RESEARCH ARTICLE

Treatment Outcomes of Gemcitabine in Refractory or Recurrent Epithelial Ovarian Cancer Patients

Saranya Chanpanitkitchot, Siriwan Tangjitgamol*, Jakkapan Khunnarong, Thaowalai Thavaramara, Kamol Pataradool, Sunamchok Srijaipracharoen

Abstract

Background: To study the response rate (RR), progression-free survival (PFS) and toxicity profiles of recurrent epithelial ovarian cancer (EOC) patients treated with gemcitabine. Materials and Methods: Recurrent EOC patients who were treated with gemcitabine between January 2000 and December 2013 at the Department of Obstetrics and Gynecology, Faculty of Medicine Vajira Hospital were identified and medical records were reviewed. Clinico-pathological features including data of gemcitabine treatment, response and toxicity were collected. Results: We identified 43 EOC patients who had gemcitabine treatment. All except one patient who did not receive any adjuvant treatment, had received platinum-based chemotherapy. Among these 42 patients, 31.0% had refractory cancer to first-line chemotherapy while 69.0% had recurrence with 48.8% being platinum-sensitive. The total cycles of gemcitabine used were 203 (median 4, range 2-9 cycles). Overall RR was 11.6%: 19% in platinum-sensitive vs 4.5% in platinum-resistant groups (p=0.158) and 42.9% in the patients having gemcitabine together with platinum vs 5.6% using gemcitabine alone (P=0.024). Median PFS was 3.6 months (95% confidence interval [CI], 2.73-4.49 months): 8.1 months (95% CI, 2.73-4.49 months) in combination regimen vs 3.2 months (95% CI, 2.01-4.42 months) in single regimen (p=0.077) and 8.1 months (95% CI, 4.73-11.48 months) with the gemcitabine combination vs 2.7 months (95% CI, 1.98-3.38 months) by single gemcitabine in platinum sensitive patients (P=0.007). Common toxicities were hematologic which were well tolerated and manageable. Conclusions: Gemcitabine has modest activity in pre-treated EOC. A combination regimen had higher activity than single agent in platinum sensitive patients with a significant improvement in RR and PFS.

Keywords: Epithelial ovarian cancer - gemcitabine - chemotherapy

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Introduction

Epithelial ovarian carcinoma (EOC) is moderately frequent throughout mainland South-East Asia. The Age-standardized Population-based Cancer Incidence Data for females in Thailand ranged between 5.4% to 6.2% per 100,000 women (Moore et al., 2010). The mainstay of EOC treatment is primary surgery followed by adjuvant chemotherapy if indicated. The standard first-line chemotherapy for EOC is paclitaxel and carboplatin in combination (Ozols et al., 2003). Although the high response rates (RR) yielded by this chemotherapeutic regimen, recurrences occur in more than half of the patients who have advanced stage diseases.

Selection of chemotherapy for recurrent EOC depends on many factors i.e. toxicity from prior treatment, drugs availability, convenience of administration, or cost or reimbursement policy of the country may influence the chemotherapy option for recurrent EOC. Platinum-sensitivity status appears to be the most important and serves as a major indicator for the type of treatment. Platinum-sensitive diseases are usually re-treated with platinum-combination therapy which could yield survival benefit over single drug (Parmar et al., 2003; Pfisterer et al., 2006). In contrast to platinum-resistant diseases which have poorer outcome when the aim of treatment emphasizes on palliative care to maintain a quality of life, single non-platinum chemotherapy is preferred. Various cytotoxic agents studied e.g. topotecan, PLD, gemcitabine, docetaxel, etoposide, paclitaxel and etc (Karaoglu et al., 2009; Kucukoner et al., 2012; Khemapech et al., 2013; Pitakkarnkul et al., 2013; Su et al., 2013; Yuan et al., 2013; Suprasert et al., 2014) could yield 27% to 65% RR and a median survival of 12-24 months in platinum-sensitive recurrent EOC (Berek et al., 2010). The same list of drugs could have only 10%-30% RR with median survival of only 4-9 months in platinum-resistant diseases.

Gemcitabine is one of the most commonly used chemotherapeutic agents in EOC. Many studies reported activity of gemcitabine, either alone or in combination with other drugs, with acceptable toxicity profile in previous treated EOC patients. As a single agent, overall

Department of Obstetrics and Gynecology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand
**For correspondence: siriwanonco@yahoo.com*

