RESEARCH COMMUNICATION

Efficacy and Toxicity of Gemcitabine and Pegylated Liposomal Doxorubicin in Recurrent Platinum-Resistant/Refractory Epithelial Ovarian Cancer

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Abstract

Background: Treatment of patients with platinum resistant/refractory ovarian cancer is a significant problem. In this study, we evaluated the efficacy and tolerability of the combination of gemcitabine and pegylated liposomal doxorubicin (PLD) in patients with platinum resistant/refractory ovarian cancer. Patients and Methods: We retrospectively evaluated the activity and toxicity of gemcitabine and PLD combination in 35 patients with recurrent platinum resistant/refractory ovarian cancer who had been treated and followed up in 7 centers in Turkey between December 2005 and June 2008. The patients received gemcitabine 1.000 mg/m^2 on day 1 and 8, and PLD 25 mg/m^2 on day 1 every 28 days. Results: A total of 187 cycles (median, 6 cycles) were delivered. An objective response rate of 28,6 % (1 complete, 9 partial response) was achieved. Additionally, 16 patients (45.7 %) had disease stabilization. The median time-to-progression was 6 months (95 % confidence interval, 4-8) and the median overall survival was 17 months (95 % confidence interval, 12-22). Grade 3-4 hematologic toxicities were as follows: leucopenia (14.3%), neutropenia (8.6%), and anemia (2.9%). One febrile neutropenic episode (2.9%) was observed. Non-hematologic toxicity was well tolerated and easily managed and no grade 3-4 palmoplantar erytrodysestesia (PPE) was observed. Conclusion: The combination of gemcitabine and PLD is an effective and tolerable treatment option, with 74.3 % disease control rate for patients with platinum resistant/ refractory ovarian cancer.

Key Words: Gemcitabine - liposomal pegylated doxorubicin - recurrent ovarian cancer - platinum resistance

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Introduction

Ovarian cancer is the fourth leading cause of death from cancer in American women and the most leading cause of deaths among gynecologic malignancies in women. Although response rates to initial adjuvant chemotherapy in ovarian cancer cases are considerably high, 50-75 % of patients will eventually develop recurrent disease (Ozols et al., 2003). The treatment-free or platinum-free interval is the most important predictive factor of prognosis and response to second-line chemotherapy in recurrent patients. The patients are classified as platinum sensitive or platinum resistant according to the length of disease free interval after an initial platinum-based chemotherapy. The platinum sensitive patients experience relapse > 6 months after the response to the platinum-based chemotherapy and this patients remain sensitive to the re-challenge with the platinum-based therapy. Whereas, the platinum-resistant patients experience relapse within 6 months after the initial platinum-based therapy or refractory if not responding to the therapy (Thigpen et al., 1993). Furthermore, platinum-resistant/refractory patients have a dismal prognosis as they have markedly lower response rates to platinum-based chemotherapy (platinum re-challenge). Hence, the management of platinum resistant/refractory patients remains important clinical challenge and the goals of treatment in these patients are to prevent tumor

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progression with minimal toxicity, maintenance of quality-of-life and palliation (Bukowski et al., 2007).

The effectiveness of various anti-neoplastic agents including gemcitabine (Markman et al., 2003), PLD (Gordon et al., 2000), topotecan (Bookman et al., 1998), oral etoposide (Rose et al., 1998), ifosfamide (Markman et al., 1992), and vinorelbine (Burger et al., 1999) has been documented in platinum resistant/refractory patients. However, the studies utilizing these agents generally yielded very low objective response rate (ORR), limited response duration and median survival period of 6-16 months. Thus, there is an extensive research targeting effective intervention in platinum resistant/refractory patients involving double combination variations of the already available agents and test of novel agents. In this respect, due to synergistic anti-tumoral activity and non-overlapping toxicity profiles, the combination of gemcitabine and PLD shows high promise and presents rationale for detailed further investigations, but the available data from this approach is limited. Hence, we evaluated the efficacy and safety of the combination of gemcitabine and PLD in platinum resistant/refractory patients.

