

## RESEARCH COMMUNICATION

# Outcome of Single Agent Generic Gemcitabine in Platinum-Resistant Ovarian Cancer, Fallopian Tube Cancer and Primary Peritoneal Adenocarcinoma

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### Abstract

Single original gemcitabine is commonly used as salvage treatment in platinum-resistant ovarian cancer, fallopian tube cancer and primary peritoneal adenocarcinoma (PPA) with a satisfactory outcome. However, efficacy data from this regimen are limited. We therefore conducted a retrospective study to evaluate the outcome of patients who received single-agent generic gemcitabine (GEMITA) after development of clinical platinum resistance. The study period was between May 2008 and December 2010. Gemcitabine was administered intravenously in two different schedules: 1,000 mg/m<sup>2</sup> on day 1, 8, and 15 every 28 days; and on days 1 and 8 every 21 days with the same dosage. Administration was until disease progression was noted. The response rate was evaluated using the Gynecologic Cancer Intergroup (GCIg) criteria while toxicity was evaluated according to WHO criteria. Sixty-six patients met the inclusion criteria in the study period. Two-thirds of them received gemcitabine as the second and third line regimen. The overall response rate was 12.1%. The median progression free survival and overall survival was 2 and 10 months, respectively. With the total 550 courses of chemotherapy, the patients developed grades 3 and 4 hematologic toxicity as follows: anemia, 1.5%; leukopenia, 13.7%; neutropenia, 27.3%; and thrombocytopenia, 3.0%. In conclusion, single agent generic gemcitabine revealed a modest efficacy in patients with platinum-resistant ovarian cancer, fallopian tube cancer and PPA without serious toxicity.

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### Introduction

Gemcitabine is effective regarding inhibiting the growth of human ovarian carcinoma both in vivo and in vitro systems (Ruiz et al., 1994; Peters et al., 1995; Distefano et al., 2001). There have been many phase I and II trials using gemcitabine as a single agent for salvage treatment of epithelial ovarian cancer with an overall response rate of about 19%. The time to progression and overall survival varied from 2.8 to 8.8 and 6 to 11.2 months, respectively (Lorusso et al., 2006). The dosage of gemcitabine ranging from 800 to 1250 mg/m<sup>2</sup> administered as a 30 minute infusion on days 1, 8, and 15 of a 28-day cycle (Lorusso et al., 2006) or day 1 and day 8 every 21-days (Ojeda Gonzalez et al., 2008).

Furthermore, a randomized controlled trial study of gemcitabine compared to pegylated liposomal doxorubicin (PLD) in patients with platinum-resistant epithelial ovarian cancer was published. The authors suggested that both gemcitabine and PLD showed comparable outcomes and single gemcitabine may be an acceptable alternative to PLD for epithelial ovarian cancer patients who are resistant to platinum and paclitaxel (Mutch et al., 2007).

Generic gemcitabine was introduced to our institute

in 2007. The drug price was about 40% lower than the original drug. To reduce the cost of gemcitabine, our institute's policy prefers the generic gemcitabine in most platinum-based resistant ovarian cancer patients for reducing the cost of chemotherapy. However, a study of generic gemcitabine in these patients has not been previously reported. All gemcitabine used in the prior studies was the original. To evaluate the efficacy and toxicity of generic gemcitabine in patients with platinum-based resistant epithelial ovarian cancer, we conducted this retrospective study to identify this outcome.

### Materials and Methods

After the protocol was approved by the Research Ethics Committee, the medical records of the patients with platinum-based resistant epithelial ovarian cancer, fallopian tube cancer and primary peritoneal adenocarcinoma who received single agent generic gemcitabine (GEMITA) at Chiang Mai University Hospital between May 2008 and December 2010 were reviewed. We included fallopian tube cancer and primary peritoneal adenocarcinoma in this study due to the similar treatment strategies to ovarian cancer.

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*Protocol of chemotherapy regimen*

The schedule of chemotherapy consisted of intravenous (IV) generic gemcitabine 1,000 mg/m<sup>2</sup> given for 30 minutes on day 1,8,15 every 28 days or day 1 and 8 every 21 days until disease progression or unacceptable toxicity. The criteria for using each schedule depended on the attending physician's preference. The complete blood count was evaluated before giving chemotherapy each week while the renal function test, liver function test and serum CA 125 were assessed each cycle. A 25% dose reduction of gemcitabine was applied in the subsequent cycle when severe toxicity occurred. All patients were required to have a hemoglobin (Hb) of more than 10 gm%, an absolute neutrophil count (ANC) of more than 1,500 /mm<sup>3</sup>, and a platelet count of more than 100,000 /mm<sup>3</sup> on the day before beginning chemotherapy. The treatment was delayed if blood counts had not returned to acceptable levels prior the next course of chemotherapy. Some patients also received granulocyte-colony stimulating factor (G-CSF) for severe neutropenia. In patients with tumor progression, further treatment was left to the responsible physician. Follow-up after completion of treatment included history taking, pelvic examination and tumor marker evaluation every three months.

