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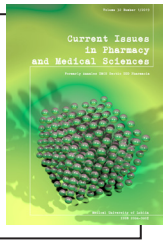

Cytoreductive surgery and HIPEC (hyperthermic intraperitoneal chemotherapy) in combined treatment of ovarian cancer: time for the beginning of personalized therapy?

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ABSTRACT

Background and objectives. During the two past decades, a new therapeutic approach to ovarian cancer (OC) has been developed. This combines cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). However, almost no data exist regarding the utility of biomarkers of morphological heterogeneity as prognostic factors in such patients.

Methods. A retrospective study of the effectiveness of CRS and HIPEC was carried out in 59 patients with ovarian cancer. Biomarkers of morphological heterogeneity of OC were studied as prognostic factors: OC pathogenic types (based on the identification of p53 mutated gene protein expression) and homologous recombination deficit (basing on the identification of BRCA 1 gene expression status).

Results. The survival of patients reliably differed with the division into two pathogenetic OC types established by immunohistochemistry: the median disease-free survival of type I OC patients was 14±1.7 months, type II – 8±1.6 months ($p = 0.007$); the median overall survival of type I OC patients was 23.5±6.7 months, type II – 12±1.9 months ($p = 0.017$). The median overall survival of patients with the somatic mutation of BRCA 1 gene and complete cytoreduction was 22±4.8 months, and without the somatic mutation of BRCA 1 gene – 12±3.3 months ($p = 0.047$).

Conclusions. These data demonstrate that identification of the pathogenetic type of OC and BRCA 1 status may be useful for the personalized therapy of ovarian cancer patients treated with CRS/HIPEC.

INTRODUCTION

Ovarian cancer (OC) is the seventh most commonly diagnosed cancer among women in the world, with a woman's lifetime risk of developing OC being 1 in 75. The disease is typically presented at late stage with peritoneal metastases; at this point the 5-year relative survival is only 29% [1].

Because the peritoneal cavity is the predominant site of the disease, over the last decades, new methods involving cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have drawn the attention of researchers. The use of intraperitoneal chemotherapy during surgery ensures effective eradication of the microscopic residual metastatic process in the abdomen. Extra heat increases the cytotoxic action of many agents by increasing the penetrability of the cell membrane [2].

Combined therapy with the use of CRS and HIPEC has already proved its effectiveness in colorectal cancer patients with implantation metastases, patients with pseudomyxoma and abdominal mesothelioma patients [3-5]. The results of using combined therapy involving HIPEC for OC still

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remain restricted to a number of retrospective studies [6-8], but are actively being investigated in a large number of prospective randomized studies [9]. Positive results of the first such randomized studies have already been published [10,11].

Important prognostic factors and objective criteria for a peritoneal carcinomatosis study are the peritoneal cancer index (PCI) and completeness of cytoreduction score (CC) [12]. The aforementioned were confirmed for OC in previous studies [6,8].

OC is recognised as a heterogeneous disease, and in the last few years, a dualistic model for the pathogenesis of this disease has emerged. This divides epithelial tumours into type I and type II ovarian carcinomas [13]. Type I cancers tend to be low-grade and indolent tumours. Type II tumours, in contrast, are very frequently associated with p53 mutations (97% of all high-grade serous cancers were associated with a p53 mutation). Approximately 20% of these tumours also carried a BRCA1/2 mutation due to a combination of germline and somatic mutations [14]. The aforesaid morphological subtypes of OC have prognostic significance, but there are almost no clinical data on morphological stratification of patients receiving CRS/HIPEC. Taking into account high OC relapses rate even after complete cytoreduction [11], the rationale of investigating the aggressive CRS/HIPEC therapeutic approach from the perspective of dividing patients on the basis of morphological heterogeneity biomarkers and the doctrine of a personalized approach are beyond any doubt.

The goal of our study was to investigate clinical outcomes of OC patients treated with CRS/HIPEC according to histopathological biomarkers, including p53 and BRCA 1, with the aim of forming a personalized approach to treating such patients.

