabine was 2nd-line chemotherapy in seven (33.3%) patients, 3rd-line – eight (38.1%), 4th-line – three (14.2%), 5th-line – one (4.9%) and 6th-line – two (9.5%). The median interval between the last course of prior chemotherapy and commencement of gemcitabine was eight weeks (range, 1-42 weeks). The median number of gemcitabine courses per patient was three (mean, 4.9; range, 1-35) courses. The median duration of gemcitabine treatment was 12 (mean, 19.8; range, 4-140) weeks. The median dose intensity (DI) of gemcitabine actually received by the patients was 687.5 (range, 250-1,000) mg/m²/week. The median relative dose intensity (RDI) was 0.91 (range, 0.33-1.33). The median average dose per course was 2,750 mg/m²/course. The median cumulative absolute dose per patient was 9,000 (range, 1,000-82,000) mg/m². The response to gemcitabine is detailed in Table 5. Two (9.5%) patients had a complete response of disease lasting for ten and 33 months, respectively. In eight (38.1%) patients the disease was stable and in 11 (52.4%) the disease progressed during gemcitabine treatment. Three (14.3%) patients had a CA-125 complete response and five (23.8%) had a CA-125 partial

Table 1. — *Patient characteristics.*

Characteristics	No. of patients	%
Primary site of malignancy		
Ovary	14	66.6
Peritoneum	6	28.5
Fallopian tube	1	4.7
Histologic type		
Papillary serous	16	76.2
Endometrioid	1	4.7
Clear cell	1	4.7
Mucinous	1	4.7
Undifferentiated	2	9.5
Stage at diagnosis		
Ic	2	9.5
IIIc	18	85.7
X	1	4.7
Type of initial surgery		
Optimal debulking	19	90.5
Non-optimal debulking	1	4.7
Inoperable	1	4.7

Table 2. — *Type of previous chemotherapy.*

Type of chemotherapy	No. of patients
1st-line chemotherapy (n = 21)	
carboplatin/paclitaxel	14
cisplatin/paclitaxel	4
cisplatin/cyclophosphamide	3
2nd-line chemotherapy (n = 14)	
carboplatin/paclitaxel	4
weekly paclitaxel	3
topotecan	2
cisplatin/paclitaxel	1
carboplatin/cyclophosphamide	1
cisplatin/cyclophosphamide	1
paclitaxel every 3 weeks	1
weekly carboplatin	1
3rd-line chemotherapy (n = 6)	
topotecan	4
carboplatin/paclitaxel	1
docetaxel every 3 weeks	1
4th-line chemotherapy (n = 3)	
topotecan	2
weekly docetaxel	1
5th-line chemotherapy (n = 2)	
weekly carboplatin	1
weekly paclitaxel	1

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

No. of regimens per patient	No. of patients	%
Any regimen		
1	7	33.3
2	8	38.1
3	3	14.2
4	1	4.7
5	2	9.5
Platinum-containing chemotherapy		
1	13	61.9
2	6	28.5
3	2	9.5
Platinum/paclitaxel combination chemotherapy		
0	1	4.7
1	16	76.2
2	4	19.0

Table 4. — *Treatment with gemcitabine.*

Gemcitabine	No. of patient	%
Number of courses		
1	5	23.8
2	2	9.5
3	6	28.6
4	3	14.3
5	2	9.5
6	1	4.7
14	1	4.7
35	1	4.7
Dose intensity (mg/m²/week)		
≥ 750	9	42.9
500-749	11	52.4
< 500	1	4.7
Relative dose intensity		
≥ 1.0	9	42.9
0.9-0.99	3	14.3
0.8-0.89	5	23.8
0.7-0.79	2	9.5
0.6-0.69	1	4.7
< 0.6	1	4.7
Average dose per course (mg/m²/course) (percentage of planned dose per course)		
> 2,400 (> 80%)	17	80.8
1,500-2,400 (50%-80%)	3	14.3
< 1,500 (< 50%)	1	4.7
Cumulative absolute dose per patient (mg/m²)		
> 12,000	5	23.8
6,000-12,000	10	47.6
< 6,000	6	28.5

