Platin sensitivity and long-term survival in Stage III epithelial ovarian cancer patients

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Summary

Purpose: The aim of the present study was to assess the effect of platin sensitivity on long-term survival of Stage III epithelial ovarian cancer (EOC) patients. *Methods:* The records of all histologically confirmed Stage III EOC and PPC patients diagnosed during 1995-2006 were reviewed. A comparison of selected characteristics was made between long-term (> 5 years) and short-term (< 3 years) survivors. *Results:* Among 58 Stage III patients, 20 had long-term and 18 short-term survival. The rate of platin sensitive patients in long-term survivors was significantly higher than in short-term survivors (95.0% vs 27.8%, $p < 0.001$). The sensitivity and specificity of platin sensitivity for long-term survival was 95% and 72.2%, respectively, and the positive and negative predictive value was 79.2% and 92.8%, respectively. No statistically significant difference between the groups was found with regard to other selected characteristics. *Conclusion:* The rate of platin sensitive patients was significantly higher among long-term survivors than among short-term survivors but the specificity and positive predictive value of platin sensitivity for long-term survival prediction were relatively low precluding its practical clinical use.

Key words: Epithelial ovarian cancer; Platin sensitivity; Primary peritoneal carcinoma; Long-term survival; Short-term survival.

Introduction

Epithelial ovarian cancer (EOC) is a major cause of morbidity and mortality among gynecological malignancies [1] and is responsible for more than 100,000 annual deaths around the world [2]. Stage, tumor grade and post-operative residual disease are the most important prognostic factors [3, 4]. About 75% of EOC patients have advanced disease (FIGO Stage III or IV) at diagnosis. Treatment consists of cytoreductive surgery and adjuvant platin-based chemotherapy. Though the majority of patients achieve complete clinical remission, most of them recur. The median survival time for patients after recurrence is approximately two years [5]. Primary peritoneal carcinoma (PPC) behaves and is treated in a similar manner [6]. The overall 5-year survival rate for women with advanced EOC and PPC disease is only 13%-29% [7-9]. Nevertheless, with modern treatment, long-term survival can be achieved in some of them [10].

The aim of the present study was to assess the effect of platin sensitivity on long-term survival of Stage III EOC and PPC patients.

Material and Methods

The records of all histologically confirmed EOC and PPC patients diagnosed during the 11-year period from 1995 to 2006 were located. Records of Stage III patients were reviewed and clinicopathological data were retrieved after obtaining institutional review board approval. A comparison was made between patients who survived, with or without disease, more than five years (long-term survivors) and patients who died within three years after diagnosis (short-term survivors). Date of primary surgery was considered as date of diagnosis. For the purpose of analysis EOC and PPC patients were combined.

All patients had debulking surgery followed by combination chemotherapy with platin and paclitaxel. Patients were categorized as being platinum-sensitive if the platin-free interval prior to recurrence was more than six months.

Differences between the groups were calculated by chi square analysis or Fisher's exact test when appropriate.

Results

During the study period 82 histologically proven EOC and eight PPC patients were diagnosed. Of these 90 patients 58 (64.4%) had Stage III disease. Among the Stage III patients 20 had long-term and 18 short-term survival. PPC was diagnosed in four long-term and four short-term survivors.

The mean age of long-term and short-term survivors was similar being 63.7 ± 7.2 (range 46-74) and 62.8 ± 13.4 (range 37-78), respectively. Platin-sensitivity and other selected characteristics of the two patient groups are presented in Table 1. No statistically significant difference between the groups was found with regard to age ≤ 50, parity, main complaint, duration of complaint, body mass index, preoperative CA 125 level, estimated amount of ascites at the original operation, histological type and diameter of residual disease.

All short-term survivors had sub-Stage IIIC disease at diagnosis compared to 80.0% of the long-term survivors ($p = 0.06$, Fisher's exact test). The rate of platin-sensitive patients was 95.0% in long-term and only 27.8% in short-term survivors. This difference was highly significant ($p < 0.001$). The sensitivity and specificity of platin sensitivity for long-term survival was 95% and 72.2%, respectively, and the positive and negative predictive value was 79.2% and 92.8%, respectively.