Patients and Methods

Subjects

We retrospectively evaluated the results of 35 patients with platinum-resistant/refractory epithelial ovarian cancer who had been treated with the combination of gemcitabine and PLD between December 2005 - June 2008. Data were collected from file records of patients by a responsible person at each institution. All had platinum refractory disease (defined as progressive disease on a platinum-based chemotherapy or persistent clinically measurable disease with best response as stable disease with at least 6 cycles of platinum-based treatment) or platinum-resistant disease (defined as recurrence within 6 months of completing platinum-based chemotherapy).

Patients had histological confirmed epithelial ovarian cancer. Eligible patients included those with 18-75 years of age, a good Eastern Cooperative Oncology Group (ECOG) performance status (0-2), adequate basal renal (blood urea nitrogen < 30 mg/dl, creatinin < 1.5 x upper limit of normal), liver (total biluribin < 2mg/dl, aspartate aminotransferase or alanine transferase ≤ 2 x upper limit of normal), bone marrow (hemoglobin ≥ 10 g/dl, absolute neutrophil count ≥1.5 x 10^9/L, platelets ≥ 100 x10^9/L), and cardiac functions (left ventricular ejection fraction (LVEF) ≥ 50 %). All patients had measurable disease that could be accurately measured in at least one dimension (>2 cm on ultrasonography (USG) and/or computed tomography (CT) or magnetic resonance imaging (MRI)). Patients previously receiving PLD or gemcitabine treatment or with a history of severe cardiac disease and another malignancy, other than non-melanoma skin cancer or *in-situ* carcinoma of cervix or breast were excluded.

Treatment Plan

Chemotherapy schedules consisted of IV gemcitabine 1000 mg/m^2 (as a 30 minutes infusion with saline) on days 1 and 8, and IV PLD 25 mg/m^2 (as a 1-hour infusion with % 5 dextrose) on day 1. Treatment cycles were repeated every 28 days. Patients had no granulocyte colony-stimulating factor (G-CSF) for primary prophylaxis, but it was used for febrile neutropenia, or grade IV neutropenia lasting over 5 days.

Toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria version 2.0 grading system (National Cancer Institute Common Toxicity Criteria). Doses for PLD were reduced by 25 % in palmoplantar erythrodyses thesia (PPE) cases > grade III-IV or stomatitis grade III-IV and were maintained at these doses for subsequent cycles.

Tumor response was assessed every 2 cycles of treatment according to Response Evaluation Criteria in Solid Tumors. A complete response (CR) was defined as the disappearance of all assessable target lesions with no evidence of new lesions by two disease assessments at least four weeks apart. Partial response (PR) defined as at least 30 % decrease in the sum of the longest dimensions of all the target lesions by two disease assessments at least four weeks apart. Progressive disease was defined as at least a 20 % increase in the sum of the longest dimensions of all target lesions or the appearance of new lesions. Stable disease (SD) was defined as any condition not meeting the above criteria.

Statistics

Time-to-progression (TTP) was defined as the period from the beginning of the treatment until documented progression or death, and overall survival (OS) as the period from the first day of treatment until the date of last follow-up or death. Survival curves (TTP and OS) were constructed by the method of Kaplan-Meier and the log rank test was used to compare durations (Kaplan and Meier, 1958). All statistical analyses performed with SPSS software (SPSS 11, Chicago, IL, USA).

Results

Patients

Characteristics of the patients are shown in Table 1. Of the total, 24 patients (68.6 %) were postmenopausal and 11 patients (31.4 %) were premenopausal. All had an ECOG performance status between 0-2. The median platinum-free interval was 2 months (range, 0-6).

Efficacy and Survival

All of the patients completed at least 2 cycles of gemcitabine and PLD chemotherapy and were evaluated for response. The ORR was 28.6 % (95 % Confidence Interval (CI) 14-42) including one (% 2.9) CR, and 9 (25.7 %) PR. Additionally, 16 patients (45.7 %) had disease stabilization at least 3 months after the treatment. Twenty-six patients (74.3 %) had clinical benefit (CR+PR+SD). The median TTP was 6 months (95 % CI, 4-8) and the median OS was 17 months (95 % CI, 12-22).

