Analysis of the treatment of ovarian cancer patients with neo-adjuvant chemotherapy – preliminary results

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Summary

Introduction: Primary surgery and adjuvant chemotherapy is the standard treatment in ovarian cancer patients. Neo-adjuvant chemotherapy is one of the treatment modes in patients with a poor general condition or advanced disease, not adjustable for primary surgery. The purpose of this study was to evaluate if the efficacy of this new option of therapy is comparable to the standard method.

Materials and methods: 319 ovarian cancer patients, FIGO Stage III and IV, have been analyzed. Within this group, 50 women were treated with neo-adjuvant chemotherapy. 18 patients were operated after three cycles of neo-adjuvant chemotherapy, and 32 patients - after six cycles. Results of treatment were evaluated, including disease-free survival, and number of complications. Factors that may influence the treatment results were also analyzed.

Results: Median disease-free survival in the group treated with adjuvant chemotherapy (group 3), and operated on after three cycles of neo-adjuvant chemotherapy (group 1), were 19 and 20 months, respectively. For the group operated on after six cycles of neo-adjuvant chemotherapy (group 2), median disease-free survival was 15 months (p = 0.27). The following factors have been found to influence treatment results: optimal cytoreduction and tumor grading. There was no difference in complication rates among the three analyzed groups.

Key words: Ovarian cancer; Interval debulking surgery; Neoadjuvant chemotherapy.

Introduction

Ovarian cancer is in sixth place for women in the Polish population taking into consideration the mortality rate. The standardized rate was 11 per 100,000 women in 2000. This year, 3,030 new cases of ovarian cancer were registered and 1,957 deaths occurred [1].

Primary surgery with adjuvant chemotherapy is the standard therapy in the treatment of ovarian cancer patients. Unfortunately, the number of non-radical operations is still high, mainly in advanced stages of disease. Therefore the standard tactics are not useful in patients without optimal cytoreduction. The definition of optimal cytoreduction is residual tumor less than 1 cm in diameter. Patients with such tumor mass have only the therapeutic benefit defined as increased 5-year survival [2-5]. In patients with advanced stage or a poor general condition, the initiation of treatment with chemotherapy seems to be justified regarding the chemo-sensitivity of ovarian cancer. This therapeutic option may reduce tumor mass, improve the patient's condition, and may also give the possibility to perform cytoreductive surgery in the future. The decreased postoperative complications after neo-adjuvant treatment should also be emphasized.

In 1999 in the Department of Gynecological Oncology, Memorial Cancer Center, Institute of M. Sklodowska-Curie, neo-adjuvant chemotherapy was introduced as a therapy option in cases where optimal cytoreduction was impossible to perform due to abdominal and pelvic CT preoperative evaluation or poor general condition.

The aim of this study was to evaluate the therapeutic usefulness and complication rate of neo-adjuvant chemotherapy in comparison to standard procedures such as primary surgery and adjuvant chemotherapy.

Materials and Methods

The study group included 319 ovarian cancer patients, FIGO Stage III and IV, treated at the Department of Gynecological Oncology Memorial Cancer Center, Institute of M. Sklodowska-Curie from 1999 to 2002. Within this group 150 patients were treated in our department from the beginning – meaning the primary surgery; 169 women were admitted to our department to receive postoperative adjuvant chemotherapy only.

Among 150 patients who started treatment in our center, neodjuvant chemotherapy was administered in 50 cases; a PT regimen was given (paclitaxel 135 mg/m^2 with cisplatin 75 mg/m^2 every 3 weeks). Twenty-nine of these 50 women were qualified for preoperative chemotherapy due to their poor general condition. Within this group ovarian cancer was diagnosed when the following criteria were fulfilled: presence of adenocarcinoma cells in ascites, negative results of gastroscopy and colonoscopy, and the ratio of CA125/CEA values > 100 x. The other 21 patients were treated with neodjuvant chemotherapy because of non-resectable lesions diagnosed at CT or exploratory laparotomy.

Eighteen patients were operated on after three courses of a neo-adjuvant PT regimen (group 1). The remaining 32 patients were operated on after six cycles of chemotherapy as mentioned above (group 2). Patients were assigned to the adequate group according to the results of chemotherapy which were evaluated after three cycles of neo-adjuvant treatment. CT and ultrasound examination results as well as CA125 level were considered. Decrease in tumor diameter of more than 50% compared to the

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primary mass, and drop in CA125 level of the same percent were the necessary conditions to perform surgery after three cycles of chemotherapy - group 1. For patients not responding to these criteria, chemotherapy was continued to six cycles, and then surgery was performed - group 2.

