The chemosensitivity of nodal metastases in recurrent epithelial ovarian cancer

F. Kataoka, H. Tsuda, H. Nomura, T. Chiyoda, E. Tominaga, A. Suzuki, N. Susumu, D. Aoki

Department of Obstetrics and Gynecology, School of Medicine, Keio University, Tokyo (Japan)

Summary

Purpose: In this study, we compared second-line chemotherapy effects of nodal metastases with other metastases sites. *Methods:* The medical records of 44 women with recurrent ovarian cancer who received second-line chemotherapy were retrospectively reviewed. *Results:* Median age at the time of second-line chemotherapy was 55 years (range: 31-74). Recurrent sites were as follows: 29 patients had a solitary site (abdominal cavity: 8; lymph node: 3; pelvic cavity: 10; liver: 4; lung: 4) and 15 patients had multiple sites In total, the response rate was 30% (CR: 8, PR: 5). The response rate in sensitive cases was higher than in refractory/resistant cases (50% vs 5% p = 0.002). However, age, chemotherapy regimen, histologic type and number of diseases were not related with chemotherapy effect. In all diseases, response rate tended to be higher in lymph node disease than in the others (44% vs 27%). In both sensitive and refractory/resistant cases, response rate tended to be higher in lymph node disease. *Conclusion:* The response rate for lymph node diseases tended to be relatively high. Further study analyzing survival will be required to conclude the chemotherapy effect.

Key words: Second-line chemotherapy; Recurrence; Lymph node; Recurrent site.

Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy, accounting for 7,000 new diagnoses and 4,000 deaths annually in Japan. Patients are usually treated with cytoreductive surgery, followed by platinum and paclitaxel chemotherapy. The initial response rate to standard treatment exceeds 70% [1]. Despite initial high responses, the majority of cases experience relapse, with a median disease-free interval of 18 to 24 months. Some retrospective studies demonstrated a survival benefit for patients undergoing optimal secondary cytoreductive surgery [2-8]. Based on NCCN guidelines, secondary cytoreductive surgery may be considered as a treatment option for clinically focal recurrence after a disease-free interval > 6 months. Recently, retrospective studies have shown that secondary cytoreductive surgery for isolated nodal recurrence is effective [9-12]. Morice et al. reported that nodal metastases of EOC are chemoresistant lesions [13]. However, Blanchard *et al*. reported that good chemotherapy response rates could be obtained in recurrent nodal metastases [10]. Thus, it is controversial if chemotherapy is effective for lymph node disease.

Cancer consists of founder cancer cells and stroma including blood and lymph endothelial cells, inflammatory cells, immunocytes and macrophages, and fibroblasts. Recently, the role of stroma is thought to be associated with tumor progression including invasion or metastatsis as well as response to therapy [14-16]. In addition, the chemotherapy effect is thought to be related to drug delivery status. From these findings, it can possibly be deduced that chemotherapy effects may differ among the locations of target disease. In this study, we compared the chemotherapy effect of nodal metastases with other metastasis sites.

Materials and Methods

Patients

We retrospectively reviewed the medical records of women with recurrent ovarian cancer who received second-line chemotherapy Recurrent cases who received surgery were excluded from the study. Forty-four patients who initiated second-line chemotherapy between February 1998 and October 2008 were included in this study All patients underwent initial surgery and primary chemotherapy consisting of a platinum/taxane regimen. All patients were followed-up at the Department of Obstetrics and Gynecology, Keio University Hospital, Tokyo. Treatment decisions for second-line chemotherapy were usually made by the attending clinician Data were collected on age, International Federation of Obstetricians and Gynaecologists (FIGO) , histologic type, the extent and outcome of surgery, prior chemotherapeutic treatments, recurrent sites, intervals between primary and secondary treatments and overall survival after receiving the second-line drug.

Definition of chemotherapy sensitivity of primary chemotherapy

Refractory, resistant, and sensitive in the first recurrence were defined as follows. Refractory: partial response, progression or stable disease on primary chemotherapy; Resistant: complete remission and relapse < 6 months after stopping primary chemotherapy; Sensitive: complete remission and relapse ≥ 6 months after stopping primary chemotherapy.

Evaluation of response of second-line chemotherapy

Response was based on two-dimensional measurements of the lesions on computed tomography (CT) or magnetic resonance imaging (MRI) images. Complete response (CR) was

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defined as no evidence of disease on imaging studies, with normalization of the serum CA125 level. Partial response (PR) was defined as a > 50% decrease in tumor size. Progressive disease (PD) was defined as a > 25 increase in tumor size or the appearance of a new lesion. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. The CA125 response criteria were not used; however, patients were not considered as having PR or SD if there was an increase of CA125.

