RESEARCH ARTICLE

Survival Outcomes of Recurrent Epithelial Ovarian Cancer: Experience from a Thailand Northern Tertiary Care Center

Natpat Jansaka, Prapaporn Suprasert

Abstract

To assess survival outcomes in a retrospective study, recurrent epithelial ovarian cancer patients were divided into three groups according to the platinum free interval as follows: platinum refractory that included the patients with tumor progression during treatment; platinum resistant and platinum sensitive that included the patients with tumor progression less than or more than six months, respectively. Clinical data for tumor progression in epithelial ovarian cancer patients treated at Chiang Mai University Hospital between January, 2006 and December, 2010 were reviewed. Thirty-nine patients were in the platinum refractory group while 27 were in the platinum resistant group and 75 in the platinum sensitive group. The mean age, the parity, the administration of neoadjuvant chemotherapy and the serous type did not significantly different across groups while the mean total number of chemotherapy regimens, the early stage patients, the patients with complete surgery and the surviving patients were significant more frequent in the platinum sensitive group. Regarding subsequent treatment after tumor recurrence, 87.2% underwent chemotherapy. With the median follow up time at 29 months, the median overall survival rates were 20 months, 14 months and 42 months in platinum refractory, platinum resistant and platinum sensitive groups, respectively ($p<0.001$). In addition, when the platinum sensitive patients developed the next episode of tumor progression, the median progression free interval time was only three to four months. In conclusion, the outcomes for platinum refractory the and platinum resistant groups was poorer than the platinum sensitive group. However, subsequent progression in the platinum sensitive group was also associated with a poor outcome.

Keywords: Ovarian cancer recurrence - platinum refractory / resistant / sensitive - overall survival

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Introduction

Epithelial ovarian cancer is the seventh ranking female cancer in the world and is the second most common gynecologic cancer in Thai women (http://globocan.iarc.fr). This cancer yielded a poor prognosis because over 75% presented in an advanced stage and about 80% developed tumor recurrence (Foley et al., 2013). The standard treatment of ovarian cancer consisted of the surgical tumor debulking followed by six courses of chemotherapy with platinum and paclitaxel (Thigpen, 2012) while the treatments after tumor recurrence depended on the platinum free interval that was classified into three groups. The first one was platinum refractory that recruited the patients who developed progression of disease while receiving chemotherapy. The second was platinum resistant including all patients who experienced tumor progression within six months after completing a course of chemotherapy. Both groups were treated with various regimen of chemotherapy such as pegylated liposomal doxorubicin (PLD), gemcitabine, oral topotecan, weekly paclitaxel with the response rate of 10-15% and a median overall survival of nine to twelve months (Thigpen, 2012; Gonzalez-Martin, 2013). The third one was platinum sensitive that recruited the patients who developed tumor recurrence more than six months after completing chemotherapy with platinum. The patients in this group were treated with single platinum or combined with paclitaxel or PLD with the response rate over 50% and median overall survival of 36 months (Foley et al., 2013).

In Chiang Mai University Hospital, the tertiary care hospital in Northern Thailand, we treated recurrence ovarian cancer by using the chemotherapy regimen provided from our national policy that was similar to the chemotherapy mentioned above but in the generic formula. However, we did not have our own data about the survival outcome of these patients. Thus, we conducted the present retrospective study to identify the clinical characteristics and the survival outcomes of the recurrence of ovarian cancer patients in platinum refractory, platinum resistant and platinum sensitive groups. Due to limited data of the treatment outcomes of recurrent ovarian cancer in Southeast Asia, this data will be beneficial for improving the management guidelines for these patients.

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Materials and Methods

After the local Ethics Committee approved our protocol, the medical records of epithelial ovarian cancer patients treated at Chiang Mai University Hospital from January, 2006 to December, 2010 were reviewed. Most of these patients were followed at our institute according to our recently published surveillance schedule in 2013 (Suprasert and Chalapati, 2013).