MATERIALS AND METHODS

Patients and specimens

To discern immediate and long-term results of using CRS/HIPEC in the combined treatment of 59 OC patients – 49 recurrent OC patients and 10 patients with primary OC – were analyzed. In addition, clinical-morphological and surgical prognostic factors were investigated and the prognostic value of biomarkers of OC pathogenic types (identification of p53 mutated gene protein expression in archival formalin fixed paraffin embedded tissues) was assessed, as well as the deficit of homological recombination (determination of BRCA 1 gene protein expression level). The patients were in-patients of the Clinic of Oncology and Medical Radiology of Danylo Halytsky Lviv National Medical University, referred by the Department of Abdominal Surgery of Lviv State Oncological Regional Therapeutic and Diagnostic Centre in 2008-2017 (retrospective single center study). OC staging was held on the basis of criteria of TNM classification, 7th edition (2009).

The main clinical and pathological characteristics of the patients participating in the study are given in Table 1.

Table 1. Clinical and pathological characteristics of 59 OC patients

Characteristics		Number (%)
Ovarian cancer	Primary	10 (17)
	Recurrent	49 (83)
Age	54.2±7.9 years (from 28 to 76)	
	< 50 years	14 (23,7)
	> 50 years	45 (76,3)
Chemo-sensitivity (for epithelial recurrent OC, n=46)	Chemo-sensitive (>6 months)	29 (63)
	Chemo-resistant (<6 months)	17 (37)
Primary stage	IB	2 (3,4)
	IC	7 (11,8)
	IIA	2 (3,4)
	IIB	3 (5,1)
	IIC	4 (6,8)
	IIIB	2 (3,4)
	IIIC	38 (64,4)
	IV	1 (1,7)
Histological structure		
epithelial OC	Serous carcinoma high-grade	36 (61)
	Serous carcinoma low-grade	9 (15,3)
	Mucinous carcinoma	6 (10,1)
	Clear cell carcinoma	3 (5,1)
	Endometrioid carcinoma	2 (3,4)
nonepithelial OC	Granulose-cellular carcinoma	3 (5,1)
Chemotherapy before CRS\HIPEC		22 (37,3)
Peritoneal cancer index (PCI)	0-10 points	23 (39)
	11-20 points	16 (27,1)
	21 and more points	20 (33,9)
Completeness of cytoreduction score	CC-0	32 (54,2)
	CC-1	12 (20,3)
	CC-2,3	15 (25,5)
Pathogenetic type in a histological way (for epithelial OC, n=56)	I pathogenetic type	19 (34)
	II pathogenetic type	37 (66)
Pathogenetic type in a IHC way (n=42)	I pathogenetic type	20 (47,6)
	II pathogenetic type	22 (52,4)
Ascites	Present	9 (15,3)
	Absent	50 (84,7)

Before combined treatment (CRS/HIPEC, systemic chemotherapy) of the progressing pathology, recurrent OC patients received from 0 to 3 lines of chemotherapy (1.3±0.7), from 0 to 4 courses (1.6±0.9) and from 0 to 24 chemotherapy cycles (8.4±4.6) on previous stages of anamnesis of the disease.

Combined treatment

In order to achieve regress of intraperitoneal relapse before the beginning of combined treatment, 22 (37.3%) patients received 4±1.8 (from 2 to 8) cycles of neoadjuvant chemotherapy, on average.

Combined therapy of recurrent OC patients was performed with the use of cytoreductive surgery in combination with HIPEC, with subsequent systemic chemotherapy of the appropriate line. Among the 10 patients with primary OC, 7 patients were given primary cytoreductive surgery and 3 patients were given cytoreduction after non-radical primary surgical treatment combined with HIPEC and subsequent systematic chemotherapy.

In order to achieve complete cytoreduction (CC-0, 1), patients were given cytoreductive surgical treatment with the use of different stages of peritonectomy according to Sugarbaker [12].