The patients in group 1 received an additional three courses of the PC regimen (cisplatin 75 mg/m^2, cyclophosphamide 750 mg/m^2) in case of lack of clinical and marker remission after six cycles of the PT regimen (3 cycles of PT before and 3 cycles of PT after surgery). Each course of PC was repeated every three weeks. The patients in group 2 received an additional three cycles of the PC regimen in case of absence of pathological remission in the postoperative report. Follow-up in both groups was provided every three months as a routine, and the date of recurrence or death was reported.

Within group 1, all patients received all cycles of chemotherapy that were planned. In group 2, topotecan was administered to two patients due to rapid progression (dose - 1.5 mg/m^2 1-5 day, every 3 weeks). These results were compared to therapy results of 269 patients who were treated conventionally – primary surgery and then adjuvant PT chemotherapy - group 3. The conventional treatment procedures were successfully finished in 238 patients. In 31 cases the treatment had to be discontinued because of serious side-effects or intolerance of chemotherapy. However, these women were also introduced into the analysis.

The side-effects were divided into two groups: caused by surgery and chemotherapy. The former meant all complications without fever lasting less than 48 hours. Only the patients operated on at Memorial Cancer Center were involved in this part of the analysis because of paucity of information in the patients' operative records from other hospitals. Chemotherapy side-effects were classified according to NCI Version 2 Criteria. Adverse effects of grade 3 and 4 were introduced into the analysis.

Statistical analysis was done by using program Statistica 5.0. The comparison of the features between groups was performed using the chi-square test. The ANOVA and Kaplan-Meier tests were used to assess disease-free survival as well as the influence of some clinical and histological parameters on treatment results and number of complications.

Results

The mean age of the analyzed group of 319 patients was 54.8 ± 11 years. FIGO stages, histological types and tumor grading are presented in Table 1. There was no statistical difference between groups 1+2 and 3.

The time interval between operation and chemotherapy administration was 38 ± 26 days for the patients operated on outside of the Memorial Cancer Center. In comparison, the patients operated on in our Department received chemotherapy after 16 ± 6 days from the surgery.

Primary optimal cytoreduction was achieved in 113 women i.e. 35.4% of cases. Lymphadenectomy was performed in only 66 cases; systematic paraaortic and pelvic lymph node excision was done in 34 women only. Table 2 presents some of the features connected with the treatment side-effects, characterizing all analyzed groups of patients.

Analysis of number of deaths confirms that all 17 women died because of ovarian cancer. The small number of deaths did not allow us to predict the 5-year survival.

The criterion of disease-free survival was used for the analysis of treatment results. Figure 1 presents a diagram showing disease-free survival within these three groups of patients. As shown, there are similar, comparable results in the disease course between the patients treated with

Table 1. — *Clinical and pathologic features in the analyzed groups.*

Feature		Number	Percent	Group 1	Group 2	Group 3	p
Clinical stage	IIIa	31	9.7	1	0	30	NS
	IIIb	9	2.8	2	1	6	
	IIIc	256	80.2	14	29	213	
	IV	23	7.3	1	2	19	
Serous adenocarcinoma		166	52.1	11	23	132	NS
Mucinous adenocarcinoma		27	8.6	0	2	25	
Endometrioides adenocarcinoma		69	21.4	3	4	62	
Clear cell adenocarcinoma		28	5.7	2	2	24	
Solid adenocarcinoma		18	9.2	2	1	15	
Others		9	2.7	0	0	9	
Lack of data		2	0.3	0	0	2	
G1		34	10.6	0	1	33	NS
G2		123	38.5	2	9	112	
G3		122	38.3	12	19	91	
Lack of data		40	12.6	4	3	37	

Table 2. — *Therapeutic and complication features in the analyzed groups.*

Feature	Group 1	Group 2	Group 3	p
Optimal cytoreduction	79%	84%	35.4%	< 0.001
Lymphadenectomy	50%	56%	10%	< 0.001
Adjuvant chemotherapy - 6 cycles	100%	96%	93%	NS
Percentage of complete remission (including pathological*)	33.3%	56.2%	64%	0.04
	5.5%*	6.2%*		NS
Percentage of surgical complications	16.6%	15.6%	19%	NS
Percentage of chemotherapy complications	5.5%	15.5%	13.2%	NS