*Outcome parameters*

The objective tumor response was determined by Gynecologic Cancer Intergroup (GCIIG) criteria that used CA 125 criteria to evaluate the outcome (Rustin et al., 2011). Progression-free survival (PFS) was defined as the period of time between the first administration of gemcitabine and the date of tumor progression or the date of last contact if the patients had not yet tumor progression. The overall survival (OS) was defined as the period of time between the first given of gemcitabine and the date of last contact or the date of patients' death. All adverse effects were evaluated by using WHO toxicity criteria (Miller et al., 1981).

*Statistical analysis*

Descriptive data of all studied patients were presented with measurement data expressed as the mean, with range and discrete data as numbers and percentages. PFS and OS were estimated by the Kaplan-Meier Method. Statistical analysis of the data was done using the SPSS for windows version 17.0 (SPSS Inc., Chicago, IL, USA).

**Results**

Sixty-six patients received generic gemcitabine during the study period. The patients' characteristics are noted in Table 1. The mean age was 52 years and over 80% of them were diagnosed with recurrent ovarian cancer. About half were initially diagnosed with stage III and the most common histology was serous cystadenocarcinoma. The majority of the patients received no more than two prior chemotherapy regimens. The most frequent site of recurrence was the abdomino-pelvis.

*Chemotherapy regimen*

About 80% of the patients were administered generic

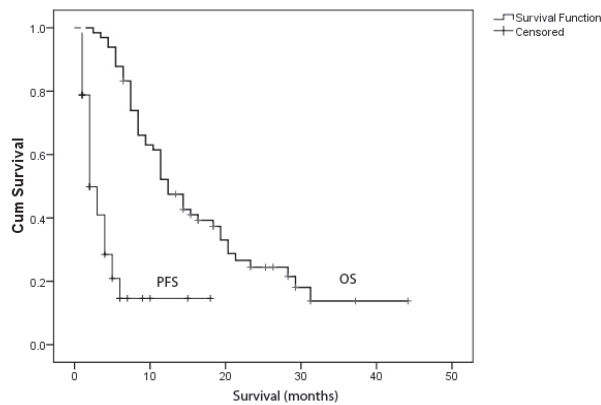
**Table 1. Patient Characteristics (N=66)**

Clinical data	Number (%)
Mean age (range: years)	52(29-68)
Disease	
CA ovary	54(81.8)
CA fallopian tube	4(6.1)
Primary peritoneal adenocarcinoma	8(12.1)
Stage	
I	9(13.6)
II	8 (12.2)
III	38(54.4)
IV	12(18.2)
Unknown	1(1.5)
Surgical type	
Complete	15(22.7)
Incomplete	51(77.3)
Residual disease after primary surgery	
No	17(25.8)
Suboptimal	27(40.9)
Optimal	12(18.2)
Unknown	10(15.2)
Histology	
Serous cystadenocarcinoma	33(50.0)
Clear cell carcinoma	12(18.2)
Endometrioid carcinoma	7(10.6)
Other	14(21.2)
First line chemotherapy	
Carboplatin + paclitaxel (PT)	57(86.4)
Carboplatin	2(3.0)
PT/carboplatin	2(3.0)
Carboplatin + cyclophosphamide	3(4.5)
Cycle of first line administration	
1-3	5(0.1)
4-6	54(81.8)
7-9	7(0.1)
Recurrence-free interval (months)	
1-5	35(53.0)
6-12	15(22.7)
13-23	8(12.10)
>24	4(0.1)
Number of prior chemotherapy regimen	
1	21(31.8)
2	24(36.4)
3	13(19.7)
>= 4	8(12.1)
Recurrence site	
Abdomen & pelvis	52(78.8)
Lung(s)	4(6.1)
Lung & abdomen	6(9.0)
Left supraclavicular lymph node	2(3.0)
Lung & abdomen & left supraclavicular lymph node	2(3.0)

gemcitabine on day 1,8,15 every 28 days and only 10% of the patients received 6 cycles of gemcitabine. Five hundred fifty total courses of gemcitabine were administered.