The HIPEC procedure was carried out using the "closed" method for 90 minutes duration at an average intra-abdominal temperature of 43.3±1.4°C (from 39 to 44.5), with the administration in platinum-sensitive cases of intraperitoneal cisplatin in the dose 100 mg/m^2 and in cases of platinum-resistant relapses – of cisplatin in the dose 75 mg/m^2 and doxorubicin 15 mg/m^2.

Systemic adjuvant chemotherapy after the surgery was given to 44/59 (74.6%) patients. The average number of

cycles was 4.7±1.6 (from 1 to 8 chemotherapy cycles). The schemes of chemotherapy applied depended on the lines of previous treatment: cisplatin/carboplatin + cyclophosphamide was used in 18 (40.9%) patients, paclitaxel ± carboplatin in 21 (47.8%) patients, caelyx in 2 (4.5%) patients, gemcitabine in 2 (4.5%) patients and topotecan in 1 (2.3%) patient.

On further stages of OC, the patients in the study were given from 0 to 4 lines of chemotherapy (1.3±1.1), from 0 to 5 courses (1.4±1.2) and from 0 to 21 cycles of chemotherapy (8.1±5.1). Repeated cytoreductive surgery was given to 9 (15.3%) patients.

Immunohistochemistry (IHC) assay

Tissue specimens were deparaffinized with xylene, and then rehydrated for antigen retrieval. Phosphate buffered saline was used to wash the slides, followed by treatment with 3% hydrogen peroxide for 20 min to quench endogenous peroxidase activity. The samples were then preincubated with 10% goat serum at room temperature for 30 min to prevent nonspecific staining. The sections were incubated with the following primary antibodies: rabbit monoclonal antibody p53 (Clone SP5 "Thermo scientific", Cat.#RM-90105-S0, 1:100 dilution) or mouse monoclonal anti-BRCA 1 antibody (clone MS110, ab 16780, "Abcam", 1:500 dilution) for 30 min in a humidified container and washed with phosphate buffered saline. Tissue slides were examined with a "UltraVision Quanto detection system HRP" by Thermo Scientific and stained with 3,3-diaminobenzidine tetrahydrochloride. The stained tissue sections were evaluated using a 4 point scale as follows: the percentage of positive cells, grades 0-3 (0: no positive cells; 1: < 25% positive cells; 2: 25-50% positive cells; 3: > 50% positive cells).

Polymerase chain reaction (PCR) of BRCA 1 gene germline mutations

For molecular genetic testing, DNA samples obtained from venous blood nuclear cells in patients with OC cancer were used. The extraction and refinement of DNA from the leukocytes of the peripheral blood was conducted by salting-out protocol extraction. Amplification of DNA *in vitro* was performed by PCR. Samples were further analysed by restriction fragment length polymorphism method or by allele specific reaction. The digested fragments were visualized on 3% agarose gel electrophoresis stained with ethidium bromide. The presence of the subsequent BRCA1 (NM_007294.3) gene mutations was analyzed: 5382insC (c.5266dupC, p. Q1756fs), 300T>G (c.181T>G, p.C61G), 185delAG (c.68_68del, p.E23fs) and 4153delA.

Follow-up

Patients were regularly followed up from the date of operation; we inspected their serum CA-125 and performed ultrasonography every 3 months and chest radiography every 6 months during the first two postoperative years and every 6 months thereafter. Patients with abnormal CA-125 or suspected ultrasonography examination underwent computerized tomography. Disease-free survival (DFS) was measured from the date of surgery to the date of recurrence, metastasis, death or last follow-up. Overall survival (OS) was measured from the date of surgery to the date of death or last followup.

Statistical analysis

Statistical processing of primary data was carried out with the use of SPSS 22 and Statistica 6 programs. To investigate the cumulative survival of patients, the censored Kaplan-Meier method was used, whereas to determine significance in the difference of survival levels in separate groups, logarithmic rank coefficient was used. Multivariate analysis was carried out using X^2 index. In order to establish correlations, Pearson's linear correlation coefficient was applied.

RESULTS

The average surgery time, including HIPEC procedure duration, was 368.3±68.1 (from 270 to 550) minutes.

