RESEARCH COMMUNICATION

Clinical Outcome of the Ovarian Clear Cell Carcinoma Compared to other Epithelial Ovarian Cancers when Treated with Paclitaxel and Carboplatin

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Abstract

Ovarian clear cell carcinoma (OCCC) has an aggressive histology. Our aim was to evaluate the progression free survival (PFS) of OCCC patients compared to other epithelial histology patients when treated with surgery followed by carboplatin and paclitaxel (PT) regimen. The medical records of them who treated with PT regimen at Chiang Mai University Hospital between January 2004 and December 2008 were reviewed. 67 ovarian clear cell patients were compared to 121 non-clear cell ovarian cancer patients. The mean age of OCCC patients was younger than that of the non-clear cell group (46.7 vs. 51.2 years old, P=0.001). OCCC patients presented in early stage more often than the non-clear cell group (76.1% vs. 38.0%, P=0.001). The surgical procedures in both groups were not significantly different. The complete response rates of OCCC patients and other epithelial histology patients were 65.7% and 55.3%, respectively (P=0.01). With a mean follow-up time of 25 months, the 3-year PFS rates of OCCC and non-clear cell patients in early stages were not significantly different (65.4% vs. 64.2%, P=0.45). However, in the advanced stage, the 1-year PFS rate of OCCC patients was significantly lower than that of non clear cell patients (6.3% vs. 49.6%, P=0.001). In conclusion, patients were commonly younger and presented in earlier stages than non-clear cell ovarian cancer patients. In early stages, clear cell ovarian cancer patients had similar outcomes to other epithelial ovarian histology patients, whereas the outcome was very poor in advanced stages.

Key Words: Ovarian cancer - clear cell carcinoma - clinical outcomes - survival

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Introduction

Clear cell ovarian cancer was originally termed "mesonephroma ovarii" by Schiller in 1939. It was described by the World Health Organization 34 years later as lesions characterized by clear cells growing in tubular, glandular or hobnail cell patterns (Serov et al., 1973). Previous publications revealed the distinctive characteristics of this histology as an aggressive cell type with a poor prognosis compared to other epithelial ovarian cancers (Omura et al., 1991; O'Brien et al., 1993). With the standard treatment for epithelial ovarian cancer, which is complete surgical staging procedure in early stages (Trimbos et al., 2003; Vergote et al., 2003) or cyto-reductive surgery in advanced stages (Hoskin et al., 1994) followed by 4-6 courses of carboplatin and paclitaxel (McGuire et al., 1996; Bookman et al., 2003), the response rate of clear cell ovarian cancer has been found to be only 32-56% (Ho et al., 2004; Pectasides et al., 2006; Takano et al., 2006; Utsunomiya et al., 2006) compared to 72.5% for other histologic types (Sugiyama et al., 2000). The 5-year specific survival was also inferior, especially when compared with serous histology (Chan et al., 2008).

However, the study of clear cell ovarian cancers in developing countries such as Thailand is still limited. A high proportion of patients receive incomplete surgery from the primary hospital prior to being referred to a cancer center for chemotherapy and/or use generic paclitaxel, so it is interesting to study the clinical outcome of ovarian clear cell carcinoma compared to other epithelial ovarian cancers when treated with paclitaxel and carboplatin regimen in this region.

This study was conducted as a retrospective trial in our institute in order to consider these issues.

Materials and Methods

After protocol approval by the Institutional Review Board, the medical records of epithelial ovarian cancer patients who underwent both complete and incomplete surgical staging procedures and received adjuvant carboplatin (AUC=5) and paclitaxel 175 mg/m^2 (PT regimen) every 21-28 days between January 2004 and December 2008 at Chiang Mai University Hospital were

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reviewed. Patients who were operated on at other hospitals and referred to our institute for PT regiments were also included in this retrospective review. All specimens or pathological slides were reviewed by our center's gynecologic pathology team. The number of chemotherapy cycles depended on the attending physician. Patients who received a PT regimen as neoadjuvant chemotherapy were also recruited in the study. The following data were extracted by chart review: demographic data, symptoms presented, FIGO stage, histological cell type and tumor grading, the number of chemotherapy cycles, the type of surgery, and the status at follow-up.

