Neoadjuvant chemotherapy in ovarian cancer

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Summary

Patients with advanced ovarian cancer have a chance of less than 50% after radical debulking surgery. In spite of the currently more effective combination chemotherapy agents that have become available as adjuvant therapy in the last decade, the prognosis of patients with residual tumor mass larger than 1 cm in diameter following surgery is still poor. Neoadjuvant or primary chemotherapy has been suggested as an alternative approach to primary laparotomy of the bulky ovarian cancer. The advantages and available data on neoadjuvant chemotherapy are discussed in this review.

Key words: Neodjuvant chemotherapy; Ovarian cancer.

Introduction

Ovarian cancer is the leading cause of death for women with gynecologic malignancies in most industrial countries. The incidence rises significantly with aging and reaches a maximum in women between 70 and 74 years. Despite significant improvement in multimodal therapy (surgery, chemotherapy, and/or radiotherapy), the final overall 5-year survival is only 40-50 % [1].

Because early-stage ovarian cancer is usually asymptomatic, more than-two thirds of cases are diagnosed at advanced stages (FIGO stage III and IV), where the tumor has spread within and even outside the abdomen. The stage of the disease at diagnosis is known to be the most important prognostic factor in ovarian cancer. The average 5-year survival rates of stage I through IV change from 80% to 15%. Thus any improvement in the treatment will give some help in the fight against ovarian cancer.

The importance of optimal debulking surgery

Approximately 70% of patients present with advanced ovarian cancer, a stage when total resection of all tumor is usually impossible. Investigations on the current treatment are still far from producing optimal results. Today's standard approach is surgery, which is required for accurate staging as well as cytoreduction and adjuvant therapy (chemotherapy and/or radiotherapy). The role of whole abdominal radiation therapy in the treatment of ovarian cancer is still controversial. However, since surgery cannot cure advanced disease, it should be supported with platinum-based combination chemotherapy. Within the last decade, after paclitaxel came on the market, the average 5-year survival for all stages significantly increased to approximately 50% [2]. The combination of paclitaxel with platinum derivates is currently accepted as the most effective systemic therapy for ovarian cancer [3].

Primary surgery for epithelial ovarian cancer consists of bilateral salpingo-oophorectomy, lymph node dissection, omentectomy, and maximal surgical reduction (debulking) of the tumor. After optimal debulking surgery, changes in the biology of the small residual tumor – which consist of increased growth fraction, less chance of drug resistance, and enhancement of immune responses – leads to increased chemosensitivity, and thus may bring about an improved prognosis.

Several non-randomized studies have shown improved survival of patients with less than 1 cm diameter of residual tumor after primary surgery compared to patients with larger ones. However, authors have defined optimal or adequate debulking differently. Hacker [4] revealed that even more cytoreduction - leaving tumors smaller than 0.5 cm - was of additional benefit when compared to 0.5-1.5 cm and >1.5 cm, leading to an increased overall survival of 40, 18 and six months, respectively. In addition, a retrospective analysis of patients with stage III carcinoma presenting with large volume extrapelvic disease, who were successfully debulked to residual tumor less than 1 cm in diameter, did not have as good a prognosis as those patients presenting with small volume extrapelvic disease, which did not need additional cytoreduction [5]. A recently published meta-analysis performed by Bristow *et al.*, confirms the importance of maximal cytoreduction on survival and it turned out that each 10% increase in cytoreduction was associated with a 6.3% increase in survival [6]. Moreover, controversy that the observed survival benefits for cyto-reduced patients are a function of surgical skill, tumor biology or both is still ongoing. Some investigators believe that surgical treatment of ovarian cancer by an experienced gynecological oncologist as a member of multidisciplinary team improves patient prognosis [7]. Additionally, the relapse risk after completion of primary therapy increases in the presence of a more advanced FIGO stage, large residual disease after initial surgery, and poor tumor grade [8]. Taken together these studies suggest that aggressive surgery is important in the treatment of epithelial ovarian cancer, and that tumor biology will also determine the success of the therapy.