RRs of 6-29% were reported (Shapiro et al., 1996; Friedlander et al., 1998; D'Agostino et al., 2003; Markman et al., 2003; Mutch et al., 2007; Ferrandina et al., 2008; Watanabe et al., 2008; Suprasert et al., 2012; Yoshino et al., 2012). Gemcitabine was also tested with other drugs as a combination regimen e.g. cisplatin (Nagourney et al., 2003; Rose et al., 2003; Brewer et al., 2006; Bozas et al., 2007) or carboplatin (Papadimitriou et al., 2004; Pfisterer et al., 2006), PLD (Ferrandina et al., 2005), paclitaxel (Garcia et al., 2004; Poole et al., 2006), topotecan (Greggi et al., 2001; Sehouli et al., 2002), producing high RRs of 13-70% (Greggi et al., 2001; Sehouli et al., 2002; Nagourney et al., 2003; Rose et al., 2003; Garcia et al., 2004; Papadimitriou et al., 2004; Ferrandina et al., 2005; Brewer et al., 2006; Pfisterer et al., 2006; Poole et al., 2006; Bozas et al., 2007).

The objective of this study was to evaluate the RR, progression-free survival (PFS), overall survival (OS) and toxicity of the EOC patients who were treated with gemcitabine in our institution.

Materials and Methods

The study was conducted with approval from the Ethics Committee for Research involving Human Subjects of the institution. Medical records of EOC patients who were treated at our institution between January 2000 and December 2013 were identified. Eligibility criteria were patients who had EOC, had refractory or recurrent cancers after primary chemotherapy, and received gemcitabine. Patients who had low malignant potential tumors or had incomplete data were excluded.

Patients starting chemotherapy must have hemoglobin ≥10 gm%, absolute neutrophil count ≥1,500/mm^3, and platelet count ≥100,000/mm^3. Gemcitabine may be used as single agent or combined with a platinum drug. As a single agent, gemcitabine was given 800-1000 mg/m^2 on days 1 and 8 every 28 days. In an event that the drug cannot be given on day 8, treatment was re-scheduled on day 15 or dose reduction. As a combination therapy, gemcitabine 800 mg/m^2 was given on days 1 and 8 while cisplatin 75 mg/mg^2 or carboplatin AUC of 4-5 was given on day 1. Treatment was repeated until progression or unacceptable toxicity was evidenced.

Clinical, surgical, pathologic, and follow-up data were obtained from the patients' medical records. Data collected were: age; FIGO stage; tumor histopathology and grade; outcome of primary surgery; first-line chemotherapy and responses; status of platinum-sensitivity; number of cycles of gemcitabine, RR, side effects; PFS and OS.

Platinum-sensitive disease was defined when response to initial platinum-base chemotherapy had lasted more than 6 months after treatment ended. Platinum-resistant disease was defined when disease did not respond to primary platinum treatment or recurred within 6 months after the end of therapy. Patients were evaluated for their response to treatment if they had minimum of 2 cycles of gemcitabine. Evaluation procedures included history, pelvic examination and tumor marker (CA125) every cycle before the next course. Response was assigned according to the Gynecologic Oncology Group response criteria. Complete response (CR) was defined when there was no clinical evidence of tumor after chemotherapy treatment while partial response (PR) was defined when tumor reduction was ≥50%. Stable disease (SD) was defined as a tumor that was unchanged in size or had decreased <50% or increased <25%. Progressive disease (PD) was defined as an increase in tumor size ≥25% or development of new lesion. For patients with elevated CA-125 as the only manifestation of disease, a response was recorded base on a Rustin's criteria. Patients who received at least one cycle of gemcitabine were included in the toxicity analysis. Both hematologic and non-hematological toxicities in each cycle were assessed through review of laboratory reports and were graded according to WHO toxicity criteria. Progression-free survival was calculated from time receiving gemcitabine until time to progression, death or last evaluation in the patients who were lost to follow-up. Overall survival was obtained from the date gemcitabine started to date of death or last evaluation date in patients who were alive at the end of study.

Data were analyzed using SPSS statistical software version 11.5 (SPSS, Chicago, IL). Descriptive statistics were used for demographic data. Progression-free survival and OS were analyzed with the Kaplan-Meier method. Survival data between groups were compared with the Log-rank test. The outcomes were significant only if $p<0.05$.

Results

Between January 2000 and December 2013, 44 patients were treated with gemcitabine. One patient who had only one cycle of treatment and was lost to follow-up was excluded. Mean age of the 43 patients included in the study was 55.9±8.5 years. Three patients, who had stage III-IV diseases with extensive metastatic diseases, had neoadjuvant chemotherapy (NAC). Two of them responded and underwent debulking surgery before further chemotherapy. Another patient remained inoperable, so continued chemotherapy. Among 40 patients who underwent primary surgery, 22 had complete surgical staging while 18 did not have lymph node resection or omentectomy. Optimal surgery (residual diseases ≤2 cm) was achieved in 19/40 patients (47.5%). The most common histopathology was either serous adenocarcinoma or adenocarcinoma, not otherwise specified (11 patients or 11.6% each). Majority (38 or 88.4%) had moderate or poorly differentiated tumor. Characteristic features of disease, types and results of primary surgery are shown in Table 1. Of 21 patients who had suboptimal surgery, interval debulking surgery after induction chemotherapy was attempted in 11 patients and successful in seven.

