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Combined PEG liposomal doxorubicin and gemcitabine are active and have acceptable toxicity in patients with platinum-refractory and -resistant ovarian cancer after previous platinum–taxane therapy: A phase II Austrian AGO study☆

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Abstract

Objectives. Platinum resistance is a significant problem in patients with ovarian cancer. The aim of this phase II study was to define the response rates, the progression-free survival and the toxicity profile of the combination of PEG liposomal doxorubicin (L-DXR) and gemcitabine (GEM).

Material and methods. Thirty one patients with histologically confirmed platinum-refractory or -resistant epithelial ovarian cancer were scheduled to receive 6 cycles of L-DXR 30 mg/m^2 on day 1 as well as GEM 650 mg/m^2 on days 1 and 8 every 28 days.

Results. The median number of chemotherapy cycles given was 4. The mean dose intensity for L-DXR and GEM on day 1 was 96% and 97%, respectively. The mean dose intensity for GEM on day 8 was 93%. The overall response rate was 33% (10 of 30 evaluable patients; 20% complete responses). The median progression-free survival was 3.8 months, and the median overall survival was 15.8 months, respectively. Toxicity was acceptable. One quarter of patients developed grade 3 or 4 neutropenia, but none developed febrile neutropenia. Palmoplantar erythrodysesthesia (PPE) grades 2 and 3 occurred in 13% and 3% only, respectively, and no grade 4 PPE was observed. Grades 1 to 3 stomatitis was found in 58% of patients (10% grade 3).

Conclusion. The combination of L-DXR and GEM is an active and acceptably tolerated option in the treatment of patients with platinum-resistant and -refractory ovarian cancer. Dose reductions seem advisable in the case of ≥grade 2 stomatitis and/or PPE ≥grade 2.

Keywords: Chemotherapy; PEG liposomal doxorubicin; Gemcitabine; Platinum resistance; Ovarian cancer

Introduction

Platinum resistance is a significant problem in patients with ovarian cancer. In this situation, patients usually carry significant tumor-related symptoms, chemotherapy is only moderately active, and the median survival is between 6 and 11 months [1,2]. New active drugs and drug combinations with limited toxicity are particularly needed for this patient population.

Single agent pegylated liposomal doxorubicin (L-DXR) and gemcitabine (GEM) have different mechanisms of action [3]. In addition, some studies have indicated a possible synergistic antiproliferative activity between L-DXR and GEM in vitro [4]. Thus, the Austrian Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO) selected this combination for evaluating its efficacy in platinum-refractory and -resistant ovarian cancer patients. The aim of this phase II study was to define the

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response rates, the progression-free survival and the toxicity profile of the combination of L-DXR and GEM.

Material and methods

From 2002 to 2004, we enrolled 31 patients with histologically confirmed epithelial ovarian cancer for a phase II study. They have been treated at the Departments of Obstetrics and Gynecology of the Medical Universities of Graz, Innsbruck, Vienna and Salzburg as well as at the Departments of Gynecology of the Hospitals Barmherzige Schwestern in Linz, Lainz/Vienna, Hall/Tirol and Wels. The study was approved by the institutional Ethics Committees, and all patients gave signed informed consent. For inclusion, patients had to have no second cancer, no previous radiotherapy, no active infections, adequate bone marrow function and liver parameters as well as a serum creatinine of less than 2.5× normal. One patient withdrew from the study before the start of therapy. Thus, the remaining 30 patients were evaluable for analysis (Table 1).

All patients had platinum-refractory or platinum-resistant disease, i.e. either disease progression during first-line platinum–taxane therapy or recurrence within 6 months following the last platinum-containing chemotherapy. Pretreatment characteristics are shown in Table 1. Previous chemotherapy regimens included carboplatin and taxane combinations in the vast majority of patients. One patient had also received carboplatin/epirubicin and another topotecan, respectively. Recurrence was defined as the occurrence of new measurable disease by computed tomography scan and/or by chest X-ray or as a significant increase of serum CA-125 based on progression criteria defined by Rustin et al. [5].

The treatment regimen consisted of 6 cycles of PEG liposomal doxorubicin (L-DXR) on day 1 and gemcitabine (GEM) on days 1 and 8 every 28 days. L-DXR 30 mg/m^2 was dissolved in 250 ml 5% glucose and infused IV as the first agent over 1 h. To reduce hypersensitivity reactions, the infusion rate was reduced to 60 ml/h during the first 15 min of the first infusion. In a parallel intravenous line, 250 to 500 ml 5% glucose was coadministered during each L-DXR cycle. GEM 650 mg/m^2 was dissolved in 250 ml NaCl 0.9% and administered IV over 30 min as the second agent. Subsequent chemotherapy cycles were postponed in the case of active infections, active stomatitis of any grade and/or palmoplantar erythrodysesthesia (PPE) >grade 1. Dose reductions of 25% were performed in the case of PPE >grade 2 or stomatitis >grade 2 during a previous cycle and were maintained at this level for all subsequent cycles. G-CSF was allowed in the case of grade 4 neutropenia. Toxicity was rated according to the NCI common toxicity criteria. No specific cardiac monitoring was performed.