The average value of surgical PCI index, which was determined intra-operatively, was 15.9±10.5 (from 0 to 36) points.

Cytoreduction completeness score was assessed after the surgical stage of treatment as follows: CC-0 cytoreduction completed in 32 (54.2%) patients, CC-1 – 12 (20.3%), CC-2 – 11 (18.7%) and CC-3 – 4 (6.8%).

In 12 (20.3%) patients, the presence of lymphogenic metastases in the retrieved iliac, paraaortal or inguinal lymph nodes was confirmed histologically. In 4 (6.8%) patients, after liver resection, hematogenic metastases in the liver were confirmed morphologically. Therefore, extraperitoneal metastases were detected in the total of 16 (27.1%) patients.

Postoperative results

The average period of stay in the in-patient facility after surgery for those treated with CRS/HIPEC was 18.3±6.8 days (from 9 to 40 days).

Postoperative morbidity developed in 26 (44.1%) patients after CRS and HIPEC. Surgical complications were experienced by 13 (22%) patients, 6 (10,2%) patients had complications of HIPEC degrees III-IV and 7 (11,9%) patients were affected by somatic morbidity. Relaparotomy was required in 9 (15.2%) patients. The 60-day postoperative mortality rate was 6.8% (4 patients). Three out of these patients reached more than 21 points by PCI.

Long-term outcomes

Median follow-up was 43.8 months (range 10-84 months).

Disease-free and overall survival of the 59 OC patients who were given CRS/HIPEC and systemic chemotherapy was 13.9 months and 30.2 months, respectively.

Among 54 non-censored patients (5 patients were censored as a result of death due to surgical complications or intercurrent pathology), disease progressed in 42 (77.8%) patients. Among these, the most common was intraperitoneal relapse that developed in 35 (83.3%) patients. Metastases of another character developed in 16.7% patients. The peak frequency of OC progression occurred at the third half-year after combined therapy completion.

By means of univariate analysis of potential prognostic factors, the following were characterized as having statistically significant impact on survival: ascites, chemosensitivity and disease-free period duration in recurrent OC patients, peritoneal cancer index (PCI), cytoreduction completeness score, presence of extraperitoneal metastases, as well as the pathogenetic type defined IHC (Table 2).

Table 2. Results of univariate analysis of prognostic factors in OC patients after CRS/HIPEC

Indicator	Median overall survival (month)	95% CI	p
Ovarian			
cancer primary	29±1.6	25.9-32.03	0.12
recurrent	19±2.4	14.2-23.8	
Ascites			
present	3±0.8	1.5-4.5	0.03
absent	23.5±3	17.6-29.4	
Recurrence			
Chemo-sensitive (>6 months)	21±1.7	17.6-24.4	0.001
Chemo-resistant (<6 months)	12±2.7	6.6-17.4	
Disease-free period before CRS/HIPEC			
0-6 months	12±2.7	6.8-17.2	0.002
7-12 months	21±4.5	12.2-29.8	
over 12 months	25±2.8	19.4-30.6	
Peritoneal cancer index (PCI)			
0-10 points	27±1.5	24.1-29.9	0.002
11-20 points	21±2	17.1-24.9	
21 and more points	11±3.4	4.4-17.6	
Completeness of cytoreduction score			
CC-0	25±3.4	18.4-31.6	0.008
CC-1	20.5±5.2	10.3-30.7	
CC-2,3	8.5±3.2	4.3-15.6	
Lymphogenous metastases			
present	19±6.4	6.5-31.6	0.05
absent	21±4.1	12.9-29.1	
Extraperitoneal metastases (lymphogenous, liver)			
present	19±6.9	5.4-32.6	0.04
absent	21±5	11.1-30.9	
Pathogenetic type (defined histologically)			
type I	23.5±4.3	15-32	0.28
type II	19±2.4	14.2-23.8	
Pathogenetic type (defined IHC)			
type I	23.5±6.7	10.4-36.6	0.017
type II	12±1.9	8.3-15.7	
Normal BRCA 1 expression	12±3.3	5.6-18.4	0.047
Decreased BRCA 1 expression	22±4.8	12.5-31.5	