All 42 patients, except one patient who had stage IA grade I tumor, had adjuvant chemotherapy. First-line chemotherapy was carboplatin alone or platinum combined with another chemotherapeutic agent. Complete response was achieved in 29 patients while 13 had refractory cancer. Among the responders, 20 patients recurred after 6 months while nine had evidence of recurrences within 6 months. The detail of primary chemotherapy treatment and responses are shown in Table 1.

Of 20 patients who had recurrences after 6 months and the one who did not receive adjuvant chemotherapy (defined as platinum-sensitive) (48.8%), 15 received re-induction treatment with platinum-base combination chemotherapy while six had non-platinum agents. The other nine patients who recurred within 6 month (platinum-resistant) and 13 who had progressive disease during first-line therapy (platinum-refractory) received various non-platinum chemotherapeutic agents.

Gemcitabine was given to 43 patients in various settings: as second-line therapy in 14 patients: nine with primary platinum-resistance and five with primary platinum-sensitive disease. The other 29 patients had gemcitabine as further-line drug. Most patients received gemcitabine as a single agent (36 patients or 83.7%). Only seven patients (16.3%) had gemcitabine with cisplatin or carboplatin. Median number of gemcitabine treatment was 4 cycles (range 2-9 cycles), making up 203 total cycles of treatment. All 43 patients were evaluable for response. Overall RR was demonstrated in five patients (11.6%): three CR and two PR. Seven patients (16.3%) achieved SD while 31 patients (72.1%) had disease progression.

We analyzed the responses according to possible influencing factors: platinum-sensitivity status (platinum-sensitive vs platinum-resistant), setting of gemcitabine treatment (second- vs further-lines), and regimens (single vs combination). The RRs were: 19.0% (four patients) in platinum-sensitive vs 4.5% in platinum-resistant diseases (p=0.158); 7.1% (one patient) in those who had gemcitabine as second-line vs 13.8% (four patients) as further-line drugs (p=0.469); and 5.6% (two patients) with single gemcitabine vs 42.9% (three patients) with combination regimen (p=0.024). With the important role of platinum-sensitivity status and higher activity of combination regimen, we stratified these two factors to evaluate the response. We found that the three platinum-sensitive patients who had combined chemotherapy had the highest RR (60%) compared to that of the one platinum-sensitive patient who had single gemcitabine (6.2%) (p=0.028) or of the one patient (5.0%) who was platinum-resistant and had single gemcitabine. Of note,

Table 1. Characteristic Features of Diseases and Primary Surgery (N=43)

Tumor characteristics and details of surgery		N (%)
Stage	I-II	7 (16.3)
	III-IV	36 (83.7)
Histology	Serous adenocarcinoma	11 (25.5)
	Endometrioid adenocarcinoma	8 (18.6)
	Adenocarcinoma, not otherwise specified	11 (25.5)
	Clear cell carcinoma	7 (16.3)
	Others	6 (14.1)
Tumor grade	I	5 (11.6)
	II	10 (23.3)
	III	28 (65.1)
Type of primary debulking surgery (N=40) *		
	Complete surgical staging	22 (55.0)
	Incomplete surgical staging	18 (45.0)
Result of primary surgery (N=40)		
	Optimal surgery	19 (47.5)
	Suboptimal surgery	21 (52.5)
First line chemotherapy (N=42) **		
	Cisplatin or carboplatin plus cyclophosphamide	14 (33.3)
	Cisplatin or carboplatin plus paclitaxel	26 (61.9)
	Cisplatin plus docetaxel	1 (2.4)
	Carboplatin	1 (2.4)
Platinum sensitivity (N=43)		
	Platinum-sensitive **	21 (48.8)
	Platinum-resistant or refractory	22 (51.2)

*Three patients had neoadjuvant chemotherapy; **One patient had no adjuvant chemotherapy (stage I) was included in the platinum-sensitive group

Table 3. Adverse Events of Gemcitabine Treatment in 43 Patients (203 Cycles of Treatment)

Toxicity	WHO toxicity G 1 n (%)	G 2 n (%)	G 3 n (%)	G 4 n (%)
Hematologic toxicity				
Anemia				
Cycles	89 (43.8)	29 (14.3)	4 (2.0)	1 (0.5)
Patients*	13 (30.2)	17 (39.5)	3 (7.0)	1 (2.3)
Leukopenia				
Cycles	45 (22.2)	34 (16.7)	5 (2.5)	-
Patients*	10 (23.3)	17 (39.5)	3 (7.0)	-
Neutropenia				
Cycles	27 (13.3)	25 (12.3)	19 (9.4)	3 (1.3)
Patients*	7 (16.2)	7 (16.2)	13 (24.5)	3 (7.0)
Thrombocytopenia				
Cycles	3 (1.5)	5 (2.5)	3 (1.5)	-
Patients*	3 (7.0)	2 (4.7)	3 (7.0)	-
Non-hematologic toxicity (patients)*				
Liver toxicity	2 (4.7)	-	-	
Gastrointestinal symptom	4 (9.3)	-	1 (2.3)	
Neuropathy	2 (4.7)	1 (2.3)	-	