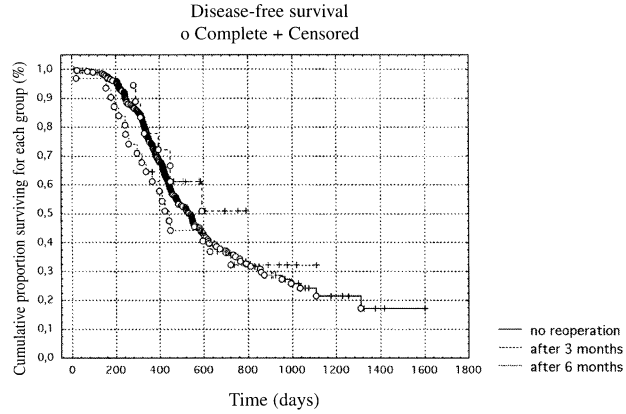

Figure 1. — Disease-free survival in the analyzed groups.

primary surgery and adjuvant chemotherapy (group 3), and the patients who received three cycles of neo-adjuvant chemotherapy (group 1). The median disease-free survival was 19 and 20 months, respectively (p = 0.42).

These results do not differ significantly from the group of patients with surgery performed after six cycles of neo-adjuvant chemotherapy (group 2). In this situation, the median disease-free survival was 15 months (p = 0.27).

Multivariate analysis confirmed that the following factors influenced the treatment results: tumor optimal cytoreduction and tumor grading. The time interval between surgery and chemotherapy initiation did not effect the therapy results at all. The outcomes of treatment in patients after lymphadenectomy performed was on the border of statistical significance (p = 0.06).

The number of complications, caused both by surgery and chemotherapy, did not differ significantly in the analyzed material. Chemotherapy duration was comparable in the analyzed groups, and lasted 118 ± 27 days on average.

Discussion

Ovarian cancer is a big challenge for gynecological oncologists due to non-satisfactory treatment results. The percent of patients who are in advanced stage at the time of diagnosis is still over 70%, and this factor has an extreme impact on the final therapy outcomes [1, 2].

The benefits of cytoreductive surgery as well as chemotherapy in the treatment of advanced ovarian cancer are well documented [2-6, 8]. Bristow *et al.* [6] showed that optimal surgery prolongs the survival interval for 11 months compared to sub-optimal operations. Moreover, every 10% increase in the extension of cytoreductive surgery is connected with a 5.5% longer survival.

However, it is not possible to achieve optimal cytoreduction in all cases. Investigations of prognostic factors that could allow prediction of tumor resectability are still continuing [7].

Operations fulfilling all the criteria of optimal cytoreduction constituted 35.4% of the analyzed material. However, it should be emphasized that there were only 66 cases of lymphadenectomy performed in the examined population which is a consequence of the fact that these patients were operated on by general gynecologists and not by gynecological oncologists. One hundred and sixty-nine patients were operated on outside of Memorial Cancer Center.

The significant number of non-optimal operations encourages us to the search for new ways and solutions in the treatment of ovarian cancer patients, paying special attention to the chemo-sensitivity of this neoplasm. Lawton *et al.* [8] reported treatment results with using neo-adjuvant chemotherapy in 36 patients. Within this group, cytoreductive operations were performed in 28 patients, with residual tumor mass less than 2,cm in 89%. Jacob *et al.* [9] presented the outcomes of their experience, emphasizing that optimal cytoreduction was achieved in 77% of patients after neo-adjuvant chemotherapy administration (residual tumor diameter < 2 cm). Within the control group that percentage was barely 39%. Survival outcomes did not differ significantly between these two groups. Similar results were published by Surwit *et al.* [10] who achieved 55% of optimal operations (residual tumor diameter less than 1 cm) in patients treated with neo-adjuvant chemotherapy based on the platinum derivative.

Our results confirm observations of other authors on the role of neo-adjuvant chemotherapy in the course of ovarian cancer. In the case of patients with primary operations, the percentage of optimal cytoreductions did not exceed 35.4%, while within the groups treated with neo-adjuvant chemotherapy there were twice as many optimal operations. An increase in the number of surgical complications was not observed. Similar observations, even with a smaller number of surgical complications, are reported by other authors [4, 8-12].

