Late relapse of epithelial ovarian cancer: A single institution experience

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Summary

Purpose of investigation: Late relapses are infrequent in ovarian cancer. We present the characteristics and outcome of patients who relapsed at least five years after first-line chemotherapy.

Methods: Six cases were retrieved from 203 patients treated from 1994 to 1998.

Results: Time to recurrence ranged from five to nine years. The initial stage was I or II in all cases, while histology was: endometrioid (4 cases), clear cell (1 case) and unspecified adenocarcinoma (1 case). Only two of five assessable patients responded to chemotherapy. Compared to earlier relapses, late relapses were characterized by earlier stages ($p < 0.001$), non serous histology ($p = 0.010$) and absence of symptoms (0% vs 46.5%, $p = 0.025$) at baseline. Five of 16 relapses (31%) among patients with Stage I or II were late relapses.

Conclusion: Late relapses of ovarian cancer occur in early stages, where they are relatively frequent, while the chemosensitivity of the disease may be less than expected.

Key words: Ovarian cancer; Late relapse; Management.

Introduction

Ovarian cancer remains the leading cause of death among all other gynecologic malignancies and the fourth among all cancers in women. Despite improvements in therapy, the risk of death remains substantial primarily because recurrent disease frequently becomes resistant to chemotherapy. Current primary treatment consists of aggressive cytoreductive surgery followed by systemic platinum-based chemotherapy. Ovarian cancer is a chemoresponsive disease since at least 50% of patients with advanced disease achieve a complete clinical response and half of these patients achieve a pathological complete response. Nevertheless most patients relapse within a median period of 24 months [1, 2]. Approximately 40% of patients with minimal residual disease but less than 10% of patients with bulky residual disease (> 2 cm) after initial cytoreductive surgery remain disease-free for five years and almost all are considered to be cured [1]. Most series of patients with adequate follow-up data indicate that late relapses are very unusual events [3-7]. Consistent with that is the absence of reports focusing on the characteristics of patients experiencing late relapses and their outcome after further treatment. We report here the experience of our center of patients with late relapses of epithelial ovarian cancer after first-line chemotherapy and we present their characteristics at diagnosis and relapse, their management and outcome.

Patients and Methods

All patients with ovarian cancer referred to the Oncology Section of our Department are entered into a prospective computerized database. Clinical characteristics, surgical details, the Federation of Gynecology and Obstetrics (FIGO) stage at cytoreductive surgery, chemotherapy details, date and sites of relapse and follow up are recorded for each patient.

The database search for late relapses following first-line chemotherapy was limited up to 1998, so that each patient would have a minimum follow-up period of five years. Relapses were categorized as "late" if they had occurred at least five years after the end of first-line chemotherapy. Patients identified as having late relapses had their diagnosis confirmed by review of their medical notes, with particular attention to initial histopathology review, initial surgery report and radiology results. Initial debulking surgery was defined as optimal if residual disease was < 1 cm and no radiological evidence of disease was present in postsurgery CT scan evaluation.

Baseline characteristics between groups were compared using the chi-square test, while time to progression (TTP) and overall survival (OS) were calculated from the start of first-line chemotherapy, computed with the Kaplan-Meier method and compared between groups using the log rank test.

Results

Patients

From 1994 to 1998 203 patients with ovarian carcinoma were entered into our database. Patients' status was updated in December 2003. All patients had had platinum-based first-line chemotherapy following cytoreductive surgery. Only one patient had received first line paclitaxel-containing chemotherapy.

Sixty-nine patients (34%) had no relapse during follow-up, six patients (3%) had late relapse, while the remaining 127 patients (63%) relapsed less than five years after first-line chemotherapy. Median TTP and OS of all 203 patients after a median follow-up of 76 months

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(60-116) were: 26.7 months (95% CI: 24.2-29.2) and 64.3 months (95% CI: 54.2-74.4), respectively.

The characteristics and outcome of the six patients identified as having late relapses are shown in Table 1. Median age at diagnosis was 63 years, ranging from 47 to 75. The initial stage of their disease was I or II in all cases. Five patients had undergone optimal debulking surgery, while in one case there was residual disease in the pelvis. All patients had an ECOG performance status (PS) of 0 at diagnosis. Histology was endometrioid carcinoma in four cases (1 case with areas of clear cell histology), clear cell in one and unspecified adenocarcinoma in one case.

In four cases relapse of the ovarian carcinoma was documented histologically or cytologically after reviewing the specimens of the initial surgery. In two cases (patients 1 and 5) relapse was diagnosed by radiological findings and increase of previously normal CA125, while other possible sites of primary tumor were excluded by clinical and radiological examination. None of our patients recurred above the diaphragm. Extraperitoneal sites of relapse occurred in three cases (retroperitoneal lymph nodes), one of which represented the sole metastatic site. There were two cases of relapse in the liver, which represented the sole site of metastases. Relapse in the peritoneal cavity occurred in three patients and it was associated with relapse at other sites (retroperitoneal lymph nodes: 2; pelvis: 1) in all cases.