*Grade of toxicity by the number of patients was the most severe toxicity in each individual

Table 2. Detail of Gemcitabine Treatment and Responses (N=43)

Clinical setting		Response rate, N (%) OR	CR	PR	SD	PD
Setting when gemcitabine was used	Second-line (n=14)	1 (7.1)	1 (7.1)	-	1 (7.1)	12 (85.7)
	Third-line (n=15)	2 (13.3)	1 (6.7)	1 (6.7)	2 (13.3)	11 (73.3)
	Fourth-line (n=8)	2 (25.0)	1 (12.5)	1 (12.5)	2 (25.0)	4 (50.0)
	Fifth-line (n=2)	-	-	-	1 (50.0)	1 (50.0)
	Sixth-line (n=2)	-	-	-	1 (50.0)	1 (50.0)
	Eight-line (n=2)	-	-	- -	2 (100.0)	
Platinum-sensitivity	Platinum-sensitive (n=21)	4 (19.1)	3 (14.3)	1 (4.8)	16 (76.2)	
	Platinum- resistant (n=22)	1 (4.5)	-	6 (27.3)	15 (68.2)	
Gemcitabine regimen	Single agent (n=36)	2 (5.6)	1 (2.8)	6 (16.7)	28 (77.8)	
	Combined (n=7) *	3 (42.9)	2 (28.6)	1 (14.3)	3 (42.9)	
Platinum sensitivity status & gemcitabine regimen						
Platinum-sensitive	Single agent (n=16)	1 (6.2)	1 (6.2)	1 (6.2)	14 (87.5)	
	Combined regimen (n=5)	3 (60.0)	2 (40.0)	-	2 (40.0)	
Platinum-resistant	Single agent (n=20)	1 (5.0)	-	5 (25.0)	14 (70.0)	
	Combined regimen (n=2)	-	-	1 (50.0)	1 (50.0)	

*Combined regimen were gemcitabine with cisplatin (n=5) or carboplatin (n=2)

Table 4. ??

First author, year	Response rate (%)	N	TFI (%)	Prior chemotherapy	OR	CR	PR	SD
I. Single agent	Markman, 2003*	51	All <3 m	Median 3 (range 1-6)	16	-	16	-
	Mutch, 2007	99	All <6 m	1 drug (61%), 2 drugs (39 %)	6	1	5	54
	Watanabe, 2008	28	All <6 m	2 drugs (39%) or more (61%)	18	-	17	21
	Shapriro, 1996	38	<6 m (29%)	1-2 drugs (50%) or more (50%)	13	-	13	19
	Friedlander, 1998	38	<6 m (42%)	Only 1 prior regimen	14	6	8	50
	D'Agostino, 2003	50	<6 m (24%)	1-2 drugs (56%) or more (44%)	17	-	17	37
	Ferrandina, 2008	77	<6 m (56%)	Only 1 prior drug	29	5	24	43
	Suprasert, 2012	66	<6 m (53%)	1-2 drugs (68%) or more (32%)	12	-	12	11
	Yoshino, 2012	27	<3 m (48%)	1-2 drugs (55%) or more (45%)	19	-	19	30
	Our study	36	<6 m (56%)	1-2 drugs (78%) or more (22%)	6	3	3	17
II. Combination regimen: platinum-sensitive								
	Papadimitriou, 2004 (carboplatin)	43	All >6 m	Only 1 prior platinum drug	41	27	14	27
	Pfisterer, 2006 (carboplatin)	178	All >6 m	Only 1 prior platinum drug	47	15	33	38
	Our study (cisplatin or carboplatin)	5	All >6 m	1-2 drugs (20%) or more (80%)	60	40	20	-
III. Combination regimen: platinum-resistant								
	Rose, 2003 (cisplatin)	36	<6 m (17%)	1-2 drugs (64%) or more (36%)	43	11	31	26
	Bozas, 2007 (cisplatin)	50	<6 m (88%)	1-2 drugs (68%) or more (32%)	31	9	23	34
	Brewer, 2006 (cisplatin)	59	All <6 m	At least 1 prior drug	16	7	9	54
	Nagourney, 2003 (cisplatin) Ferrandina, 2005 (PLD)	27	<6 m (52%)	1-2 drugs (52%) or more (48%)	70	26	44	26
	Garcia, 2004 (wkly paclitaxel)	101	<6 m (40%)	1-2 drugs (73%) or more (27%)	34	9	26	34
	Poole, 2002 (wkly paclitaxel)	35	All <6 m	Median 2(1-3)	40	6	12	37
	Greggi, 2001 (topotecan)	39	<6 m (41%)	At least 1 prior drug	41	5	36	51
	Sehouli, 2002 (topotecan)	24	All <6 m	NA	13	8	4	38
	Our study (cisplatin or carboplatin)	21	<6 m (24%)	1-2 (96%) or 3 drugs (4%)	64	27	36	18