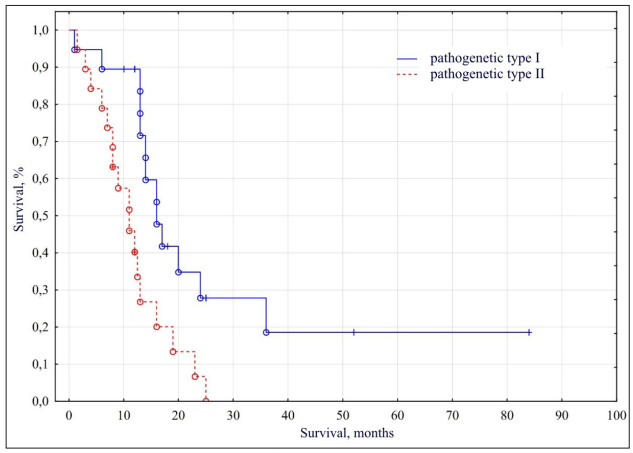

Figure 1. DFS of OC patients given combined therapy involving CRS/HIPEC, depending on division into pathogenetic types, using the IHC method (p = 0.007)

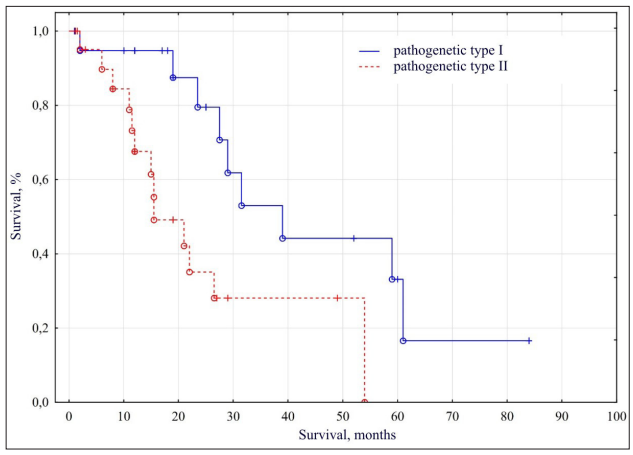

Figure 2. OS of OC patients given combined therapy involving CRS/HIPEC, depending on division into pathogenetic types, using the IHC method (p = 0.017)

Influence on the prognosis of pathogenetic types of OC

Statistically significant differences in disease-free and overall survival between patients of I and II pathogenetic types of epithelial OC, determined histologically, were not observed (Table 2).

Using the IHC method, pathogenetic type was identified in 42 epithelial OC patients: pathogenetic type I (absence p53 mutated gene protein expression) was detected in 20 (47.6%) patients and pathogenetic type II (p53 mutated gene protein expression from 10% to 90% of all cells) in 22 (52.4%) patients. In 10 (23.8%) patients, the pathogenetic type changed to the opposite, in comparison with histological conclusions: in 8 patients, type II (established histologically) became type I (IHC) and in 2 patients, type I (established histologically) became type II (IHC).

Therefore, at OC division into pathogenetic types using the IHC method, a statistically significant difference of patient survival appears within univariate analysis: median DFS of OC type I patients was 14±1.7 months (95% CI 10.7-17.3) and of type II patients was 8±1.6 months (95% CI 4.9-11.1), p = 0.007 (Figure 1). Median OS of OC type I patients was 23.5±6.7 months (95% CI 10.4-36.6) and of type II patients was 12±1.9 months (95% CI 8.3-15.7), p = 0.017 (Figure 2).

Influence of BRCA 1 gene expression status on prognosis

Among the patients with OC pathogenetic type II, the status of the BRCA1 gene was studied in 24 patients. By means of the IHC method, somatic mutation (mutation in tumor cells) of BRCA 1 gene was detected in 21 (87.5%) patients. Among these, germline mutations (inherited mutations in all cells of the body) of BRCA 1 gene were detected using PCR only in 2 (8.3%) patients. One had the 300 T>G mutation of BRCA 1 gene, the other had the 5382incC mutation of BRCA 1 gene.