After completing treatment, patients were scheduled to follow up every 3 months in the first year, every 4 months in the second year, every 6 months in the third to fifth years, and then annually thereafter. During follow-up, progression of disease was defined by physical examination, rising of tumor markers, or imaging study showing re-growth of the tumor.

The response rate of treatment was evaluated according to World Health Organization response criteria (Miller et al., 1981) . Progression free survival (PFS) was defined as the interval from the date of primary surgery or the date of first administration of chemotherapy in patients with neoadjuvant chemotherapy setting to the date of tumor progression or the date of last contact. Platinum refractory was defined as tumor progression during platinum therapy whereas platinum resistant and platinum sensitive were defined as tumor relapse within 6 months and more than 6 months after complete treatment of platinum administration, respectively.

Statistical analysis of the data was carried out by the SPSS for Windows program (Version 11.5). Progression free survival and overall survival were estimated by the Kaplan-Meier Method. The significance of the survival distribution in each group was tested by the log-rank test. Both Pearson Chi-square test and Fisher's exact test were used to test independent variables. A p-value of less than 0.05 was considered statistically significant.

Results

Between January 2004 and December 2008, a total of 188 epithelial ovarian cancer patients who met the studied criteria were identified. Of these patients, 67 patients were diagnosed with ovarian clear cell carcinoma. Most of the rest had a histology of serous cystadenocarcinoma followed by endometrioid carcinoma, mixed histology, and mucinous cystadenocarcinoma, as shown in Table 1. The patients' characteristics of clear cell and non-clear cell epithelial histology were compared as listed in Table 2. Compared to the non-clear cell ovarian carcinoma patients, the mean age at diagnosis was significantly younger for those with clear cell carcinoma: 51 years vs. 46 years (P=0.001). Patients with clear cell carcinoma were more likely diagnosed with stage I disease compared to the non-clear cell group (64.2% vs. 21.5%; P < 0.001). The percentage of optimal surgery patients in clear cell group was higher than that of non-clear cell group (76.8% vs. 56.7%; P = 0.013). The median number of PT regimen cycle was equal to 6 cycle in both groups but the percentage of patients receiving at least six cycle of PT regimen in non-clear cell group was higher than that of clear cell group (80% vs. 68%;P=0.009) . The presenting symptoms, the initial place of surgery and the complete surgical staging procedure were similar in these two groups.

About 90% of studied patients received generic paclitaxel. The clinical outcome of clear cell and non-clear cell groups are noted in Table 3. The response rate in all stages was lower in the clear cell group at 77.6% compared to 86.7% in the non-clear cell group. When subdividing the patients into early (stage I&II) and advanced stage (stage III&IV), the response rate in both the clear cell and the non-clear cell group in early stages were in excess of 90%. However, in the advanced groups, the response rate in the clear cell group was significantly

Table 1. Frequencies of Epithelial Ovarian Histology

Histologic cell type	N (%)
Clear cell carcinoma	67 (35.6)
Serous cystadenocarcinoma	60 (31.9)
Endometrioid carcinoma	32 (17.0)
Mixed	18 (9.6)
Mucinous cystadenocarcinoma	7 (3.7)
Other	4 (2.1)
Total	188 (100)