Treatment and outcome of late relapses

Laparotomy at relapse was performed in only one case (patient 6) following four cycles of salvage chemotherapy. There was only one site of residual tumor, which was removed. In the remaining cases response to salvage treatment was assessed radiologically. Another patient (no. 4) underwent radiotherapy to the localized retroperitoneal lymph node (RPLN) site of relapse following salvage chemotherapy

Information regarding response to second-line chemotherapy was available in five of six patients. Two patients achieved a partial response and one patient remains in remission. Two patients died due to disease progression two and 16 months after the diagnosis of late relapse, respectively. All other patients remain alive 5-18 months following relapse.

Comparison with patients relapsed < 5 years

Baseline characteristics of patients who relapsed grouped according to the time elapsed from first-line chemotherapy, are shown in Table 2. Patients with late relapses had lower initial stage of disease: all patients had Stage I or II, as opposed to 11 patients (8.8%) in the group of earlier relapses ($p < 0.001$). Optimal debulking surgery was performed in five patients (83.3%) with late relapses, while optimal debulking was performed in only 21 patients (16.5%) in the group of earlier relapses ($p < 0.001$). All patients with late relapses had predominantly endometrioid and clear cell histology and no symptoms at the start of first-line chemotherapy, while serous histology was the predominant histology ($p = 0.010$) and 59 patients (46.5%) had PS $\geq$ 1 at the start of first-line chemotherapy ($p = 0.025$) in the other group. In addition, most patients with relapses within five years received first-line paclitaxel (90.6%), as opposed to only one patient (16.7%) in the group with late relapses ($p < 0.001$).

Median TTP and OS for patients with relapse within five years from first-line treatment were 15.8 months (95% CI: 13.9-17.8) and 40.1 months (95% CI: 32.2-48), respectively. TTP of patients with late relapses ranged from five to nine years (median 7.5 years). Two patients died 62 months and 88 months from surgery, while the remaining four patients are alive at 102, 113, 114 and 116 months, respectively.

Patients with initial Stage I or II

Since all late relapses occurred in patients with Stages I or II, we analyzed these patients separately. The total number of patients retrieved from the database was 48 (Stage I: 35, Stage II: 13). Sixteen patients relapsed during follow up: seven with Stage I and nine with Stage II. From these patients 11 (69%) relapsed within five years from first-line treatment, while five (31%) had late relapses. Comparison of baseline characteristics between these two groups revealed that more patients in the earlier relapses group had received first line paclitaxel (8/11 vs 1/5, $p = 0.049$) and had serous histology (6/11 vs 0/5, $p = 0.087$) but the latter difference was non-significant.

Table 1. — *Patients and disease features.*

Patient No.	1	2	3	4	5	6
Age at diagnosis	47	65	71	62	75	53
FIGO stage	Ic	IIb	Ib	IIc	IIc	IIa
Histology	endometrioid	clear cell	unspecified adenoca	endometrioid	endometrioid	endometrioid
Grade	II	II	III	III	II	II
Initial Rx	CyCarbo	CyCDDPEpi	Carbo	CyCDDP	IfoTCDDP	CyCarbo
Years to relapse	5	9	9	7	6	8
Sites of relapse	Liver	Abd implants, RPLN	Abd implants, RPLN	RPLN	Liver	pelvis, Abd implants
CA125 at relapse	164	139	3208	7	258	136
Salvage chemotherapy	Carbo/Caelyx	TCarbo	Carbo	TCarbo	Unknown	TCarbo
Response	PD	PD	PR	SD	Unknown	PR
Survival after relapse (mo)	2	5+	8+	18+	16	18+

Cy: cyclophosphamide; Epi: epirubicin; CDDP: cisplatin; Carbo: carboplatin; T: paclitaxel; Ifo: ifosfamide; LN: lymph nodes; RP: retroperitoneal; Abd: abdominal; CR: complete response; PR: partial response; SD: stable disease; NA: not applicable; RD: response duration.

Table 2. — *Patient characteristics.*

	Early relapse (n = 127)	Late relapse (n = 6)	p
Age			0.543
Median	63	63	
Range	34-81	47-75	
Histology			0.010
Serous	76 (60.3%)		
Mucinous	6 (4.8%)		
Endometrioid	17 (13.5%)	4 (66.6%)	
Clear cell	11 (8.7%)	1 (16.7%)	
Adenocarcinoma, unspecified	18 (13.7%)	1 (16.7%)	
Initial stage			< 0.001
I	5 (4%)	2 (33.4%)	
II	6 (4.8%)	4 (66.6%)	
III	89 (69.8%)		
IV	27 (21.4%)		
Grade			0.713
1	4		
2	52	4 (66.6%)	
3	66	2 (33.4%)	
Surgical debulking			< 0.001
Optimal	21 (16.5%)	5 (83.3%)	
Suboptimal	106 (83.5%)	1 (16.7%)	
PS			0.025
0	68 (53.5%)	6 (100%)	
1, 2, 3	59 (46.5%)		
Weight loss			0.423
Yes	25 (19.8%)	2 (33.3%)	
No	101 (80.2%)	4 (66.7%)	
First-line paclitaxel (+platinum)			< 0.001
Yes	115 (90.6%)	1 (16.7%)	
No	12 (9.4%)	5 (83.3%)	