The patients who developed disease progression during or after completed treatment were included in the study. The definition of tumor progression utilized WHO criteria. The patients who were lost to follow up were excluded.

These patients were recruited and classified into three groups depending on the platinum free interval time from the time of the last platinum dosage to the time of tumor progression. The details of each group were as the follows:

Group 1 was the platinum refractory group. This group included the patients who developed disease progression while receiving the platinum drug.

Group 2 was the platinum resistant group. This group included the patients who developed tumor progression within six months after completing treatment of platinum.

Group 3 was the platinum sensitive group. This group included the patients who developed tumor progression equal to or more than six months after completing treatment of platinum.

The clinical characteristics of each group were recorded and compared by using Chi-square, Fisher's Exact and Anova test. The overall survival was defined as the time between the month of the initial treatment and the month the patient died or the last contact. This survival time was estimated by the Kaplan-Meier method and compared within each group by using the log rank test. In the platinum sensitive group, the progression free interval was defined as the time between the month that subsequent chemotherapy started and the time further progression was identified.

All statistical analysis was carried out using the SPSS for window program (Version 17.0, Chicago, II, USA). Statistical significance was set at P value less than 0.05.

Results

The patients in the platinum refractory group, resistant group and sensitive group were 39, 27 and 75 cases, respectively. The comparison of clinical data among each group was noted in Table1. The parity, the patients who administered neoadjuvant chemotherapy, the serous type, and the mean age among 3 groups were not significantly different while the early stage patients , the patients who underwent optimal surgery, the mean number of total chemotherapy regimen and the survived patients were significant different when compared the platinum sensitive group with the rest 2 groups. In addition, the patients who underwent a complete surgical staging procedure showed significant more frequently in the platinum resistant and sensitive groups than in platinum refractory group.

The subsequent treatment after first episode of tumor progression was displayed in Table 2. Most of these patients received chemotherapy with over 80% of the patients in the platinum sensitive group received carboplatin plus paclitaxel. Only eight patients were operated on before chemotherapy was administered. However, seven patients in the platinum refractory and resistance group and one in the platinum sensitive group received only palliative treatment. Two patients died before being given any further treatment.

The overall survival in each group was shown and

Table 1. Clinical Characteristics of Recurrence Ovarian Cancer Patients Divided by Platinum type (N=141)

Platinum type Characteristic	Refractory (%) N = 39	Resistant (%) N = 27	Sensitive (%) N = 75	P value
Mean age (range)	53.6 (27-71)	52.9(36-74)	50.9(33-76)	0.32
Mean total chemotherapy regimens (range)	2.8(1-6)a	2.7(1-5)b	3.4(1-7)a,b	0.03
Young age*	3 (7.7)	2(7.4)	7(9.3)	0.93
Nulliparity	17 (43.6)	11(40.7)	28 (37.3)	0.8
Early stage	4(10.3)	7(25.9)	39(52.0)	<0.01
Received neoadjuvant chemotherapy	6(15.4)	2(7.4)	13(17.3)	0.46
Complete surgical stage surgery	5(12.8)	10(37.0)	26(35.1)	0.03
Optimal surgery	11 (31.4)	9(37.5)	49(76.6)	<0.01
Histology				
Serous type	18(46.2)	10(37.0)	34(45.3)	0.72
Survivor patients	2(5.1)	1(3.7)	30(40.0)	<0.01

(% in type of platinum) Young age = Age less than or equal 40 years old a = compare refractory vs sensitive P = 0.03 (Post Hoc) b = compare resistant vs sensitive P = 0.03 (Post Hoc)

Table 2. Further Treatment after First Episode of Tumor Progression

Platinum type	Refractory (%) N=39	Resistant (%) N = 27	Sensitive (%) N = 75	Total
Chemotherapy	34 (87.2)	21 (77.8)	68[a] (90.7)	123 (87.2)
Surgery &chemotherapy	1 (2.6)	1 (3.7)	6(8.0)	8 (5.7)
Palliative care	3 (7.7)	4 (14.8)	1(1.3)	8 (5.7)
Death	1 (2.6)	1 (3.7)	-	2 (1.4)