Table 2. Patient Characteristics by Histological Type

	Clear cell	Non-clear cell	p-value
Number (%)	67 (35.6%)	121 (64.4%)	
Age, mean (range)	46.7 (26-65)	51.2 (19-77)	0.001
Menopause	24 (35.8%)	73 (60.3%)	0.001
Presenting symptoms			
Pelvic mass	32 (47.8%)	51 (42.1%)	NS
Abdominal distension	15 (22.4%)	38 (31.4%)	
Abdominal pain	11 (16.4%)	22 (18.2%)	
Other	9 (13.4%)	10 (8.3%)	
FIGO stage			
I	43 (64.2%)	26 (21.5%)	<0.001
II	8 (11.9%)	20 (16.5%)	
III	12 (17.9%)	61 (50.4%)	
IV	4 (5.9%)	14 (11.6%)	
Place of surgery			
University Hospital	30 (44.8%)	70 (57.9%)	NS
Other	37 (55.2%)	51 (42.1%)	
Surgical staging procedure			
Complete	27 (40.3%)	40 (33.1%)	NS
Incomplete	40 (59.7%)	81 (66.9%)	
Residual tumor			
Unknown	11 (16.4%)	24 (19.8%)	
Known residual size	56 (83.6%)	97 (80.2%)	
≤ 1 cm	43 (76.8%)	55 (56.7%)	0.013
>1 cm	13 (23.2%)	42 (43.3%)	
Grade			
1	-	16 (13.2%)	<0.001
2	-	40 (33.1%)	
3	67 (100%)	56 (46.3%)	
Unknown	-	9 (7.4%)	
PT times, med (range)	6 (2-7)	6 (1-9)	
PT ≥six cycles	46 (68.7%)	96 (79.3%)	0.009

NS: Not statistical significant; PT, Carboplatin and paclitaxel

Table 3. Clinical Outcomes by Histological type

Tumor response	Clear cell	Non-clear cell	p-value
All stage (N)	67	121	0.01
Complete	44 (65.7)	67 (55.4)	
Partial	8 (11.9)	38 (31.4)	
Stable	3 (4.5)	1 (0.8)	
Progression	12 (17.9)	15 (12.4)	
Median Progression free survival(months)			
	31	22	Log rank 0.67
Early stage (N)	51	46	0.46
Complete response	44 (86.3)	36 (78.3)	
Partial response	4 (7.8)	7 (15.2)	
Stable	-	1 (2.2)	
Progression	3 (5.9)	2 (4.3)	
Median Progression free survival(months)			
	30	41	Log rank 0.45
Advanced (N)	16	75	0.00
Complete response	-	31 (41.3)	
Partial response	4 (25.0)	31 (41.3)	
Stable	3 (18.8)	-	
Progression	9 (56.3)	13 (17.3)	
Median Progression free survival (months)			
	5	13	Log rank

Table 4. Characteristics of Recurrent Epithelial Ovarian Cancers Stratified by Histology and Stage

Tumor response	Clear cell	Non-clear cell	p-value
All stages	67	121	
Recurrence	31 (46.3)	67 (55.4)	0.219
Platinum refractory	21 (67.7)	33 (49.3)	
Platinum resistant	6 (19.4)	17 (25.4)	
Platinum sensitive	4 (12.9)	17 (25.4)	
Early stage	51	46	0.677
Recurrence	15 (29.4)	11 (23.9)	
Platinum refractory	7 (46.7)	5 (45.5)	
Platinum resistant	5 (33.3)	2 (18.2)	
Platinum sensitive	3 (20.0)	4 (36.4)	
Advanced stage (N)	16	75	0.003
Recurrence	16 (100)	56 (74.7)	
Platinum refractory	14 (87.5)	28 (50.0)	
Platinum resistant	1 (6.2)	15 (26.8)	
Platinum sensitive	1 (6.2)	13 (23.2)	

lower than in the non-clear cell group. The overall response rate in the advanced clear cell group was only 25% and none achieved complete response.

The number of recurrent patients is summarized in Table 4. About half of the studied patients in both groups were recurrent. Of these patients, the proportion of platinum refractory in patients in the clear cell group was as high as 70% while only 50% in the non-clear cell group. However, when subdividing patients into early and advanced stages, the proportion of platinum refractory in early stage in both the clear cell and the non-clear cell groups were similar at nearly 45% whereas all patients in the advanced clear cell group were recurrent and most of them were platinum refractory.