Statistical analysis

The relationship between response rate or non-PD rate and chemosensitivity, age, regimen, histology, and disease site were analyzed by Fisher's exact testStatistical calculations were performed using SPSS Statistics software version 17.0 for Windows (SPSS, Chicago, IL).

Results

Patients

Median age at the time of second-line chemotherapy was 55 years (range: 31-74). Clinical stage and histology were as follows: clinical stage (I: 5; II: 3; III: 24; IV: 12); histology (serous: 22; clear cell: 12; endometrioid: 8; undifferentiated: 2). At first recurrence, 24 patients were platinum-sensitive and 20 patients were platinum-resistant. Recurrent sites were as follows: 29 patients had a solitary site (abdominal cavity: 8; lymph node: 3; pelvic cavity: 10; liver: 4; lung 4) and 15 patients had multiple sites. Performance status (PS) was zero-one in 40 cases, and two in four cases at second-line chemotherapy Twenty-four patients received a platinum/taxane regimen, 13 patients received cisplatin+irinotecan, four patients received cisplatin+doxorubicin+cyclophosphamide, and three patients received irinotecan, doxil or topotecanas second-line chemotherapy.

Relationships between clinical factors and the response rate or non-PD rate

Relationships between clinical factors and the response rate or non-PD rate of second-line chemotherapy are shown in Table 1. In total, response rate and non-PD rate were 30% and 51% (CR: 8, PR: 5, SD: 9), respectively. The response rate in sensitive cases was higher than in refractory/resistant cases (50% vs 5% $p = 0.002$) and the non-PD rate in sensitive cases was higher than in refractory/resistant cases (67% vs 30% $p = 0.03$). However, age, chemotherapy regimen, histologic type and number of diseases were not related with the chemotherapy effect.

Table 1. — *Effect of second-line chemotherapy.*

Clinical factor		CR+PR	CR+PR+SD
All cases		30% (13/44)	50% (22/44)
Sensitivity	Sensitive	50% (12/24)*	67% (16/24)**
	Refractory/Resistant	5% (1/20)*	30% (6/20)**
Age	Median >	23% (5/22)	36% (8/22)
	Median <	36% (8/22)	64% (14/22)
Regimen	Mono	0% (0/3)	33% (1/3)
	Comb	32% (13/41)	51% (21/41)
Histology	Serous	41% (9/22)	55% (12/22)
	Non-serous	18% (4/22)	45% (10/22)
Disease site	Solitary	31% (9/29)	48% (14/29)
	Multiple	27% (4/15)	53% (8/15)

p = *0.002, p = **0.03.

Table 2. — *Relationship between chemotherapy response and recurrent site.*

Recurrent site	CR+PR	CR+PR+SD
All cases		
Lymph node	44% (4/9)	89% (8/9)
Other	27% (13/48)	50% (24/48)
Pelvic cavity	15% (2/13)	54% (7/13)
Abdominal cavity	41% (7/17)	53% (9/17)
Liver	10% (1/10)	30% (3/10)
Lung	38% (3/8)	63% (5/8)
Sensitive		
Lymph node	100% (4/4)	100% (4/4)
Other	44% (11/25)	64% (16/25)
Pelvic cavity	20% (1/5)	60% (3/5)
Abdominal cavity	55% (6/11)	73% (8/11)
Liver	33% (1/3)	33% (1/3)
Lung	50% (3/6)	67% (4/6)
Refractory/Resistant		
Lymph node	0% (0/5)	80% (4/5)
Other	8.7% (2/23)	35% (8/23)
Pelvic cavity	13% (1/8)	50% (4/8)
Abdominal cavity	17% (1/6)	17% (1/6)
Liver	0% (0/7)	29% (2/7)
Lung	0% (0/2)	50% (1/2)

Table 3. — *Relationship between chemotherapy response and recurrent site in multiple recurrent cases.*