response. In six (28.5%) patients CA-125 levels were defined as stable and in seven (33.3%) CA-125 levels progressed during gemcitabine treatment. In all 21 patients, the median CA-125 level before and after gemcitabine treatment was 325 (mean, 924.75; range, 29-3,766) U/ml and 499 (mean, 940.42; range, 18-3,058) U/ml, respectively. Fifteen patients (71.4%) had, sometime during gemcitabine treatment, a reduction in CA-125 level. The median nadir of reduction was 116 (mean, 455.13; range, 15-1,919) U/ml; it represented a 49% reduction (mean, 58%; range, 28%-97%) of the pretreatment CA-125 level, and it occurred after a median of two (mean, 2.46; range, 1-11) courses of gemcitabine.

Toxicity was mainly hematological (Table 6). Hemoglobin concentration < 8.0 g% was observed in one (4.7%) patient, white blood count < 2,000/mm³ – two (9.5%), absolute neutrophil count < 1,000/mm³) – four (19%) and platelet count < 50,000 – three (14.3%). Blood transfusions were given to three (14.3%) patients (hemoglobin, 5.9 g%, 8.9 g% and 8.9 g%, respectively) and two (9.5%) patients were treated with erythropoetin. Neutropenic fever, requiring hospitalization, was observed in only one patient. Granulocyte colony-stimulation factor (G-CSF) was administered to five patients (23.8%). Although severe thrombocytopenia was never complicated by bleeding episodes, platelet transfusion was given to two patients (9.5%) (platelet count, 19,000/mm³ and 22,000/mm³, respectively). Non-hematological toxicity was negligible. None of the patients experienced allergic reaction to gemcitabine.

Table 5. — *Response to gemcitabine.*

Response	No. of patients	%
Disease response		
Complete	2	9.5
Partial	–	–
Stable	8	38.1
Progressive	11	52.4
CA-125 response		
Complete	3	14.3
Partial	5	23.8
Stable	6	28.5
Progressive	7	33.3

Table 6. — *Hematological toxicity associated with gemcitabine treatment.*

Toxicity	Anemia	Leukopenia	Neutropenia	Thrombocytopenia
None	4 (19%)	7 (33.3%)	11 (52.4%)	10 (47.6%)
Grade 1	5 (23.8%)	7 (33.3%)	5 (23.8%)	3 (14.3%)
Grade 2	11 (52.4%)	5 (23.8%)	1 (4.7%)	5 (23.8%)
Grade 3	–	2 (9.5%)	3 (14.3%)	2 (9.5%)
Grade 4	1 (4.7%)	–	1 (4.7%)	1 (4.7%)

Discussion

Previous studies investigating the efficacy of gemcitabine in heavily pretreated patients with platinum-resistant recurrent ovarian carcinoma demonstrated an objective response rate of 11.1%-27.3% (partial response rate, 8.3%-19%; complete response rate, 5.6%-9.1%) and stable disease rate of 13.6%-52%, with a median duration of response ranging from three to 10.6 months (Table 7) [2-10]. We observed a complete response in two (9.5%) patients (lasting 10 and 33 months, respectively) and stable disease in eight (38.1%) patients. Some authors

Table 7. — *Literature review of response to salvage chemotherapy with gemcitabine.*

Author	No. of patients	Dose of gemcitabine (mg/m²)	PR (%)	CR (%)	OR (%)	SD (%)	Median duration of response (months)
Lund *et al.*, 1995 [2]	42	800	19	–	19	?	8.1
Shapiro *et al.*, 1996 [3]	31	1,000	13	–	13	19.3	7
Friedlander *et al.*, 1998 [4]	36	1,200	8.3	5.6	13.9	50	10.6
von Minckwitz *et al.*, 1999 [5]	36	1,250	16.7	5.6	22.3	47	9
Silver & Piver, 1999 [6]	27	800	11.1	–	11.1	52	?
Coenen *et al.*, 2000 [7]	22	1,000	14	–	14	41	5
Markman *et al.*, 2003 [8]	51	1,250→1,000	16	–	16	?	4
Bilgin *et al.*, 2003 [9]	22	1,000	18.2	9.1	27.3	13.6	3
D'Agostino *et al.*, 2003 [10]	50	1,000	17	–	17	37	5
This study	21	1,000	–	9.5	9.5	38.1	21.5

PR: partial response. CR: complete response. OR: objective response. SD: stable disease.