Revised manuscript accepted for publication February 11, 2008

Table 1. — *Selected characteristics of long- and short-term survivors.*

	Survivors				p
	Long-term		Short-term		
	No.	%	No.	%	
Total	20	100.0	18	100.0	
Parity					NS
0	4	20.0	3	16.7	
1-2	7	35.0	10	55.5	
2+	9	45.0	5	27.8	
Main complaint					NS
Abdominal pain ± distension	16	80.0	15	83.3	
Other	4	20.0	3	16.7	
Duration (months)					NS
≤ 1	7	35.0	9	50.0	
2-3	5	25.0	5	27.8	
3+	8	40.0	3	16.7	
Not recorded	–	–	1	5.5	
Body mass index					NS
18.5-24.9	8	40.0	10	55.6	
25-30+	12	60.0	8	44.4	
Preoperative CA 125 (IU/ml)					NS
< 500	6	30.0	7	33.3	
500-1000	5	25.0	4	16.7	
1000+	9	45.0	7	50.0	
Sub-Stage III					0.06
A, B	4	20.0	0	0.0	
C	16	80.0	18	100.0	
Ascites (ml)					NS
None	3	15.0	2	11.1	
< 1000	8	40.0	4	22.2	
1000+	9	45.0	12	66.7	
Grade					NS
1-2	6	30.0	4	22.2	
3	14	70.0	14	77.8	
Histological type					NS
Serous	19	95.0	15	83.3	
Non-serous	1	5.0	3	16.7	
Residual disease (cm)					NS
None	5	25.0	1	5.6	
≤ 2	7	35.0	4	22.2	
> 2	8	40.0	13	72.2	
Platin sensitive					< 0.001
Yes	19	95.0	5	27.8	
No	1	5.0	13	72.2	

NS = not significant.

Discussion

Our main finding was that in women with Stage III EOC and PPC there was a highly significant larger percentage of platin-sensitive patients among long-term (> 5 years) than among short-term (< 3 years) survivors (95.0% vs 27.8% respectively; $p < 0.001$).

It has been previously shown that the most important favorable prognostic factors in advanced EOC and PPC, granting an improved chance for long-term survival, include younger age, cell type other than mucinous and clear cell, lower stage, well differentiated tumor, absence of ascites and smaller residual tumor following primary cytoreductive surgery [11, 12].

While there was a lower rate of sub-Stage IIIC patients among the long-term survivors when compared to short-term survivors ($p = 0.06$), the other mentioned favorable factors were not found to be significant predictors of long-term survival in our study.

It has been shown that obesity [13] is a risk factor and that parity has a significant protective effect [14] in ovarian carcinoma, but we have not found them to be predictors of long-term survival. Preoperative CA 125 level has been shown in some investigations to be of prognostic significance [15, 16] but it also seems not to be a predictor of long-term survival.

Inconsistent results have been obtained in studies dealing with the effect of symptom duration on prognosis. In some studies longer duration of symptoms unfavorably affects prognosis [17, 18] while in others no effect on survival was observed [19-23]. Our finding that duration of symptoms is not a predictor of long-term survival concurs with the latter studies.

Some of our findings are in contrast to a similar study by Kaern *et al.* [24] who compared 28 short-term survivors to 23 long-term survivors. Their definition of long-term survival was identical to ours but they defined short-term survival as death from ovarian cancer within 18 months from diagnosis. They found that the absence of ascites, debulking surgery to < 1 cm residual disease, clear-cell histology and normal postoperative prechemotherapy CA 125 levels to be of prognostic importance. In addition they found that negative Ki-67 expression also predicted a more favorable prognosis. Goff *et al.* [25], who compared 22 patients with Stage III ovarian cancer followed for a median of 66 months with 30 with a median survival of 18 months, reported that long-term survivors were more likely to have had an optimal cytoreduction and lower levels of Ki-67 antigen expression and less likely to overexpress p53 than were short-term survivors. These biomarkers and BRCA mutation status were not assessed in our study.

The main weaknesses of our study are its retrospective nature, the unequal arms for Stage IIIC disease and the long study period which allows for heterogeneity of the chemotherapy employed as second line or after relapse. The lack of association between most of the selected clinicopathological characteristics in our study and long-term survival may possibly be due to the small sample size. However in spite of the small sample size, platin sensitivity was a highly significant predictor of long-term survival. This factor has not been assessed in previous studies that compared long-term to short-term survivors. It is in line with that of Hunter *et al.* [26] who showed that cytoreductive surgery probably has only a small effect on the survival of women with advanced ovarian cancer but platinum-containing chemotherapy improved median survival time substantially.

While the rate of platin-sensitive patients was significantly higher among long-term survivors it should be noted that among short-term survivors about 28% of the patients were also platin sensitive. Thus the sensitivity and negative predictive value of platin sensitivity were high, however the specificity and positive predictive value were relatively low. Therefore the clinical useful-

ness of platin sensitivity as a predictor of long-term survival is limited. An accurate predictor of long-term survival could alleviate anxiety and be used to reassure EOC and PPC patients. Regretfully, no single characteristic assessed by us has demonstrated sufficient accuracy for any definitive clinical prediction of long-term survival. Microarray gene profiling [27] may in the future be used for more accurate prediction of long- term survival.

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