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The value of debulking surgery after induction chemotherapy has been largely debated in the last decade. Since successful cytoreductive surgery is feasible in approximately 50% of patients with advanced ovarian cancer [9] and for all others who have only about a 15% 5-year survival rate [10], the concept of "primary or neoadjuvant chemotherapy followed by interval debulking surgery" has emerged. The term "neoadjuvant chemotherapy" has been used to define two different situations: the first is the application of chemotherapy soon after histopathologic verification of ovarian cancer by biopsy. In this group, after several courses of combination chemotherapy, surgical cytoreduction is performed during interval laparotomy. The second one is treatment with chemotherapy after suboptimal debulking surgery followed by interval laparotomy which is more commonly referred as induction therapy.

The preceding platinum-based combination chemotherapy could possibly reduce tumor masses, allowing for adequate surgical debulking at the laparotomy, thus improving the patient's prognosis. Several studies have been published on the rationale for "interval debulking surgery" which is a surgical procedure with debulking followed by chemotherapy. Many authors support [11, 12] or oppose [13, 14] this approach.

To date, only two prospective randomized trials have been published on the subject of neoadjuvant chemotherapy followed by interval surgery in advanced ovarian cancer. The first one evaluated the benefit of interval laparotomy in patients with suboptimally debulked ovarian cancer [15]. In this study, Redman *et al.*, randomized 79 women with residual tumor masses greater than 2 cm in diameter following primary surgery to receive either chemotherapy alone (n = 42) or chemotherapy in combination with interval laparotomy (n = 37). Median survival in the interval laparotomy group was 15 months versus 12 months in the chemotherapy alone arm. The difference was not statistically significant, but the total number of the patients was small for reliable interpretation.

The second randomized phase III trial by the EORTC study evaluated the benefit of interval surgery following three courses of chemotherapy with cisplatin + cyclophosphamide (CP) in patients with suboptimal surgical cytoreduction for ovarian cancer in FIGO stages IIb-IV [16]. Four hundred and twenty-five women with residual tumor >1 cm after debulking surgery were enrolled in the study, but only 278 patients' follow-up data were analyzed. After the diagnostic procedure, patients received three courses of cisplatin + cyclophosphamide (CP), and were then randomized to undergo interval laparotomy followed by another three courses of CP (n = 140) or three cycles of CP alone (n = 138). The patients who presented at surgery with tumor residue less than 1 cm following three cycles of CP had the best prognosis (mean survival 41.6 months), followed by those whose tumors could be adequately debulked (26.6 months) and had unsuccessful laparotomy (20 months). As a result, this study demonstrated the benefit of neoadjuvant chemotherapy.

In addition to these two randomized trials, several nonrandomized studies that evaluated the feasibility of neoadjuvant chemotherapy have been published (Table 1) [12, 14-24]. Most of them include small patient groups and both study design and chemotherapy regimens are different. Moreover, while some studies employed chemotherapy after unsuccessful debulking surgery, the other few trials were given chemotherapy prior to any cytoreductive surgery in patients unlikely to get optimal tumor reduction by primary surgery. In all studies, the indication for interval surgery was generally based on the response to chemotherapy. Overall, more than half of the patients were found eligible for interval laparotomy after systemic therapy. If interval laparotomy was performed,

Table 1. — *Neoadjuvant chemotherapy trials in patients with advanced ovarian cancer.*

Author	Stage (FIGO)	Neoadj. CT (n)	Residual tumor size before CT	CT regimen	IL (n)	Survival (Months)	Ref. no
Wils, 1986	n.d.	50	> 1.5 cm	CAP	24	3-year survival 25%	2
Neijt, 1987	n.d.	47	n.d.	CHAP or CP	47	3-year survival 30%	14
Lawton, 1989	III: 28 IV: 8	36	> 2 cm	PM or PABWC	28	n.d.	17
Ng, 1990	III: 32 IV: 11	27	> 1cm	CP	27	n.d.	18
Jacob, 1991	III: 17 IV: 4	22	> 2 cm	P-based	22	16	19
Lim, 1993	III: 20 IV: 10	30	> 5 cm	Carbo/Ifos	11	10.2	20
Redman, 1994	IIb: 6 III: 62 IV: 11	79	> 2 cm	CP or PABWC	25	15 (IL +) 12 (IL -)	15
van der Burg, 1995	IIb: 14 III: 203 IV: 61	278	> 1cm	CP	130	26 (IL +) 20 (IL -)	16
Surwit, 1996	III: 21IV: 8	29	n.d.	Carbo x 2 orP x 329	22.5	21	
Schwartz, 1999	III: 18 IV: 38	59	n.d.	P-based	41	17.5(IL+) 8 (IL -)	22
Huober, 2000	IIb: 2 III: 28 IV: 8	38	> 2 cm	PT	33	n.d.	23
Kayıkçıoğlu, 2001	III : 21 IV : 24	45	n.d.	CFP or TP	45	27	24

