Frequent disease progression and early recurrence in patients with familial ovarian cancer primarily treated with paclitaxel and cis- or carboplatin (preliminary report)

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Summary

Purpose: To evaluate frequencies of early disease progressions and recurrences in patients with familial vs sporadic ovarian cancers following primary paclitaxel/cis- or carboplatin chemotherapy.

Methods: The frequencies of disease progression up to six months following primary paclitaxel/cis- or carboplatin and of early disease recurrences were analysed in 18 Stage III patients with familial ovarian cancers, both carriers and non-carriers of 5382 insC *BRCA1* mutation, and in 35 patients with Stage III sporadic ovarian tumors.

Results: Progressive disease within first six months following chemotherapy developed in 5/18 patients with familial cancers vs. 5/35 patients with sporadic tumors. Early disease recurrences (up to 6 months after treatment) occurred in 3/18 patients with familial vs. 2/35 patients with sporadic tumors. Recurrences after 7-12 months following treatment occurred, respectively, in 3/13 and 3/31 patients from these groups.

Conclusion: The results of this preliminary report may suggest that patients with familial ovarian tumors respond less favourably to paclitaxel/cis- or carboplatin treatment than patients with sporadic ovarian tumors. These findings should be however confirmed in a prospective study on a larger group of patients.

Key words: Familial ovarian cancer; *BRCA1* mutations; Primary treatment failures; Paclitaxel/platin.

Introduction

Hereditary ovarian cancers, both site-specific and associated with a high risk of breast cancer, may contribute to the overall incidence in about 10% of malignant epithelial ovarian tumors as calculated from family studies [1], while results of a recent large twin study suggest that strong hereditary predispositions may be the major cause of over 20% of these tumors [2]. Of the known predisposing genes, *BRCA1* and *BRCA2* carrying various germline mutations appear to account for a large fraction of these tumors, both in families with the breast ovary-syndrome and with site-specific hereditary ovarian cancer [1].

The clinico-pathological features of familial ovarian tumors, both in *BRCA1* germline mutation carriers and non-carriers, were subject to several studies. In general, these tumors develop on a average in younger patients, are predominantly of the serous histological type and are frequently poorly differentiated [3-7]. Data on survival as compared to survival of patients with sporadic ovarian tumors are divergent. In a series of early publications patients with familial ovarian cancers in general [8] and those who were identified as carriers of *BRCA1* germline mutations [3, 4] were reported to have a substantial survival advantage over patients with sporadic ovarian tumors. However, it has been pointed out that the results of the largest of these studies [3] could be biased due to inadequate methodology [9-13]. In some subsequent studies actually shorter mean survivals of patients with familial ovarian cancer [5] and carriers of *BRCA* germline mutations [5, 14], as compared to patients with sporadic tumors, were reported. The results of two recent large studies [6, 7] imply however, that both *BRCA1* and *BRCA2* mutation carriers may indeed have a significant survival advantage, although much less impressive than reported earlier.

Since both *BRCA1* and *BRCA2* genes are involved in repair of DNA damage [15, 16] a hypothesis was put forward that the survival advantage of patients with ovarian tumors who are carriers of germline mutations of these genes might result from enhanced sensitivity to drugs which interact with DNA. While all drugs previously used in the standard post-operative treatment of ovarian carcinoma, i.e., platinum derivatives, cyclophosphamide and anthracyclines, act respectively, through double strand DNA co-valent binding, alkylation or intercalation [17], paclitaxel and other taxanes, introduced for treatment of ovarian carcinoma more recently, exert their cytotoxic action mainly through the disruption of cellular microtubular structures [18].

The problem of relationship between the type of post-operative chemotherapy and survival of patients with familial ovarian tumors has so far not been directly

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addressed. No data on type of chemotherapy were given in some of the early reports [3, 14], whereas in some others survival was evaluated in patients who were postoperatively treated with cisplatin-based chemotherapy [4, 8]. The two most recent reports [6, 7] included patients treated both by cisplatin/cyclophosphamide and paclitaxel/cisplatin, but survival in the respective subgroups was not evaluated separately.

In this preliminary study we report a much higher frequency of primary treatment failures and early recurrences in patients with familial ovarian tumors, both carriers nod non-carriers of *BRCA1* germline mutations, as compared to patients with sporadic epithelial ovarian tumors. This finding may encourage further prospective studies on the relationships between the clinical course and outcomes in patients with familial ovarian cancers and drug combinations used and in postoperative chemotherapy.