Treatment was discontinued in the case of disease progression, patient's withdrawal or a >grade 3 non-hematologic toxicity. Quality of life was evaluated using the EORTC QLQ-C30 evaluation form for ovarian cancer.

Table 1
Pretreatment characteristics of the 30 evaluable patients with platinum-refractory or -resistant ovarian cancer who received PEG liposomal doxorubicin and gemcitabine

Characteristics	No. of patients
Median age (range)	59.4 (27.2–74.2) years
Median Karnofsky performance status (range)	90 (80–100)
Platinum-refractory disease	13 (43%)
Platinum-resistant disease	17 (57%)
FIGO stage I or II	2 (7%)
FIGO stage III or IV	28 (93%)
Grading [a]	
G1	2 (7%)
G2	6 (20%)
G3	19 (63%)
No. of previous chemotherapy regimens	
1	23 (77%)
2	6 (20%)
3	1 (3%)
Median no. of non-platinum-containing regimens (range)	0 (0–1)
Median no. of previous platinum-chemotherapy cycles (range)	6 (1–14)
Median no. of previous taxane chemotherapy cycles (range)	6 (1–14)
Median no. of months after diagnosis (range)	10.5 (0.23–160.8)

[a] Not available for 3 patients.

Table 2
Efficacy data on the 30 patients with platinum-refractory or -resistant ovarian cancer following 6 cycles of combination chemotherapy with PEG liposomal doxorubicin and gemcitabine

	No. of patients
Complete response	6 (20%) [a]
Partial response	4 (13%)
Stable disease	4 (13%)
Progressive disease	16 (54%)
Median response duration	3.0 months
Median progression-free survival	3.8 months
(95% confidence interval)	(0.0–11.7)
Median overall survival	15.8 months
(95% confidence interval)	(9.0–22.7)

[a] Including 3 patients with platinum-refractory disease.

Statistical analysis

Data are expressed as absolute and relative frequencies or median and range. Data from survival analysis are shown as mean or median survival rates and 95% confidence interval. Fisher's Exact Test was used to compare statistical differences between patient subgroups. Statistical significance was defined as $P < 0.05$. SPSS for Windows 11.5 software (SPSS, Chicago, Illinois, USA) was used for all analyses.

Results

Treatment efficacy

Seventeen of 30 patients (57%) received the scheduled number of 6 cycles. The median number of cycles of L-DXR/GEM given was 4 (range 0–6). Nine patients were dose-reduced. The mean dose intensity for L-DXR and GEM on day 1 was 96% and 97%, respectively. The mean dose intensity for GEM on day 8 was 93%. Dose reductions were due to stomatitis, weight loss, neutropenia, PPE and thrombocytopenia or a combination of these factors. Dose reductions mainly occurred during the 2nd and 3rd cycle.

The overall response rate of the 30 patients, all of whom initially had measurable disease, was 33% (10 of 30 patients) (Table 2). The response rate was 41% (7/17) in platinum-resistant and 23% (3/13) in platinum-refractory patients, respectively. The median time until response was 3 months (range 3–6 months). Compared to tumor evaluations after cycle 3, the partial response of three additional patients was converted into a complete response after the 6th cycle. The overall survival in responding and non-responding patients was 23.5 months and 11.1 months, respectively.

CA-125 values over the study period were available for 25 patients. Overall, the median CA-125 value before therapy was 467.9 U/ml (SD ±1972.4). Fig. 1 shows the course of the median

serum CA-125 percentages in responding versus non-responding patients (25th percentiles and 75th percentiles of 9 and 41 in responders as well as 130 and 166 in non-responders, respectively).

Toxicity

12 (40%) and 8 patients (27%) received G-CSF or erythropoietin during the study period, respectively. None of the patients stopped therapy due to toxicity. The most severe toxicities per patient are shown in Table 3. No febrile neutropenia, clinical cardiotoxicity or drug-related mortality was observed.

Quality of life

The median score of the global health status decreased from 73 at study entry to 58 after cycle 3 and 50 after cycle 6. The mean fatigue score increased over the study period from 23 initially to 67 after 6 cycles. With regard to physical functioning, the median score was 86 at study entry, and this value was maintained over the study period.