Discussion

Epithelial ovarian cancer is a chemosensitive disease but despite recent advances in its management, most patients who present with advanced stage relapse and die. Most relapses occur within the first five years from surgery, as shown by several series with mature follow-up [8], while relapses beyond five years are unusual but well documented events. Omura *et al.* reported long-term follow-up data of 726 patients and observed only two deaths beyond seven years from diagnosis [3], while Del Campo *et al.* reported no relapses beyond five years [5]. This tendency seems to remain unaffected by the use of intraperitoneal chemotherapy or second-look surgery [4, 7]. Furthermore, survival curves of patients with ovarian carcinoma usually reach a plateau at six years and progression-free survival rates at five years and eight years being 23.9% and 20.6%, respectively, consistent with the rarity of relapse after the first five years [6].

There are only scarce data about the clinical characteristics, pattern of relapse and outcome after relapse of patients with ovarian cancer relapsing after five years from the initial diagnosis. The patients included in this study were selected from the database of our institution and, therefore, there was access to all medical details of their disease. The diagnosis of late relapses was accurate, since specimens from the relapse were obtained in four cases and showed identical histology to the initial histological type, while in the remaining cases relapses were associated with significant elevation of CA125, while there was no clinical or radiological suggestion of another primary. In concert with previous reports [3, 4, 7], we found that late relapses accounted for only 4.5% of the total number of relapses. Nevertheless, when patients with FIGO Stages I or II were analyzed separately, this percentage rose to 31%. This result is similar to that reported by Raymond *et al.* [9], who found that 25% of the relapses occurred at least three years after surgery for Stage I or II ovarian carcinoma. These data indicate that late relapses are relatively frequent in the early stages of ovarian carcinoma and this might account for the low frequency of its reporting in other series, where most or all patients had Stages III or IV disease [2-7]. Furthermore, it questions the validity of the 5-year disease-free interval as a surrogate point for cure in early stage ovarian carcinoma.

Patients with late relapse had better PS and earlier stages than those with earlier relapses. These factors have been associated with favorable prognosis [2, 8], which may be characterized by late relapses in certain cases.

Late relapses were associated with non serous histology in our series. Endometrioid subtype has been shown to be more frequent in early stages and especially Stage II ovarian carcinoma [9]. This could partially explain the predominance of this subtype in our study, since FIGO stages were I or II in all our cases. Clear cell histology, which was found in two of our cases, was even more surprising, since it has been associated with a worse prognosis [8, 9] and would not be expected in cases of long disease-free intervals. These findings should be viewed with caution due to the small number of patients with late relapses.

Retroperitoneal lymph nodes was a frequent site of late relapse, while the abdomen and pelvis have been reported as the most frequent sites of relapse in most series [8-10]. Nevertheless retroperitoneal lymph node involvement represented the second most frequent site of relapse in a series of 283 patients with Stage I or II ovarian carcinoma [9]. The reason for this is unclear but a long disease-free interval has been associated with other infrequent sites of metastases in ovarian carcinoma, namely CNS [11]. This finding indicates that some patients with localized relapse might benefit from local treatment (surgery or radiotherapy) of their metastases. This strategy is supported by data suggesting a survival advantage for patients at relapse whose disease could be reduced to a small volume compared with patients whose tumors could not be cytoreduced and with patients who did not undergo surgery [14, 15]. Furthermore, radiotherapy may be a therapeutic option for patients who recur with disease at the lymph nodes or the vagina, especially when radical excision is not considered feasible. One of our patients, who did not respond to salvage chemotherapy, remains progression-free 18 months after the diagnosis of relapse after receiving radiotherapy to the retroperitoneal lymph nodes.

The likelihood of response to chemotherapy at the time of recurrence is directly proportional to the length of time between discontinuation of primary chemotherapy and the documentation of recurrent disease. Several studies have shown that when this interval exceeds 18 months the chance of response to salvage platinum therapy approaches that of primary therapy in the chemotherapy-naïve patient [12, 13]. Based on these data patients with late relapses should have an excellent response to second-line treatment. However, only two of five patients who were evaluated for response achieved a partial response, while there were no complete responses. Our results should be viewed with caution due to the small number of patients.

Overall survival of patients with late relapses was better than that of patients with earlier relapses, although definitive statistical comparisons cannot be made due to the small number of patients included in our study. This is in agreement with the prognostic significance of the interval between initial diagnosis and relapse already shown by others [9]. Unfortunately, the relatively short follow-up period following late relapse precludes any meaningful comparison with patients with earlier relapses, regarding their outcome after relapse.

We conclude that late relapse is associated with early-stage ovarian carcinoma. These patients seem to have distinct features, which may help clinicians to choose the most appropriate therapeutic strategy. Because our patient population is limited, our observations need to be validated with larger number of patients and longer follow-up is necessary to define the outcome of these patients following their relapse.

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