Patients and methods

Patients characteristics

Subject to this study were 53 Stage III patients with malignant epithelial ovarian tumors, mostly referred for chemotherapy following surgery in other hospitals, to the Great Poland Cancer Center, Poznań and to the Oncology Department of the Medical School in Poznań in the years 1998-2001. Only patients who were primarily treated with five to eight courses of paclitaxel (135 or 175 mg/m^2) and cisplatin (75 mg/m^2) or carboplatin (in doses calculated according to the formula proposed by Calvert) were included [19]. In some of the patients only explorative surgery was performed prior to chemotherapy and in several others the initial tumor debulking was sub-optimal. Excluded were patients who were subject to a second-look operation shortly after primary treatment and early second debunking, since these procedures were applied in a minority of patients only. Otherwise, the patients were non-selected.

Disease progression and disease recurrence were diagnosed using standard clinical and radiological criteria [20] confirmed, in most patients, by serial measurements of serum CA 125 levels, evaluated by the criteria proposed by Gordon *et al.* [21].

Data on tumors in relatives of patients and on results of molecular screening for *BRCA1* mutations were already collected after initiation of chemotherapy. Basing on these data patients were subdivided into two groups: 1. with familial ovarian and breast and ovarian cancers; 2. with sporadic ovarian cancers. All patients who had either ovarian tumors diagnosed metachronously to breast carcinoma or who had at least one 1st or 2nd degree relative with either ovarian or breast cancer were enclosed into the group with familial cancer. Tumors in relatives at other sites, including "gynecological cancers" at unspecified sites were not taken into account in this subdivision.

Data describing the clinico-pathological features of patients with familial and sporadic cancers are summarised in Table 1. Data on number of ovarian and breast cancers in probands and relatives and results of molecular screening for *BRCA1* mutations in the respective subgroups are presented in Table 2.

BRCA1 mutation screening:

Genomic DNA was isolated from peripheral blood of all patients with familial tumors by the phenol-chloroform method using proteinase K [22]. The PCR-SSCP - electrophoresis procedure, as described in details elsewhere [23], was used to search for *BRCA1* gene mutations found so far in the Polish population (exon 2 - 185delAG, exon 5 - T300G and T309C, exon 22 - G5465A and fragments of exon 11: 110 - 3819delGTAAA and 11P - 4153delA). Exons and fragments suspected of mutation were subjected to nucleotide sequencing. The 5382insC mutation in exon 20, which is the most frequent mutation in the Polish population, was sought by direct sequencing without prior SSCP analysis. The primers used for the PCR reaction were those proposed by Friedman *et al.* [24].

Table 1. — *Clinical and pathological characteristics of patients with familial and sporadic ovarian cancers.*

	Familial cases		Sporadic cases
	All	*BRCA1* mutation carriers	
Number of cases	18	8	35
Median age at diagnosis, yrs (age range, yrs)	54 (39-73)	53.5 (39-66)	58 (35-78)
Histopathological types			
– serous	7	5	16
– mucinous	0	0	3
– endometrioid	4	1	6
– other adenocarcinoma or unspecified	7	2	10
Histopathological grade			
1	0	0	5
2	6	4	7
3	6	2	14
unspecified	6	2	9
CA 125 before treatment			
< 35 U/ml	4	1	11
> 35 U/ml	14	7	24
Months of follow-up median (range)	13 (6-15)	13 (10-52)	19.5 (6-33)

Table 2. — *Characteristics of patients with familial ovarian cancer.*

	All families	Families of *BRCA1* mutation carriers
Number of ovarian and breast cancers in family		
2	11	3
3	4	2
> 4	3	3
Number of probands with ovarian cancer metachronous to breast cancer	4	2
Number of families with breast and ovarian cancers	15	7
Number of families with 2 or more ovarian cancers	9	6
Number of families with ovarian cancers only	3	0

Results

As shown in Table 1 the median age of patients with familial tumors was somewhat lower than the median age of patients with sporadic ovarian carcinomas. We found no mucinous adenocarcinomas among our patients with familial cancers, and grade 1, well differentiated tumors were found by in the group of patients with sporadic tumors only.

Eight of the 18 patients included in the group of familial ovarian or breast and ovarian cancers were identified as carriers of the 5382 ins C mutation of the *BRCA1* gene. No mutations at other common sites of this gene were found in this group. As shown in Table 2, germline *BRCA1* mutations appeared to occur more frequently in probands from families with three or more ovarian and/or breast cancers than in families where only two cases of ovarian or breast and ovarian cancers were recorded. We note, that of four patients with ovarian carcinoma metachronous to breast cancer, two had no close relatives with either breast or ovarian cancer.