Abbreviations: IL: Interval Laparotomy; n.d.: Not determined; CT: Chemotherapy; P: Platinum; Carbo: Carboplatin; Ifos: Ifosfamide; C: Cyclophosphamide; CP: Cisplatin + Cyclophosphamide; CAP: Cisplatin + doxorubicin + cyclophosphamide; PAB: Cisplatin + doxorubicin + bleomycin; PM: Cisplatin + mitoxantrone, CHAP: Doxorubicin + cisplatin + hexamethylmel-amine + cyclophosphamide; PT: Cisplatin + treosulfan; CFP: Cisplatin + farmarubicin + cyclophosphamide; TP: Cisplatin+paclitaxel.

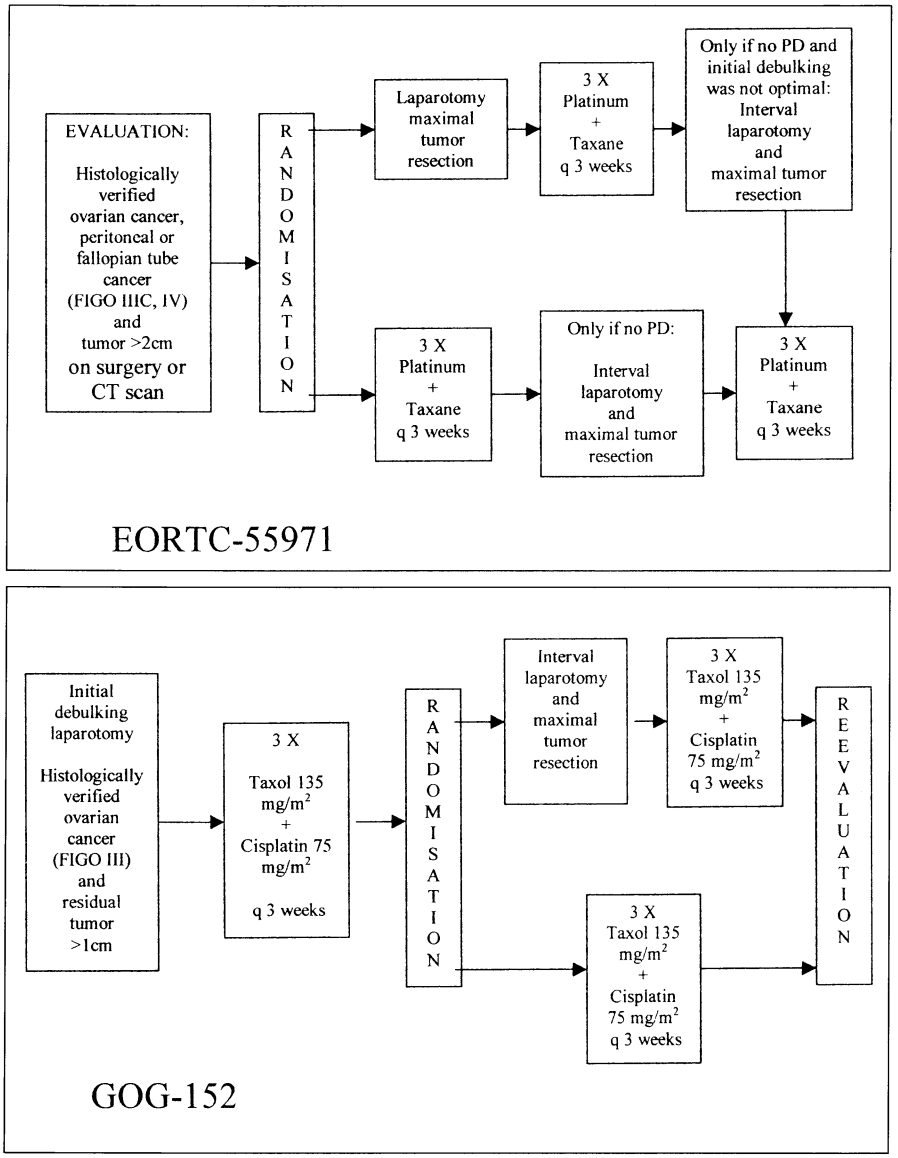

Figure 1. — Design of EORTC and GOG trials in patients with advanced ovarian cancer as a neadjuvant setting.