Safety

A total 187 cycles of chemotherapy were administered to the patients with a median 6 cycles per patient (range,

Table 1. Patients (n=35) and Tumor Characteristics

Parameters		N (%)
Age, years Median (range)		58 (31-77)
Histology	Serous adenocarcinoma	31 (88.6)
	Endometrioid	2 (5.7)
	Undifferentiated	2 (5.7)
Platinum status	Refractory	6 (17.1)
	Resistant	29 (82.9)
Recurrence site	Locoregional	21 (60.0)
	Distant metastasis	2 (25.8)
	Both	12 (34.3)
Baseline CA 125	< 40 (U/ml)	5 (14.3)
	> 40 (U/ml)	30 (85.7)

Table 2. Adverse Events for the 35 Patients (%)

NCI-CTC Grade	0	1	2	3	4
Anemia	34.3	48.6	14.3	0.0	2.9
Leucopenia	34.3	34.3	17.1	14.3	0.0
Neutropenia	42.9	37.1	11.4	5.7	2.9
Thrombocytopenia	71.4	17.1	8.6	2.9	0.0
Mucositis	71.4	14.3	5.7	5.7	2.9
Nausea	28.6	62.9	8.6	0.0	0.0
Vomiting	54.3	40.0	5.7	0.0	0.0
Diarrhea	82.9	17.1	0.0	0.0	0.0
Constipation	74.3	20,0	2.9	2.9	0.0
Anorexia	31.4	51.4	8.6	8.6	0.0
Dyspnea	85.7	14.3	0.0	0	0.0
Febrile neutropenia	0.0	0.0	0.0	2.9	0.0
PPE	84	10.0	7.0	0	0.0
Fatigue	29	52.0	10.0	10.0	0.0
Alopecia	65.7	25.7	5.7	2.9	0.0
Hypersensitivity	91.4	5.7	2.9	0.0	0.0

NCI-CTC, National Cancer Institute - Common Toxicity Criteria; PPE, Palmoplantar erythrodysesthesia

2-10). The combination was generally well tolerated, adverse events being listed in Table 2. The recorded toxicity represents the maximum grade seen for a patient during all cycles of therapy. Hematological toxicity was generally mild and manageable. Grade II anemia observed in 5 patients (14.3 %) and grade III in one patient (2.9 %), and a total of 9 units blood transfusion were required anemic patients. Grade III leucopenia observed in 5 patients (14.3 %), and grade III/IV neutropenia in 3 patients (8.6 %). One febrile neutropenic episode (2.9 %) was observed. Three patients (9.7 %) treated with granulocyte-colony stimulating factor (G-CSF). Four patients (11.4 %) were hospitalized for neutropenia, febrile neutropenia, and mucositis. A 20 % dose reduction was performed in 5 patients (14.3 %) due to hematologic adverse effects. Non-hematological toxicity was rare. No severe (grade III/IV) PPE was observed at the PLD dose we used. PPE grades 1 and 2 occurred in 10 % and 7 % of the patients, respectively. Nausea and vomiting were generally manageable with anti-emetic agents containing serotonin antagonist, and grade III/IV problems were not observed. There were no treatment-related deaths.