Both disease progression during the first six months in patients who did not respond to paclitaxel/cis- or carboplatin therapy as well as early recurrences following initial response to treatment, were more frequent in patients with familial vs. sporadic ovarian tumors (Table 3). These differences could not be accounted for either by the type of surgery preceding chemotherapy, by differences in paclitaxel doses, or by the number of chemotherapy courses since both groups were quite comparable with respect of these variables. Disease progression shortly after primary chemotherapy appeared to occur more frequently in patients with familial tumors who did not carry the *BRCA1* mutations. However, since the subgroups of carriers and non-carriers were small, these differences require further evaluation in larger studies. In addition we noted, that of four patients who developed ovarian carcinoma metachronously to breast cancer, one had progressive disease and two had recurrences up to six months after primary chemotherapy.

Table 3. — *Number of patients who had disease progression in first six months or early recurrences following treatment with paclitaxel and cis- or carboplatin.*

	Progressive disease (%)	Disease recurrence (%)		
		up to 6 mos.	7-12 mos.	13-18 mos.
Familial tumors	5/18 (33)	3/18 (17)	3/13 (23)	0/4
BRCA1 status:				
carriers	1/8 (13)	2/8 (25)	2/7 (29)	0/3
non-carriers	7/10 (70)	1/10 (10)	1/6 (17)	0/1
Sporadic tumors	3/35 (9)	2/35 (6)	3/31 (10)	0/19

Discussion

We found in this preliminary study that disease progression and early recurrences following surgery and primary chemotherapy with paclitaxel and platin derivatives occurred more frequently in patients with Stage III familial ovarian carcinoma than in Stage III patients with sporadic malignant ovarian tumors. The explanation for this difference, which may be of important significance for the selection of optimal treatment for patients with familial ovarian tumors, remains hypothetical and warrants further studies.

We noted, similarly to others [3, 4, 5, 6], that patients with a positive family history developed ovarian tumors on average at a somewhat younger age and that tumors in these patients were either poorly or moderately differentiated [3, 5, 14]. We found no mucinous carcinomas in patients with familial tumors, similarly to others who found such tumors only in a small percentage of such patients [5, 14].

We used less stringent criteria in defining familial cancer than those which are usually employed [5]. However, as apparent from *BRCA1* mutation screening, *BRCA1* mutation carriers were also found in families with only two ovarian or breast and ovarian tumors in close relatives.

In most of the previous studies, the clinicopathological features and survival were compared respectively in groups of *BRCA1* mutation carriers and non-carriers. However, Pharoah *et al.* [5] have already noted that differences in survival in familial vs. sporadic ovarian cancers, occurred independently of the *BRCA* carrier status of the former. This may imply, that either not all germline mutations of these genes can be identified by techniques presently employed [25] or that some other, yet unknown predisposing genes may affect the course of ovarian cancers in the same way and possibly through similar mechanisms.

In our study we screened for *BRCA1* germline mutations only, since *BRCA2* germline mutations contribute little to familial breast and/or ovarian cancer in Poland [26]. Moreover, among our patients we found only carriers of the *BRC1* 5382 insC mutation, which is most prevalent in the Polish population [26, 27]. The types and sites of germline BRCA mutations do not seem to affect the disease course, since, as reported by others [5-7], there were no significant survival differences between ovarian cancers patients who were *BRCA1* and *BRCA2* mutation carriers nor between carriers of the 185delAG and the 5382 insC mutations of the *BRCA1* gene [7] .

Analysis of overall survival is the best endpoint in evaluating differences in the disease course in patients with tumors which develop respectively, through "inherited" vs. "somatic" pathways. Our present study addressed only differences in the early course of disease following primary chemotherapy. However, others have reported a positive correlation between survival and disease-free intervals, following primary treatment in patients with familial ovarian cancer [6].

There are some clinical variables affecting the course of disease which have not been evaluated in the present study. In particular, many of the patients included were referred for chemotherapy by other hospitals following exploratory surgery or sub-optimal tumor debulking only, and it is known that the extend of sugery is one of the major factors affecting prognosis in ovarian cancer [6]. Therefore, while our preliminary results strongly suggest that patients with familial ovarian or breast and ovarian cancers, fail to respond to paclitaxel/cis-or carboplatin therapy more frequently than patients with sporadic ovarian tumors, these results have to be confirmed by a larger prospective trial on patients receiving standardized treatment.

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