*Prior chemotherapy in one study (*) and our study did not regard platinum re-induction as second-line drug

no platinum-resistant patients responded to gemcitabine combination therapy. Detail of responses to gemcitabine according to various factors is shown in Table 2.

Among the patients who responded to gemcitabine, only one patient with platinum-sensitive disease (primary recurrence interval of 12 months) who had CR with 6 cycles of carboplatin/gemcitabine remained in remission at the time of this report (eight months). All other patients who responded or had SD as the best response eventually progressed. The median PFS after gemcitabine treatment was 3.6 months (95% confidence interval [CI], 2.73-4.49 months). We analyzed the PFS according to the platinum sensitivity status and regimen of gemcitabine. We found that median PFS of 21 patients with platinum-sensitive was not significantly different from that of 22 patients with platinum-resistant: 4.0 months (95% CI, 2.13-5.87 months) vs 3.4 months (95% CI, 2.13-4.59 months), p=0.635. Although median PFS of seven patients who had gemcitabine combination tended to be longer than that of 36 patients who had single agent: 8.1 months (95% CI, 4.07-12.14 months) vs 3.2 months (95% CI, 2.01-4.42 months), the difference was not statistically significant (p=0.077).Nevertheless, PFS of those who had platinum-sensitive and had combination drugs was significantly longer than platinum-sensitive patient who had only single agent, 8.1months (95% CI, 4.73-11.48 months) vs 2.7months (95% CI, 1.98-3.38 months) (p=0.007).

Except for the one patient with a sustained CR from gemcitabine, the other 42 patients who had PD (31 patients), SD or PR (nine patients), or CR but recurred (two patients) had further treatment: chemotherapy in 27 patients (64.3%); radiation treatment in one (2.4%), and palliative treatment in 14 (33.3%). At the time of this report, 40 patients were dead. Median OS was 9.8 months (95% CI, 5.39-14.18 months). Although we found that OS of the patients who were platinum-sensitive or had combination drugs tended to be longer than those comparative groups, the differences were not statistical significant (data not shown).

From 203 total cycles of gemcitabine treatment, most patients had varying degrees of hematologic toxicity. The most common was anemia which was found in 123 cycles (60.6%) in 34 patients (79.1%). Neutropenia was encountered in 74 cycles (36.5%) in 30 patients (69.8%). Only 23 of them had treatment delayed without administration of granulocyte colony stimulating factor. No febrile neutropenia was observed. Thrombocytopenia was found in 11 cycles (5.3%) in eight patients (17.4%). Non-hematologic toxicities found in our study were as the followings: neuropathy, gastrointestinal toxicity, and elevated liver enzymes. Grade I-II neuropathy in three patients (6.5%) occurred when they had cisplatin and gemcitabine regimen as the fourth- and sixth-line of treatment. Grade I gastrointestinal toxicity was observed in four patients (8.7%) and grade III nausea and vomiting in another one who was subsequently found to have mechanical bowel obstruction. Two patients (4.7%) had elevated liver enzymes before cycle 3 of gemcitabine. Systematic investigation revealed progressive hepatic metastases. The numbers and percentages of patients (and cycles of treatment) experienced toxicities from gemcitabine are shown in Table 3.

Discussion

Gemcitabine, which is one of the most commonly drugs studied in recurrent EOC, showed a wide range of RR from 6% to 70% in previous studies (Table 4). This may lie on multiple factors. First, some studies strictly included only patients with platinum-free interval <6 months (platinum-resistant) when the RRs were only 6-18% (Markman et al., 2003; Mutch et al., 2007; Watanabe et al., 2008) while