With a mean follow-up time of 25 months, the progression free survival rates in the clear cell and non-clear cell groups were not significantly different, as shown in Figure 1 and Table 3. However, in early stages, the progression free survival rate was not significantly different (Figure 2a) while it was significant lower in the advanced stage clear cell group (Figure 2b). All advanced

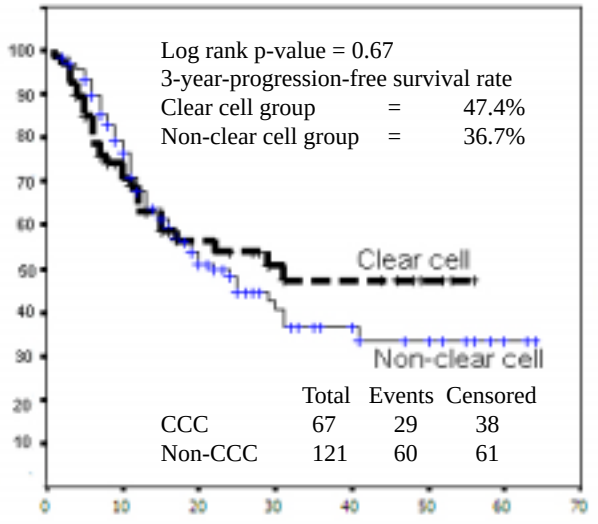

Figure 1. Progression Free Survival Curves

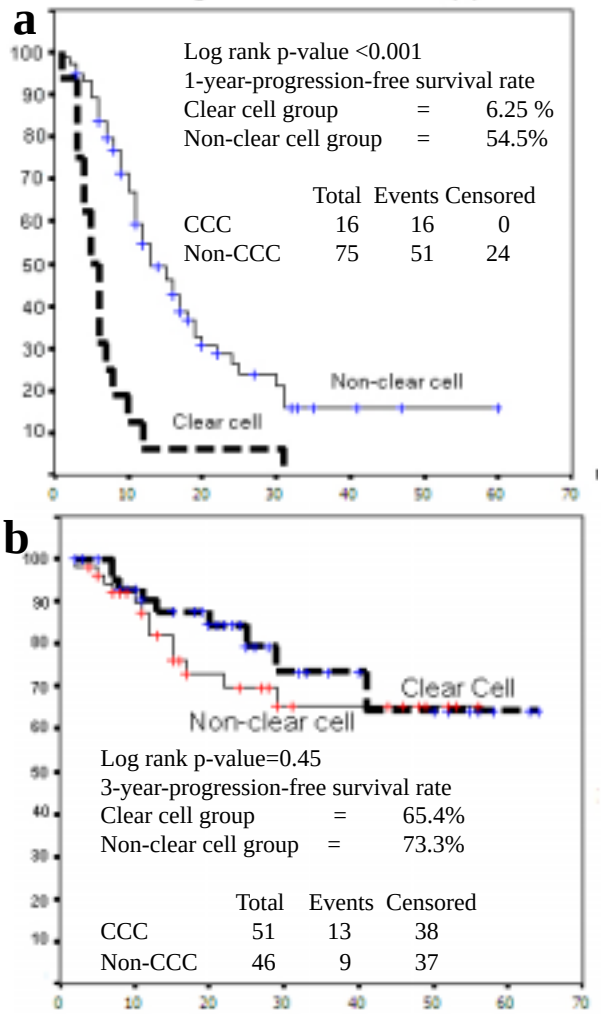

Figure 2. Subgroup Analysis of Progression Free Survival Curves. a): Advanced stage (stages III&IV); b) Early stage (stage I&II); CCC, clear cell carcinoma

clear cell cancer patients were recurrent within 1 year.

Discussion

In the present study, the mean age of patients with clear cell ovarian cancer was 46 years old, which was significant younger than that of non-clear cell patients.

This finding corresponds with data from the Surveillance, Epidemiology and End Results (SEER), which studied 1,141 clear cell ovarian cancers compared to other epithelial ovarian cancer. They reported that the youngest patients among epithelial ovarian cancer were clear cell type (Chan et al.,2008). However, in the SEER study, the mean age of clear cell ovarian cancer patients was 55 years old, which is older than the patients in our report. This difference may be because our inclusion criteria only included patients who were suitable to receive a PT regimen while the SEER study recruited all patients with clear cell ovarian cancer.