Univariate analysis was performed in sub-groups of patients to reveal somatic mutations of BRCA 1 (IHC). By this method, median OS of OC patients with BRCA 1 gene somatic mutation was 15.5±5.7 months (95% CI 4.3-26.7), whereas in those without BRCA 1 somatic mutation, this was 12±3.3 months (95% CI 5.6-18.4), p = 0.08. Median DFS of OC patients with BRCA 1 somatic mutation was 12±2.1 months (95% CI 7.9-16), whereas of those without BRCA 1 somatic mutation, this was 8±3.3 months (95% CI 1.6-11.4), p = 0.21. However, analysis of patients with complete cytoreduction (CC-0, 1) suggests a significant difference in overall survival: median OS of OC patients with BRCA 1 somatic mutation was 22±4.8 months (95% CI 12.5-31.5),

whereas in those without BRCA 1 somatic mutation, this was 12±3.3 months (95% CI 5.6-18.4), p=0.047.

DISCUSSION

Cytoreductive surgery for OC involves maximum reduction of macroscopic implant foci on the peritoneum with the aim of furthering the effect of cytostatic agents on residual microscopic actively proliferating tumor elements. The main purpose of HIPEC is to destroy such a residual intraperitoneal pool of cells by means of locoregional application of two synergic antitumor factors – chemotherapeutic agents and hyperthermia.

The immediate and long-term results of using CRS/HIPEC in OC patients in our study are in line with the results of other clinics [6-8]. The majority of cases of postoperative mortality of the patients in our series are also associated with sub-maximum PCI indices.

The results of univariate analysis of this study confirmed the significant impact of the main clinical and surgical factors of prognosis of OC patients given CRS/HIPEC as part of combined therapy on survival. These include peritoneal cancer index, completeness of cytoreduction score, and ascites presence. The aforementioned prognostic factors are widely covered in literature and are currently used in medical practice [7,8].

However, the results of a recent randomized study by van Driel and co-authors [11] that confirmed effectiveness of using HIPEC in primary OC patients, demonstrate that if the level of complete cytoreductions (CC-0,1) reaches 87%, median DFS in the experimental group is only 14.2 months and 3-year DFS is only 17%. In a study by Deraco and co-authors [6], on condition of achieving microscopically complete cytoreduction (CC-0) in 84% of recurrent OC patients, median DFS was only 10.8 months. In a study by Bakrin and co-authors [8], at the level of complete cytoreductions in recurrent OC patients as high as 74.9%, a median OS of 45.7 months was achieved, but the majority of patients had intraperitoneal recurrence. Therefore, it becomes obvious that taking into consideration only clinical and surgical prognostic criteria while using CRS/HIPEC does not allow the attainment of high survival in a potentially favorable group of patients with complete cytoreduction of implants from peritoneum, and necessitates searching for personalized approach opportunities.

The prognostic role of the two pathogenetic types of OC in conditions of standard treatment has been discussed previously [15]. This study is the first to demonstrate different survival of patients with different pathogenetic types of OC treated with CRS/HIPEC. The survival of pathogenetic type I patients is almost twice as high as that of pathogenetic type II patients. In conditions of low effectiveness of systemic chemotherapy in pathogenetic type I patients (low-grade OC), the exceptional role of aggressive CRS/HIPEC therapy in achieving favorable prognosis for such patients becomes obvious.