others included heterogeneous group of patients with platinum-free interval ranging from <6 months or <12 months altogether when the RRs were 12-29% (Shapiro et al., 1996; Friedlander et al., 1998; D'Agostino et al., 2003; Ferrandina et al., 2008; Suprasert et al., 2012; Yoshino et al., 2012). Second, the status of platinum-resistance in these studies may be primary after first-line platinum drug or secondary after platinum re-induction. Third was the regimen of gemcitabine. Some studies found RRs of 6-29% from single agent (Shapiro et al., 1996; Friedlander et al., 1998; D'Agostino et al., 2003; Markman et al., 2003; Mutch et al., 2007; Ferrandina et al., 2008; Watanabe et al., 2008; Suprasert et al., 2012; Yoshino et al., 2012) while others could demonstrate RRs of 13-70% from gemcitabine in combination with platinum or other agents (Greggi et al., 2001; Sehouli et al., 2002; Nagourney et al., 2003; Rose et al., 2003; Garcia et al., 2004; Papadimitriou et al., 2004; Ferrandina et al., 2005; Brewer et al., 2006; Pfisterer et al., 2006; Poole et al., 2006; Bozas et al., 2007). Another reason which might be under-recognized was the setting when gemcitabine was used or numbers of prior chemotherapy. The activity of drug may be lower when it was used later in the course of treatment: either from increasing resistance after several prior chemotherapeutic agents or a suboptimal performance status of the patients precluding effective treatment.

Our study found modest RR of 12% from gemcitabine in patients with various characteristic features. When we studied RR in the platinum-sensitive group (specific to disease-free more than 6 months), our 19% RR was quite high. Unfortunately, there were limited data regarding the activity of single gemcitabine focusing only to platinum-sensitive group. We demonstrated greater benefit with the combination regimen of gemcitabine/ platinum than gemcitabine alone: higher RR (60 vs 6%, p=0.028) and longer PFS (8 months vs 3 months, p=0.007). This was consistent with previous reports showing high or better RR and improved survival of gemcitabine in combination with platinum (Papadimitriou et al., 2004; Pfisterer et al., 2006). Pfisterer et al. randomized 356 patients with platinum-sensitive disease to have combination regimen (carboplatin and gemcitabine) with single regimen (carboplatin). Treatment outcomes were significantly improved in the combination arm in terms of RR (47% vs 31%) and PFS (9 months vs 6 months) (Pfisterer et al., 2006). Another phase II prospective study by Papadimitriou et al. also showed high RR of 41% and PFS of 9 months with combined treatment (Papadimitriou et al., 2004).We were humbly aware that the number in this particular group of patients was very small (five patients) and might have exaggerated the RR to much higher than those found in the two previous studies (60% compared to 47% or 41%).

The RR of single gemcitabine in platinum-resistant patients was less than 20% in previous reports (Shapiro et al., 1996; Friedlander et al., 1998; D'Agostino et al., 2003; Markman et al., 2003; Mutch et al., 2007; Ferrandina et al., 2008; Watanabe et al., 2008; Suprasert et al., 2012; Yoshino et al., 2012). An exception was the trial by Ferrandina et al. (1998) who demonstrated high RR from gemcitabine (29%) which was significantly higher in comparison to PLD (16%) (Ferrandina et al., 2008). Their high RR may be due to nearly half of the patients (44%) having treatment-free interval more than 6 months and may not be really platinum-resistant. Other studies did not report such favorable data. One RCT by Mutch et al. compared gemcitabine and PLD in 195 platinum-resistant patients. No difference between the activity of gemcitabine or PLD in terms of RR, PFS, or OS: 6% vs 8% RR, 4 months vs 3 months of PFS, and 13 months vs 14 months of OS. The low RR in this trial was probably due to a short treatment-free interval from previous treatment (median of only 3 months) (Mutch et al., 2007). Different RRs in these studies may lie partly on different inclusion criteria or patients' characteristics regarding treatment-free interval or number of treatment prior to gemcitabine. Our RR of 5% among 22 platinum-resistant patients was lower than those found in other studies. This may be due to a definition of platinum-resistance in our study (based on response to first-line platinum treatment). These patients in our study will have intrinsic poor prognosis than those who had primary a platinum-sensitivity but later found to be secondary platinum-resistant from re-induction treatment. On the other hand, by defining platinum-resistant as either primary or secondary as in other reports, all of our patients would be classified as platinum-resistant.

In contrast to the recommendation of single chemotherapy in platinum-resistance, gemcitabine combination has a role to reverses platinum-resistant status in EOC (Rose, 2005). The drug has synergistic activity with platinum by forming platinum-DNA adduct which inhibits ribonucleotide reductase. Several clinical studies have demonstrated high efficacy of the combined drugs: RRs of 16-70% with cisplatin (Nagourney et al., 2003; Rose et al., 2003; Brewer et al., 2006; Bozas et al., 2007), 40% with paclitaxel (Garcia et al., 2004; Poole et al., 2006), 13-64% with topotecan (Greggi et al., 2001; Sehouli et al., 2002), or 34% with PLD (Ferrandina et al., 2005). Our study could not demonstrate any RR by a combination regimen in platinum-resistant patients except one patient who could achieve SD. However, the number of patients in this group was too small for a meaningful clinical interpretation. A summary of gemcitabine studies is shown in Table 4.