In the present study, 76.1% of clear cell carcinoma patients were in the early stages. This was significantly more common than non-clear cell ovarian cancer, which found in early stages in only 38.0% of patients. Sukiyama et al studied 101 patients with ovarian clear cell carcinoma compared to 235 patients with serous histology in a retrospective setting. They also reported more significant number of FIGO stage I clear cell ovarian cancer patients than serous type patients (58.4% vs. 22.1%, P<0.0001) (Sugiyama et al., 2000). Furthermore, Behbakht et al (1998) also reported that early stage patients with ovarian clear cell in their series were as high as 71%. The frequency of ovarian clear cell carcinoma among epithelial ovarian cancer patients in earier papers was 3.7-15.3% (O'Brien et al.,1993; Pectasides et al.,2006; Utsunomiya et al.,2006; Sugiyama et al.,2000; Aure et al.,1971; Crozier et al.,1989) and was more common in Asians than in Black or White patients (Chan et al.,2008).

Although generic paclitaxel was used in most of our study's patients, the overall response rate of ovarian clear cell cancer in all stage was still as high as 77.6%. However, in the advanced stage, the response rate was quite low at 25% and none achieved a complete response. This result was in the range of previous reports that revealed an overall response rate between 11% and 67%(Ho et al.,2004 ; Pectasides et al.,2006, Utsunomiya et al.,2006; Sugiyama et al.,2000; Behbakht et al.,1998) . This high variation in the response rate might be due to differences in the number of patients studied, the proportion of residual tumor, or the chemotherapy regimen in each study. The lowest response rate was reported in Sugiyama et al (2000). They found that only 3 of 27 stage III&IV patients with clear cell who had measurable disease after initial surgery responded to platinum-based chemotherapy.

Regarding tumor response in the present study, the significant inferior response rate in ovarian clear cell patients in advanced stage was similar to previous reports. Pectasides et al studied advanced stage clear cell ovarian cancer compared to serous type treated with platinum-based chemotherapy. The overall response rate was only 45% in clear cell ovarian cancer while as high as 81% in serous type (Pectasides et al., 2006). The cause of relative chemoresistance in ovarian clear cell cancer was explained by Itamochi et al (2008). They suggested that lower proliferation rates of tumor cells in clear cell ovarian cancer when compared to other epithelial cell type was the important reason.

With a mean follow-up time of 25 months, nearly 50% of both clear cell and non-clear cell type ovarian cancers were recurrent. Platinum refractory patients were more common in patients with clear cell ovarian cancer. The progression free survival rate was not significantly different between the clear cell and non-clear cell groups. However, in subgroup analysis, patients with advanced stage revealed significantly lower progression free survival rate in the clear cell group than the non-clear cell group while there was no significant difference in early stage. These results correspond to the study of Sugiyama et al, who reported that the overall survival rate of advanced stage ovarian clear cell cancer was significantly lower than the serous type especially in patients who had residual disease. They also studied patients with stage IC disease and found no significant difference of overall survival rate in either clear cell or serous type (Sugiyama et al., 2000).

Chan et al (2008) used data obtained from the Surveillance, Epidemiology and End Result Program (SEER) between 1988 and 2001 to compare the survival rates of patients with clear cell cancers to those of patients with other epithelial ovarian cancers. They also found a significantly poorer 5-year disease specific survival rate with clear cell than other histologies adjusted for stage, especially when compared to serous type (Chan et al., 2008) On the other hand, Pectasides et al studied 35 stage III and IV clear cell ovarian cancer patients compared to 70 stage III and IV serous ovarian cancer patients. They found a lower response to platinum-based first line chemotherapy in patients with advanced stage clear cell carcinoma patients but no significant differences in term of median progression free survival and overall survival (Pectasides et al.,2006). This dissimilar outcome might be due to a different of number of studied patients, the adjuvant chemotherapy, and the proportion of suboptimal disease.

The strength of our study is that all pathological reports were reviewed and used the same chemotherapy regimen with a larger number of studied patients. Its limitation is that we did not report the overall survival rate due to unavailable data.

In conclusion, our data found patients with clear cell ovarian cancer were younger and more commonly presented at early stages than patients with non-clear cell ovarian cancer. Although ovarian clear cell cancer patients had the lower response rate to paclitaxel and carboplatin regimen when compared to the non-clear cell group, the progression free survival in both group were not significantly different. However, in subgroup analysis divided by stage, only advanced stage clear cell ovarian cancer revealed significantly poorer progression free survival when compared to the non-clear cell group.

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