The significant increase of optimal cytoreduction proportion after neo-adjuvant chemotherapy, however, did not cause considerable improvement in the overall treatment results of advanced ovarian cancer patients. Both in the reported data and in our study, therapy results are similar between the adjuvant and the neo-adjuvant (3 cycles) groups. It should be simultaneously emphasized that, within the neo-adjuvant groups there were patients who were not qualified for primary surgery due to their poor general condition. There were 29 patients with such indications for neo-adjuvant chemotherapy in our group. This fact gives undeniable evidence that the "non-operable" patients at the beginning of therapy achieve measurable therapeutic benefit from such treatment.

Kuhn *et al.* [13], while analyzing therapy results after neo-adjuvant chemotherapy in the selected group of FIGO Stage IIIC, accomplished a significant improvement in median survival in the group treated with cytotoxic drugs preoperatively. The median survival was 42 and 23 months, respectively (p = 0.007). In most of the reported data, the number of neo-adjuvant chemotherapy cycles varied from two to five (average - 3). Such procedure seems to be the most justifiable.

The treatment outcomes of patients who were primarily "non-resectable" and who were later operated on after six cycles of chemotherapy have not been analyzed so far. The results of our study, evaluating the efficacy of surgery performed after six cycles of neo-adjuvant chemotherapy, bring the sense of purpose of such procedure into question. As a matter of fact, the difference in disease-free survival between groups 1 and 2 is not significant statistically, however, the marked trend concerning the shortening of disease-free survival in group 2 (20 vs 15 months) is rather embarrassing. Therefore re-operations in patients after administration of six chemotherapy cycles seem to be an idea that requires further studies.

Within group 2, the larger number of complete clinical remissions was achieved as compared to the group operated on after three chemotherapy cycles. However, this fact did not have a beneficial effect on median disease-free survival. The distinctive feature is the comparable number of complete pathological remissions within both groups of re-operated women; a fact that may give evi-

dence to the difference in tumor biology between the two groups. This fact is indirectly confirmed by the difference in the rate of CA125 level dropping, as well as the regression of tumor size measured objectively with CT scans. It seems to be justifiable to operate on patients after three cycles, or to continue chemotherapy to the standard six cycles in cases with no clinical or marker remission. The analyzed material concerning re-operations was composed of 50 patients, of which 18 patients only were operated on after three cycles of chemotherapy; therefore this report is treated as a preliminary one.

Unfortunately, the following factors affected the quality of the analyzed material: the small number of the patients operated on according to the FIGO protocol, i.e., lymphadenectomy, and the considerable number of patients operated on outside Memorial Cancer Center, where the extension and size of the intraabdominal tumors were not always described in detail. These factors may have influenced the objective evaluation of the residual disease. Therefore, it is quite difficult to form and draw any final conclusions, even more so as the average observation time was 35 months (5 to 62 months).

The prognostic value of lymphadenectomy in advanced ovarian cancer is not precisely defined, and requires further studies. Allen *et al.* [14] showed that in Stage III ovarian cancer patients, the 5-year survival was 38% in the lymphadenectomy group, whereas it was only 22% in the group without lymphadenectomy performed. Di Re *et al.* [15] also showed a much better prognosis in the group with the lymph nodes dissected (46% vs 30%). In our study analysis the prognostic value of lymphadenectomy is on the border of statistical significance. An interesting, although controversial, observation is that the time interval from surgery to chemotherapy administration did not influence the treatment results. However, this factor will be the subject of a separate analysis, because the time criteria have not been defined precisely in this study.

The adjuvant treatment using paclitaxel improved the chemotherapy results in the treatment of ovarian cancer. This was confirmed by the GOG 111 and OV – ten studies [16, 17]. Unfortunately, the introduction of this drug as the neo-adjuvant chemotherapy can not be evaluated univocally as more effective than the regiments using cisplatin itself.

At present, there are two randomized clinical studies going on, with the endpoint to evaluate the efficacy of neo-adjuvant chemotherapy. The PC regimen is used and evaluated in the EORTC study, whereas the GOG 152 study evaluates paclitaxel and carboplatin. The results presented so far, unfortunately, do not allow for any final evaluation of the usefulness of such procedure.

Conclusions

On the basis of our material analysis, it should be emphasized that the number of treatment complications, both surgical and chemotherapeutic, did not differ significantly between the adjuvant and neo-adjuvant groups. This fact also confirms the thesis that the value of neo-adjuvant chemotherapy should be accurately studied and evaluated; however, the results of retrospective analyses which have been reported up to now, give evidence of the usefulness of this method in selected groups of patients with advanced ovarian cancer.

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