Regarding gemcitabine toxicity, 10-30% grade 3-4 hematologic toxicity was reported (Shapiro et al., 1996; Friedlander et al., 1998; Ferrandina et al., 2008; Suprasert et al., 2012). This event is generally manageable with dose reduction or delay of subsequent dose. Our study found grade 3-4 neutropenia in 11% of cycles of treatment or in 37% of patients. All of them were managed with dose delay or drug abandon on day 8. No serious adverse events or febrile neutropenia were encountered.

Non-hematologic toxicities were infrequently reported in previous studies (Shapiro et al., 1996; Friedlander et al., 1998; Markman et al., 2003; Suprasert et al., 2012). Most toxicities were grade I with single agent (Shapiro et al., 1996; Friedlander et al., 1998) and up to 15% were grade III-IV with combined regimen with platinum or another non-platinum agent (Nagourney et al., 2003; Ferrandina et al., 2005). Our study infrequently found non-hematologic toxicities: peripheral neuropathy, emesis, and increased

in hepatic enzymes. Nevertheless, peripheral neuropathy was pre-existing before an aggravation during gemcitabine treatment. Emesis or hepatic enzyme derangement was found only in patients who had progressive diseases in GIT or liver respectively.

In conclusion, gemcitabine had modest activity in pre-treated EOC. The chemotherapy was well tolerated and had manageable toxicity. A greater benefit was likely in platinum-sensitive disease (not significant). Combination gemcitabine regimens had a significant higher activity than single agent in terms of improved response rate and progression-free survival in platinum-sensitive. We could not demonstrate the benefit in platinum-resistant group as has been reported. However, the number of patients in each group was quite small to allow a definite conclusion from our study. Further study in a large trial or a systematic review and meta-analysis to evaluate its activity in each particular group of patients with similar characteristic features seems reasonable.

References

Berek JS, Friedlander M, Hacker NF (2010). Epithelial ovarian, fallopian tube, and peritoneal cancer. In: Berek JS, Friedlander M, Hacker NF (eds) Berek & Hacker's Gynecologic oncology. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 484-508.

Bozas G, Bamias A, Koutsoukou V, et al (2007). Biweekly gemcitabine and cisplatin in platinum-resistant/refractory, paclitaxel-pretreated, ovarian and peritoneal carcinoma. *Gynecol Oncol*, **104**, 580-5.

Brewer CA, Blessing JA, Nagourney RA, Morgan M, Hanjani P (2006). Cisplatin plus gemcitabine in platinum-refractory ovarian or primary peritoneal cancer: a phase II study of the gynecologic oncology group. *Gynecol Oncol*, **103**, 446-50.

D'Agostino G1, Amant F, Berteloot P, Scambia G, Vergote I (2003). Phase II study of gemcitabine in recurrent platinum- and paclitaxel-resistant ovarian cancer. *Gynecol Oncol*, **88**, 266-9.

Ferlay J, Soerjomataram I, Ervik M, et al (2014). GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012.

Ferrandina G, Ludovisi M, Lorusso D, et al (2008). Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer. *J Clin Oncol*, **26**, 890-6.

Ferrandina G, Paris I, Ludovisi M, et al (2005). Gemcitabine and liposomal doxorubicin in the salvage treatment of ovarian cancer: updated results and long-term survival. *Gynecol Oncol*, **98**, 267-73.

Friedlander M, Millward MJ, Bell D, et al (1998). A phase II study of gemcitabine in platinum pre-treated patients with advanced epithelial ovarian cancer. *Ann Oncol*, **12**, 1343-5.

Garcia AA, O'Meara A, Bahador A, et al (2004). Phase II study of gemcitabine and weekly paclitaxel in recurrent platinum-resistant ovarian cancer. *Gynecol Oncol*, **93**, 493-8.

Greggi S, Salerno MG, D'Agostino G, et al (2001). Topotecan and gemcitabine in platinum/paclitaxel-resistant ovarian cancer. *Oncology*, **60**, 19-23.

Karaoglu A, Arslan UY, Ozkan M, et al (2009). Efficacy and toxicity of gemcitabine and pegylated liposomal doxorubicin in recurrent platinum-resistant/refractory epithelial ovarian cancer. *Asian Pac J Cancer Prev*, **10**, 63-6.

Khemapech N, Oranratanaphan S, Termrungruanglert W, Lertkhachonsuk R, Vasurattana A (2013). Salvage chemotherapy in recurrent platinum-resistant or refractory epithelial ovarian cancer with carboplatin and distearoylphosphatidylcholine pegylated liposomal doxorubicin (lipo-dox®). *Asian Pac J Cancer Prev*, **14**, 2131-5.