Discussion

Second-line chemotherapy remains a major dilemma for platinum resistant/refractory patients. These patients usually do not satisfactorily respond to treatment with

Table 3. Phase II Studies of Gemcitabine and Pegylated Liposomal Doxorubicin in Combination for Platinum Resistant/Refractory Ovarian Patients

Author	Patients (n)	Therapy	RR	RR+SD	OS
D'Agostino	36	PLD 30 D1, GEM 1,000 D1, 8 E3W	25	60	-
Skarlos	37	PLD 25 D 1, GEM 650 D1,8 E3W	22	28	8.4
Ferrandina	66	PLD 30 D1, GEM 1,000 D1,8 E3W	22	55	11.6
Petru	30	PLD 30 D1, 8 GEM 650 D1,8 E4W	33	46	15.8
Tas	18	PLD 20 D1, GEM 2,000 D1,15 E4W	28	56	17.0

GEM, Gemcitabine; PLD, Pegylated Liposomal Doxorubicin; RR, Response Rate; SD, Stable Disease;OS, Overall Survival; D, days; E, every; W, week

short response duration and limited survival. The main goal of therapy in these patients is the palliation of symptoms and maintenance of quality of life, and therefore the toxicity profile of applied therapy is of importance. Single agent therapies are still preferred since the combination chemotherapies have not been proven to be superior to monotherapy. However combination chemotherapy in patients with platinum-resistant ovarian cancer can be feasible and different combination modalities are subject of the ongoing studies.

The liposomal pegylated formulation of doxorubicin has been developed for increasing antitumoral activity through increased intracellular accumulation rate and obtaining decreased toxicity (Ceh et al., 1997; Waterhouse et al., 2001). Thereby, a prolonged circulation time, small distribution volume and higher doxorubicin (about 3-15 times) accumulation in tumor site and reduced cardiac side effects are obtained (Gabizon and Martin, 1997). Phase II trials with single agent PLD showed significant activity in platinum resistant/refractory ovarian cancer patients with overall response rates ranging from 12 % to 26 % (Muggia et al., 1997; Gordon et al., 2000; 2001). PPE, mucositis and stomatitis are reported to be the most common serious side effects in these trials. Gemcitabine, a primidine nucleoside antimetabolite, has been extensively used in recurrent ovarian cancer. In several phase II trials of single agent gemcitabine, overall response rates ranged from 14 % to 22% in the platinum resistant patients (Lund et al., 1994; Shapiro et al., 1996; Markman et al., 2003) with moderate hematological toxicity and mild non-hematological toxicity. In addition to the acceptable toxicity profile and moderate efficacy of gemcitabine, its non-cross-resistance with other antineoplastic agents, make it an ideal and attractive candidate for combination.

The following reasons could account for combination of gemcitabine and PLD which are proven to exert similar efficacy as single agents: (1) Both agents are active in ovarian cancer, (2) Gemcitabine and doxorubicin have shown synergistic anti-proliferative effect *in vitro* and *in vivo* trials (3) The gemcitabine and antracyclines do not show cross-resistance as their mechanism of action are different (4) Gemcitabine and PLD do not have

overlapping toxicity profiles (Zoli et al., 1999; Chow et al., 2000; Gallo et al., 2006).

In this retrospective study, the ORR was higher than reported by Skarlos et al, (2005), Ferrandina et al (2005), and D'Agostino et al (2003) and was consistent with Tas et al (2008) but lower than from Petru et al (2006) (Table 3). Additionally, in this study we achieved stabilization in 46 % (16/35) patients thereby the clinical benefit rate (ORR+SD) of 74 % was achieved with gemcitabine and PLD combination.

In our study, leucopenia and neutropenia rates were comparable with those reported by others (37.2 % and 40.0 % of patients respectively). However, febril neutropenia occurred in one case (2.9 %). The febrile neutropenia is not reported in all phase II studies with gemcitabine and PLD combination even those using gemcitabine 1000 mg/m^2 1-8 days in every 21 days. Due to the retrospective nature of our study, myelotoxicity may be better reflected, since our results reflect clinical application directly, without close follow-up and selection bias. In our series, the non-hematologic safety profile was very good. Of the patients,10 % had grade I PPE, 7% had grade II, and none developed grade 3 and grade 4 PPE.

In conclusion, the combination of gemcitabine and PLD is an effective and tolerable regimen in platinum resistant/refractory patients. To increase the activity, different dose schedules or addition of new agents such as bevacizumab to this combination should be investigated in larger studies.

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