*[a]=received carboplatin & plalitaxel 54 cases (79.4%)

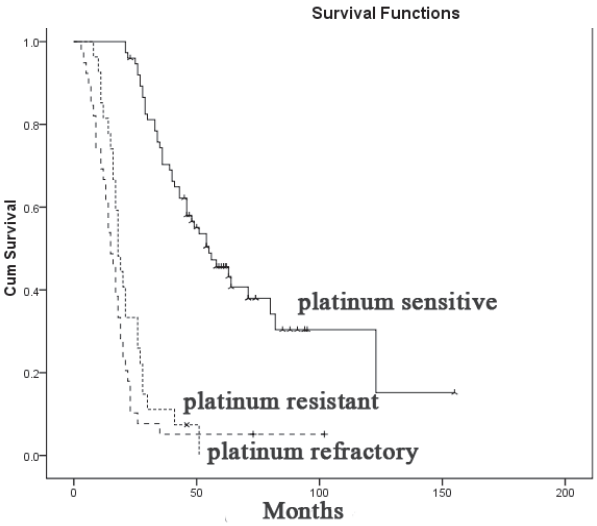

Figure 1. Overall survival of Recurrent Ovarian Cancer Patients Divided by Platinum Response Type. Median follow up time 29 months; (range 3-155 months); Median overall survival; Platinum refractory=20 months; Platinum resistant=14 months; Platinum sensitive=42 months p<0.01; Total death=108 cases (76.6%)

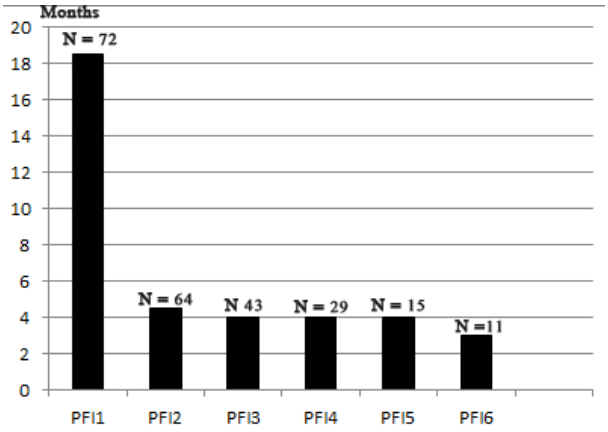

Figure 2. Median Progression Free Survival in Platinum Sensitive Group in Each Episode of Tumor Progression. PFI=median progression free interval The number means the sequence of PFI eg: PFI1=The median PFI after first progression

compared in Figure 1. With the median follow up time of 29 months, over 76% of the patients died. The median overall survival was significantly longer in the platinum sensitive group at 42 months while the median survival in the platinum refractory and resistant groups were only 20 months and 14 months, respectively.

Among the platinum sensitive group patients, the median progression free interval in each subsequent episode of tumor progression was dramatically decreased after the first treatment of tumor progression as shown in Figure 2.

Discussion

Recurrent epithelial ovarian cancer is usually classified into three groups according to platinum free intervals as mentioned above. In the present study, we found more patients with early stage and optimal surgery in the platinum sensitive group. Both early stage and optimal surgery were the favorable prognostic factors for epithelial ovarian cancer patients (Thigpen, 2012). However, only one third of these recurrence patients in the platinum sensitive and platinum resistance groups and only 12% of the platinum refractory group received complete surgical staging. This might be explained from a greater frequency of initial presentation with advanced disease in our studied patients and the major role of surgery in this setting was debulking the tumor instead of a complete surgical staging procedure. Whether the histology was a serous type nor non-serous type in the present study was not significantly different among these three groups in spite of the previous knowledge that suggested a better outcome in the serous type (Barlin et al., 2012). Ciucci et al recently reported that the anomalies of ERβ2 cytoplasmic expression in some serous types was an independent prognostic marker causing chemoresistance (Ciucci et al., 2014). Unfortunately, in the present study, we did not have any data of immunohistochemistry in these studied patients.