No.	Age	Histology	Sensitivity	Site	Response
1	55	Clear	Sensitive	Lymph node	CR
				Abdominal cavity	CR
2	62	Clear	Resistant	Liver	SD
				Pelvic cavity	SD
3	36	Clear	Sensitive	Lymph node	CR
				Liver	CR
				Lung	CR
4	62	Clear	Sensitive	Abdominal cavity	SD
				Lung	SD
5	53	Serous	Sensitive	Pelvic cavity	PD
				Liver	PD
6	50	Clear	Resistant	Pelvic cavity	PD
				Abdominal cavity	PD
7	57	Clear	Resistant	Abdominal cavity	PD
				Liver	PD
8	38	Endometrioid	Resistant	Liver	PD
				Lung	SD
9	63	Clear	Resistant	Abdominal cavity	CR
				Liver	SD
10	31	Endometrioid	Resistant	Lymph node	SD
				Lung	PD
11	52	Serous	Resistant	Lymph node	SD
				Abdominal cavity	PD
12	56	Serous	Resistant	Lymph node (PAN)	SD
				Lymph node (virchow)	SD

Relationship between chemotherapy response and recurrent site

The relationship between response rate or non-PD rate and recurrent sites is shown in Table 2. In all diseases, the response rate and non-PD rate tended to be higher in

lymph node disease than in other diseases; however, this difference was not significant (44% vs 27%, 89% vs 50%), respectively. CR was achieved in two cases of lymph node disease and in ten cases of other disease sites. In both sensitive and refractory/resistant cases, response rate and non-PD rate tended to be higher in lymph node disease. The relationship between chemotherapy response and recurrent sites in 12 multiple recurrent cases is shown in Table 3. In eight of 12 cases, similar chemotherapy responses were obtained despite differing disease sites. In four of 12 cases (case 8, 9, 10, 11), chemotherapy responses were different among recurrent sites. In two cases (10 and 11) chemotherapy responses for lymph node disease were stable, however, responses for other recurrent sites were PD.

Discussion

Recurrence of EOC are almost always fatal. For recurrent EOC, therapeutic options consist of surgery, chemotherapy, and radiotherapy. The NCCN guidelines recommend surgical treatment for clinically focal recurrence after a disease-free interval > 6 months. Recently, retrospective studies have shown that secondary cytoreductive surgery for isolated nodal recurrence was effective [9-12]. However, there have been no high-quality reports which compared salvage chemotherapy with surgery for focal recurrence after a disease-free interval > 6 months. Before 1990, lymphadenectomy was often performed at a second-look operation after chemotherapy; positive nodes were found just as frequently at second-look operations as in patients undergoing lymphadenectomy at primary surgery [17-19]. Recently, Morice *et al*. examined the rates of nodal involvement in 205 EOC patients and reported that the rates of nodal involvement in patients who underwent lymphadenectomy prior to or after chemotherapy were not statistically different [13]. These findings may indicate that chemotherapy may have little effect against the retroperitoneal lymph nodes metastases. In contrast, Banchard *et al*. reported that a good response rate could be obtained for lymph node metastasis (11 CR out of 20 treated patients) [10]. In this study, response rate and non-PD rate for lymph node diseases were 100% and 100% for sensitive cases, and 0% and 80% for refractory/resistant cases, and the chemotherapy effect for lymph node disease tended to be better than that for other recurrent sites.

In contrast, response rate and non-PD rate for liver diseases were 33% and 33% for sensitive cases, and 0% and 29% for refractory/resistant cases. Kusumoto *et al*. examined the chemosensitivity of 16 pairs on samples obtained simultaneously from primary and metastatic lesions of clinical gastric cancer by in vitro chemosensitivity test (succinate dehydrogenase inhibition test) and reported that the lymph nodes were more chemosensitive to carboquone, doxorubicin, mitomycin C, cisplatin, aclacinomycin A and 5-FU, while the liver was less sensitive than the primary lesions to carboquone, doxorubicin, mitomycin C, cisplatin, aclacinomycin A and 5-FU [20]. These findings are concordant with the findings of this study.

The effect of chemotherapy on survival for isolated lymph node relapse was thought to be essential to conclude the chemotherapy effect. However, there were only three cases who had isolated lymph node relapse in this study. The remaining six cases with lymph node relapse were accompanied by other recurrent diseases. Isolated lymph node relapse of EOC is reported to be a rare event and its prevalence has been reported to be about 5% [5, 9-12, 21].

In conclusion, response rate and non-PD rate for lymph node disease tended to be relatively high. Further study analyzing survival will be required to conclude the chemotherapy effect.

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Address reprint requests to:
H. TSUDA, MD., Ph.D.
Department of Obstetrics and Gynecology
School of Medicine, Keio University
35 Shinanomachi, Shinjyuku-ku
Tokyo (Japan) 160-8582
e-mail: htsud@sc.itc.keio.ac.jp