BRCA 1 is a tumor-suppressing gene that plays a leading role in the processes of homological recombination. Around 70% of inherited OC are associated with mutation of the BRCA 1 gene. Besides this, a large number of sporadic OC are characterized by somatic mutation or lowered expression of this gene in the cells of tumors [16]. To date, data have been published on increased sensitivity to platinum-containing (or DNA damage-based) chemotherapy at lowered BRCA 1 expression [17]. Moreover, BRCA 1 mutation can be accompanied by the increased effectiveness of intraperitoneal chemotherapy. Thus, in a study by Lesnock and co-authors [18], aberrant expression of BRCA 1 protein (established by IHC) was found in 48% of primary OC patients. It is in the group of patients with lowered BRCA 1 expression that statistically significant difference was shown in the survival of patients given intraperitoneal vs intravenous chemotherapy. The latter was recognized as the only independent prognostic factor in patients receiving normothermic intraperitoneal chemotherapy. In our study, lowered BRCA 1 expression was found in 87.5% of all patients, which is obviously connected with the absolute majority of recurrent OC cases. Nevertheless, results of our study are the first to demonstrate the prognostic value of lowered BRCA 1 expression in OC patients given CRS/HIPEC. A significant difference in survival was found in the group of patients with complete cytoreduction, where the use of HIPEC has the highest chances for effective implementation. Taking into consideration all study results, the following algorithm of personalized use of CRS/HIPEC in OC patients is suggested for further discussion (Figure 3).

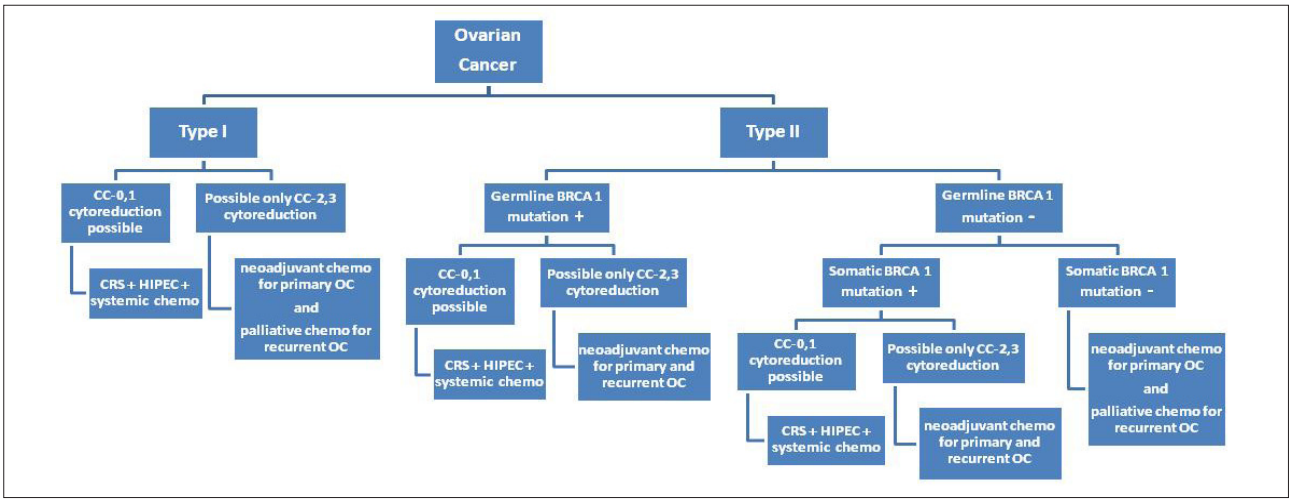

Figure 3. Algorithm of combined therapy of OC patients that involves CRS/HIPEC

CONCLUSIONS

The use of CRS/HIPEC in the combined treatment of OC patients is an effective and safe method of treatment. Overall and disease-free survival of OC patients treated with combined therapy involving CRS/HIPEC is likely to depend on the pathogenetic type of OC (I or II) as established by the IHC method. Moreover, overall survival of OC patients treated with CRS/HIPEC is likely to increase with a lowered BRCA 1 gene expression in the cells of the tumor, but only if cytoreduction is complete (CC-0,1).

The established clinical and surgical prognostic factors, as well as the biomarkers of morphological heterogeneity of OC indicate the necessity of a discussion on personalized approaches to selecting patients for aggressive combined therapy involving the use of CRS/HIPEC.

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