Kucukoner M, Isikdogan A, Yaman S, et al (2012). Oral etoposide for platinum-resistant and recurrent epithelial ovarian cancer: a study by the anatolian society of medical oncology. *Asian Pac J Cancer Prev*, **13**, 3973-6.

Markman M, Webster K, Zanotti K, et al (2003). Phase 2 trial of single-agent gemcitabine in platinum-paclitaxel refractory ovarian cancer. *Gynecol Oncol*, **90**, 593-6.

Moore MA, Attasara P, Khuhaprema T, et al (2010). Cancer epidemiology in mainland South-East Asia - past, present and future. *Asian Pac J Cancer Prev*, **11 Epidemiology Suppl**, 67-80.

Mutch DG, Orlando M, Goss T, et al (2007). Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. *J Clin Oncol*, **25**, 2811-8.

Nagourney RA, Brewer CA, Radecki S, et al (2003). Phase II trial of gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed ovarian cancer patients. *Gynecol Oncol*, **88**, 35-9.

Ozols RF, Bundy BN, Greer BE, et al (2003). Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a gynecologic oncology group study. *J Clin Oncol*, **21**, 3194-200.

Papadimitriou CA, Fountzilas G, Aravantinos G, et al (2004). Second-line chemotherapy with gemcitabine and carboplatin in paclitaxel-pretreated, platinum-sensitive ovarian cancer patients. A hellenic cooperative oncology group study. *Gynecol Oncol*, **92**, 152-9.

Parmar MK, Ledermann JA, Colombo N, et al (2003). Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet*, **361**, 2099-106.

Pfisterer J, Plante M, Vergote I, et al (2006). Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol*, **24**, 4699-707.

Pitakkarnkul S, Tangjitgamol S, Srijaipracharoen S, et al (2013). Treatment outcomes of paclitaxel for refractory or recurrent epithelial ovarian cancer patients in Thailand. *Asian Pac J Cancer Prev*, **14**, 2421-7.

Poole CJ, Perren T, Gawande S, et al (2006). Optimized sequence of drug administration and schedule leads to improved dose delivery for gemcitabine and paclitaxel in combination: a phase I trial in patients with recurrent ovarian cancer. *Int J Gynecol Cancer*, **16**, 507-14.

Rose PG (2005). Gemcitabine reverses platinum resistance in platinum-resistant ovarian and peritoneal carcinoma. *Int J Gynecol Cancer*, **15**, 18-22.

Rose PG, Mossbruger K, Fusco N, et al (2003). Gemcitabine reverses cisplatin resistance: demonstration of activity in platinum- and multidrug-resistant ovarian and peritoneal carcinoma. *Gynecol Oncol*, **88**, 17-21.

Sehouli J, Stengel D, Oskay G, et al (2002). NOGGO study group. A phase II study of topotecan plus gemcitabine in the treatment of patients with relapsed ovarian cancer after failure of first-line chemotherapy. *Ann Oncol*, **13**, 1749-55.

Shapiro JD, Millward MJ, Rischin D, et al (1996). Activity of gemcitabine in patients with advanced ovarian cancer: responses seen following platinum and paclitaxel. *Gynecol*

Oncol, **63**, 89-93.

Su A, Zhang J, Pan ZH, Zhou QM, Lv X (2013). Salvage therapy of gemcitabine plus endostar significantly improves progression-free survival (PFS) with platinum-resistant recurrent epithelial ovarian cancer. *Asian Pac J Cancer Prev*, **14**, 1841-6.

Suprasert P, Cheewakriangkrai C, Manopunya M (2012). Outcome of single agent generic gemcitabine in platinum-resistant ovarian cancer, fallopian tube cancer and primary peritoneal adenocarcinoma. *Asian Pac J Cancer Prev*, **13**, 517-20.

Suprasert P, Manopunya M, Cheewakriangkrai C (2014). Outcomes with single agent LIPO-DOX in platinum-resistant ovarian and fallopian tube cancers and primary peritoneal adenocarcinoma - Chiang Mai University Hospital experience. *Asian Pac J Cancer Prev*, **15**, 1145-8.

Watanabe Y, Koike E, Nakai H, Etoh T, Hoshiai H (2008). Phase II study of single-agent gemcitabine in heavily pretreated Japanese patients with recurrent ovarian cancer. *Int J Clin Oncol*, **13**, 345-8.

Yoshino K, Hiramatsu K, Enomoto T, et al (2012). Salvage chemotherapy using gemcitabine for taxane/platinum-resistant recurrent ovarian cancer: a single institutional experience. *Anticancer Res*, **32**, 4029-33.

Yuan SF, Zhang LP, Zhu LJ, et al (2013). Phase II clinical study on the GEMOX regimen as second- line therapy for advanced ovarian cancer. *Asian Pac J Cancer Prev*, **14**, 3949-53.