Further treatment after the first episode of tumor progression also depended on the platinum free interval. In platinum refractory and resistant groups, the previous randomized clinical studies with paclitaxel, topotecan, pegylated liposomal doxorubicin (PLD), gemcitabine, docetaxel and etoposide showed to be non-superior among these single agents with the response rate of 10-15% and median overall survival of nine to twelve months (Gonzalez-Martin, 2013). In our center, most of the platinum refractory and resistant groups received subsequent chemotherapy with generic gemcitabine, oral etoposide, PLD and weekly paclitaxel with the median overall survival at 14-20 months which was slightly longer than previously reported. This might be from the small number of our studied patients in these groups. However, we also published the outcome of generic gemcitabine and PLD (Lipodox®) in the setting of salvage treatment with the response rate of 12.1-13.8 % and median overall survival at ten and eleven months, respectively (Suprasert et al., 2012; Suprasert et al., 2014). Currently, the adding of Bevacizumab, an anti-angiogenesis drug, to standard chemotherapy provided significant improvement in the progression-free survival when compared to chemotherapy alone (Gonzalez-Martin, 2013). In patients with platinum sensitivity, the recent meta-analysis study clearly showed more benefits in terms of both progression-free survival and overall survival when compared to single platinum with the hazard ratio at 0.68 and 080, respectively (Raja et al., 2013). A previous largest randomized study, ICON 4 revealed the median overall survival of platinum sensitivity to be 24 months in patients who received single platinum and 29 months in patients with a combined regimen (Gonzalez-Martin , 2013). In the present study, most of the patients received combination chemotherapy with carboplatin plus paclitaxel and showed a median overall survival at 42 months which was longer than previously reported. The difference might be explained by the small number of our studied patients that recruited only 75 patients while ICON4 enrolled about 400 cases patients in each arm.

The role of surgery in the recurrent patients revealed a limited role with the benefit occurring only in the patients

who achieved complete resection (Harter et al., 2012). In the present study, only 5.7% of the studied patients underwent a secondary surgery. Thus, surgery did not influence the outcome of our patients.

The outcomes of treatment in our studied patients confirmed the previous reports that showed better survival outcomes in platinum sensitive patients than in patients in the platinum refractory and resistant group despite the use of generic chemotherapy regimen in our patients (Thigpen, 2012; Foley et al., 2013). However, when the patients in the platinum sensitive group developed subsequent progression, the median progression free survival was quite short at only three to four months. Chien et al reviewed the resistant mechanism of platinum-based chemotherapy in patients who initially presented with platinum-sensitivity. They mentioned that in platinum sensitive patients, the heterogeneous chemo-naïve tumor may contain a clonal population of chemo-sensitive tumor cells, quiescent tumor cells and the chemo-resistant tumor cells. Both quiescent and chemoresistant tumor cells may contribute to small proportions in the tumor. Thus, after initial treatment with platinum chemotherapy, most of the tumor was destroyed resulting in long term remission. However, quiescent and chemoresistant tumor cells still persisted and begin to regrow and repopulate especially in the optimal microenvironment causing in tumor progression. In addition, some quiescent and chemoresistant tumor cells reacted with specific components of the extracellular matrix protein that promoted the protected tumor cells from chemotherapy (Chien et al., 2013).

The strength of our study was to show the real outcomes of Thai recurrent epithelial ovarian cancer patients who received treatment according to the Thai national guidelines. From the best of our knowledge, no published studies were found regarding this issue. This data is beneficial for the improvement of the Thai national policy of treatment recurrence for ovarian cancer patients. However, the limitation of the present study was the retrospective nature with some data missing and a limited number of studied patients.

In conclusion, the survival outcomes in patients with platinum refractory tumors and resistance were quite poor when compared to patients in the platinum sensitive group. However, when the patients in the platinum sensitive group developed tumor progression in the second and following episodes, they also showed very poor outcomes too.

Acknowledgements

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