Table 3
Maximum toxicity per patient in the 30 patients treated with PEG liposomal doxorubicin and gemcitabine chemotherapy (NCI-common toxicity criteria)

Toxicity	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Anemia	19	48	29	3	0
Neutropenia	48	10	16	23	3
Leukopenia	23	19	35	22	0
Thrombocytopenia	52	32	6	10	0
Stomatitis	42	26	23	10	0
Mucositis	77	10	10	3	0
Infections	65	3	26	6	0
Palmoplantar erythrodysesthesia	58	23	13	3	0
Edema	81	13	3	3	0
Myalgia, arthralgia	68	26	6	0	0
Dyspnea	81	10	3	3	3
Nausea	45	19	29	6	10
Vomiting	71	13	10	6	0
Constipation	48	29	10	10	3
Diarrhea	87	10	3	0	0
Pain	35	35	19	10	0
Peripheral neuropathy	87	10	3	0	0
Alopecia	58	32	10	0	0
Hypersensitivity reactions	97	3	0	0	0
CNS toxicity	94	6	0	0	0

Discussion

In this phase II study of patients with platinum-resistant ovarian cancer, the combination of L-DXR and GEM achieved an overall response rate of 33%, a median progression-free survival of 3.8 months and an acceptable toxicity profile.

Recent studies, most of them published in abstract form, have reported a high efficacy of combined L-DXR and GEM in ovarian and breast cancer [3,6–13]. The use of L-DXR is limited by its palmoplantar erythrodysesthesia (PPE) and stomatitis. As a single agent, GEM is moderately active in ovarian cancer but can cause significant myelosuppression. Previous studies have shown positive antiproliferative drug interactions in cell lines [4]. Thus, we chose this combination for the treatment of platinum-resistant or -refractory ovarian cancer. In this situation, most patients are expected to die from disease within the next year [1,2]. Thus, the combination of L-DXR and GEM was hypothesized to induce relevant responses associated with acceptable toxicity.

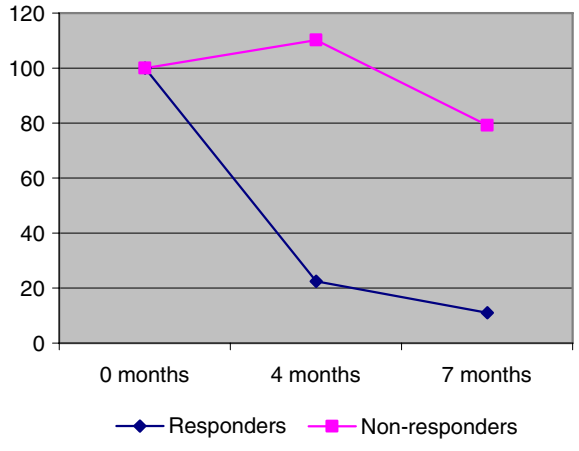

Fig. 1. Course of the median serum CA-125 percentages in responding versus non-responding patients.

One third of patients responded to the combination. This is in the upper range of previously reported phase II studies in platinum-resistant disease [1,2] but may also be due to the relatively low number of previously applied platinum-based chemotherapy regimens in our study population (Table 1).

The toxicity profile in this series of patients with particularly advanced disease was acceptable. However, only one patient had received previous chemotherapy for platinum-resistant disease (Table 1). One quarter of patients developed grade 3 or 4 neutropenia, but none developed febrile neutropenia. No drug-related mortality was observed, and the rate of hypersensitivity reactions was particularly low (grade 1 in 3%). No patient developed new alopecia. PPE grades 2 and 3 occurred in 13% and 3% only, respectively, and no grade 4 PPE was observed (Table 3). In our study, grade 1 to 3 stomatitis was found in 58% of patients; 23% of patients experienced grade 2 and 10% grade 3 stomatitis. We consider stomatitis the most concerning toxicity in the present study. Continued and intensified patient information regarding the prophylactic avoidance of consumption of hot and spicy drinks and meals on the day before and several days after treatment with L-DXR may contribute to a lower rate of stomatitis in patients treated with this combination.

Quality of life evaluations reflected the clinical situation usually found in patients with heavily pretreated ovarian cancer. Usually, patients with disease progression suffer from significant symptoms including increasing abdominal girth and cramps, constipation and/or diarrhea, dyspnea, meteorism and fatigue. Over the study period, the median global health status decreased from 73 to 50, respectively. In parallel, the mean

fatigue score increased steadily over the 6 cycles. However, stabilization of their physical functioning at a median score of 86 was observed over the whole study period, we consider this remarkable. This result was achieved although more than 50% of our patients experienced disease progression.

In conclusion, the combination of L-DXR and GEM is an active and acceptably tolerated option in the treatment of patients with platinum-resistant and -refractory ovarian cancer. This combination at the dosages chosen seems suitable for this patient population. According to our study, dose reductions seem advisable in the case of >grade 2 stomatitis and/or PPE >grade 2. A phase III trial comparing the combination of L-DXR/GEM with monotherapy in platinum-resistant ovarian cancer seems warranted.

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