*Tumor response and survival*

The overall response rate was 12.1% with no complete response observed. There were 10.6% who developed stability of disease while the rest (77.3%) showed progression of disease. After tumor progression, further therapy consisted of other chemotherapy (56.1%), pelvic radiation (6.1%), hormone (4.5%) and palliative care (19.7%). With the mean follow up time of 13 months, 49



**Figure 1. Progression-free Survival (PFS) and Overall Survival (OS)** . The median PFS was two months (1-18 months), the median overall survival was 11 months (range 1-65 months)

**Table 2. Grade 3 and 4 Toxicity (550 courses)**

Toxicity	Courses (%)	Patients (%)
Anemia	1(0.2)	1(1.5)
Leukopenia	10(1.8)	9 (13.7)
Granulocytopenia	23(4.2)	18(27.3)
Thrombocytopenia	2(0.4)	2(3.0)
Non-hematologic toxicity	2(0.4)	1(1.5)
Liver toxicity		

Adjusted dosage, 11 courses (2.0%); Granulocyte stimulating factor (GCSF) used, 22 courses (4.0%); Delayed treatment, 64 (11.6%) courses

patients (74.2%) died of disease and 17 patients (25.8%) were living with their disease. The median PFS was 2 months and median OS was 10 months as showed in Figure 1.

#### Toxicity

Of the 550 courses of generic gemcitabine, the common grade 3 and 4 hematologic toxicity was neutropenia that developed in 27.3% of patients followed by leukopenia that occurred in 13.7% of patients as noted in Table 2. Granulocyte stimulating factor (GCSF) was given in 22 courses for those patients with neutropenia. The adjusted dosage was done in 11 courses (2.0%) and about 10% of total courses were delayed due to improper hematologic toxicity. Other serious liver toxicity was found in only one patient (1.5%).

## Discussion

Gemcitabine (2',2'-difluorodeoxycytidine, dFdC) is a nucleoside analogue of cytidine (Van Moorsel et al., 1997) . It enters the cell through a membrane nucleoside transporter and is activated by phosphorylation to gemcitabine monophosphate that subsequently phosphorylated again to be the 5'-diphosphate and triphosphate derivatives, which represent the active forms of gemcitabine. Both gemcitabine diphosphate and triphosphate prevent DNA repair and RNA synthesis, respectively (Heinemann et al., 1988; 1990; Huang et al., 1991; Ruiz van Haperen et al., 1993; Mackey et al., 1998). Many previously published studies revealed the outcome of single original gemcitabine in treating

platinum-resistant epithelial ovarian cancer in terms of the response rate at 19%, the median progression free survival of three to nine months and the overall survival of six to eleven months with minimal toxicity (Lorusso et al., 2006). However, the data about the efficacy of generic gemcitabine used as salvage treatment in this setting is still limited. Only one study reported the comparative in vitro cytotoxicity of the generic gemcitabine (GEMITA) and reference products of gemcitabine on various cancer cell lines (Hahnvajjanawong et al., 2011). To our best knowledge, this present study was the first one that revealed the response rate of generic gemcitabine in patients with recurrent epithelial ovarian cancer, fallopian tube cancer and primary peritoneal adenocarcinoma. The response rate in our study was 12.1% while the median PFS was 2 months and median overall survival was 10 months. These outcomes were comparable to the previous reports from the administration of original gemcitabine.

Regarding toxicity, Watanabe et al (2008) administered single gemcitabine to 28 patients with a dosage of 1,000 mg/m<sup>2</sup> on day 1,8, and 15 of a 28-day cycle. About 17.9% of the patients needed dose reduction to 800 mg/m<sup>2</sup> secondary to thrombocytopenia and granulocytopenia. They reported the response rate and the survival similar to our study. However, the toxicity in their report was higher than our study. They showed grade 3 and 4 hematologic toxicities including leukopenia 35.7%, granulocytopenia 39.3%, anemia 46.4% and thrombocytopenia 10.7% whereas our report found grade 3 and 4 leukopenia 13.7%, granulocytopenia 27.3%, anemia 1.5% and thrombocytopenia only 3.0%. The dissimilar outcome might be from the differences of the studied patients. All patients in Watanabe's study initial received at least 2 chemotherapy regimens while about one-third of our patients were pretreated with only one regimen. However, when compared to other reports such as Mutch et al. (2007) that used gemcitabine as a second line drug, they showed grade 3 and 4 neutropenia 38%, anemia 3% and thrombocytopenia 3%. These adverse effects were similar to our study.

In conclusion, generic gemcitabine seems to have comparable outcomes with generic gemcitabine in treating platinum-resistant epithelial ovarian cancer with minimal toxicity especially in patients who received the treatment as a second line drug after resistance to platinum-based chemotherapy.

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