[15] have shown that stable disease is associated with a significant survival benefit. Thus, it has been suggested that stable disease, like objective disease response, represent a potential benefit of chemotherapy and should be taken into consideration when the efficacy of salvage chemotherapy is evaluated [15].

Although most previous studies included follow-up of CA-125 levels, the data with respect to CA-125 response are scanty. Markman *et al.* [8] reported a ≥ 75% decline in CA-125 levels for ≥ 4 weeks in four (7.8%) of 51 patients. Shapiro *et al.* [3] demonstrated a > 50% reduction in CA-125 level in three (9.7%) of 31 patients (with 2 patients achieving a > 90% reduction). In 24 patients evaluable for CA-125 response, von Minckwitz *et al.* [5] observed a CA-125 complete response in three (12.5%) and CA-125 partial response in nine (37.5%), resulting in an overall CA-125 response rate of 50%. Nine (37.5%) patients were stable on CA-125 and three (12.5%) had progression [5]. We observed a CA-125 complete response rate of 14.3% and a CA-125 partial response rate of 23.8%, resulting in an overall CA-125 response rate of 38.1%. Stable CA-125 levels were observed in 28.5% of the patients and progressive CA-125 levels were observed in 33.3%. It has been suggested that since determination of disease response by clinical evaluation and with common imaging techniques (ultrasound, computerized tomography) in relapsed ovarian carcinoma is often disappointing and not very reliable, CA-125 levels may be used as a marker for response evaluation in salvage chemotherapy [16].

In most reported series, the toxicity associated with 1,000 mg/m^2 gemcitabine administered intravenously on days 1, 8 and 15 of every 28 days, is low, well tolerated, and mainly hematological. Markman *et al.* [8] had to reduce the gemcitabine dose from 1250 mg/m^2 to 1,000 mg/m^2 since 1,250 mg/m^2 resulted in unacceptable excessive non-hematological toxicity, especially grade 3 fatigue and fever/chills without neutropenia. Shapiro *et al.* [3] demonstrated grade 3-4 neutropenia in 29% of the patients. Bilgin *et al.* [9] noticed grade 3-4 neutropenia and grade 3-4 thrombocytopenia in 9.1% and 18.2% of the patients, respectively. D'Agostino *et al.* [10] demonstrated grade 3-4 neutropenia, grade 3-4 thrombocytopenia and grade 3-4 anemia in 42%, 8% and 18% of the patients, respectively. We observed grade 3-4 leukopenia, grade 3-4 neutropenia, grade 3-4 thrombocytopenia and grade 3-4 anemia in 9.5%, 19%, 14.3% and 4.7% of the patients, respectively. We are not aware of previous studies reporting calculations of dose intensity and relative dose intensity of gemcitabine. In this study, the median relative dose intensity (RDI) actually received by the patients was 0.91, with 17 (81%) patients receiving more than 80% of the planned standard dose intensity. These figures reflect the infrequent need for dose reduction because of hematological toxicity in patients receiving salvage chemotherapy with 1,000 mg/m^2 gemcitabine on days 1, 8 and 15, every 28 days.

In conclusion, gemcitabine has modest activity and low and well-tolerated toxicity in heavily pretreated patients with platinum-resistant ovarian, peritoneal and fallopian tube carcinoma. Because of the ease of administration and low and well-tolerated toxicity, gemcitabine is a very attractive agent for salvage chemotherapy in ovarian carcinoma patients who failed on prior lines of chemotherapy. Nevertheless, there is a need for further evaluation of the role of gemcitabine as a single agent, or in combination with other cytotoxic drugs, in the treatment of ovarian, peritoneal and fallopian tube carcinoma.

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Address reprint requests to:
B. PIURA, M.D., F.R.C.O.G.
Unit of Gynecologic Oncology
Department of Obstetrics and Gynecology
Soroka Medical Center
and Faculty of Health Sciences
Ben-Gurion University of the Negev
P.O. Box 151
84101 Beer-Sheva (Israel)