successful debulking surgery was possible in 52-82% of the patients, and in all studies (except Neijt *et al.*), this group had a better prognosis than those in which optimal cytoreduction was not possible after primary chemotherapy. Median survivals ranged from 10 to 27 months; these low results can be explained in that the highest fraction of patients were in stage IV disease. On the other hand, perioperative morbidity following combination chemotherapy was not increased. Moreover, some authors described less intraoperative hemorrhage and shorter stays in hospital [21, 22].

This does not imply that all patients should get interval cytoreduction. In most patients, it is still preferable to perform primary cytoreduction if the patient is referred to gynegological oncology departments where the relevant expertise is available. However, if primary suboptimal laparotomy has been performed at another hospital, it is reasonable to give two or three courses of chemotherapy before further surgery.

Neoadjuvant chemotherapy in other ovarian tumors

Germ cell tumors of the ovary are the most frequently seen in children and teenagers and are commonly divided into two groups, dysgerminomas and non-seminomatous malignant germ cell tumors. The last one consists of immature teratomas and different types of germ cells. Since these tumors are less common in adulthood and rarely diagnosed before a surgical procedure, there is no data on the neoadjuvant chemotherapy. Baranzelli *et al.*, stressed that up-front chemotherapy or chemotherapy following limited biopsy might be a rational approach to the pediatric patient group with advanced stage (III, IV and unsuccessfully resected I-II) non-seminomatous germ cell tumors of the ovary [25]. In another case report,

Chao claimed that GNRH-agonists can be used to manage testosterone secreting ovarian tumors in a neoadjuvant setting especially as an alternative therapy for the patients who have had some problems with urgent surgery.

Ongoing clinical trials

There are currently two ongoing prospective randomized trials studying the impact of the different approaches employing interval debulking surgery with or without neoadjuvant chemotherapy (GOG-152 and EORTC-55971). The designs of the GOG and the EORTC trials are demonstrated in Figure 1.

The GOG-152 protocol has the same design of the former EORTC trial (16) except for substituting CP with the current standard combination of cisplatin and paclitaxel. The EORTC trial was started with the plan to recruit approximately 700 patients with advanced ovarian cancer or presence of tumor masses greater than 2 cm after surgery or CT scan.

Conclusion

Based on the above reported data one could conclude that tumor reduction with primary surgery even in patients with suboptimal cytoreduction results in a survival benefit. With neoadjuvant approaches to patients with bulky disease several advantages may be added: reduction in tumor volume, ascites or pleural effusions could improve patient performance status before the surgical procedure, and preceding debulking of the tumor with combination chemotherapy might result in an increased rate of maximal surgical cytoreduction which could translate into an improvement in survival and decrease in operative morbidity.

Preoperative diagnostic tools have been applied to estimate the extent of disease and distinguish patients suitable for primary surgery or primary chemotherapy. CT scans are highly accurate in predicting cytoreductibilty (67%) with some limits (e.g., retroperitoneal nodes, tumor in the gallbladder fossa or liver surface inadequately evaluated) [26]. Other clinical parameters such as preoperative ascites volume or CA-125 levels did not prove to be an additional factor. Laparoscopy could be used with lower morbidity than laparotomy to improve accurate estimation of the extent of disease. In fact, Vergote reported laparoscopic staging as a non-invasive and useful approach with low morbidity to evaluate the operability of gynecologic tumors and emphasized the advantage of visuality of metastatic disease on the upper abdomen, liver, diaphragm, and other sites of peritoneum [27]. Trocar-site metastases may occur but can be excised easily in all patients and will not influence outcome. Both the EORTC and GOG trials will clarify the feasibility and safety of laparoscopic staging and other non-invasive diagnostic methods.

After the use of platinum with taxanes in the treatment of advanced ovarian cancer, no additional progress has been made. Other newly developed drugs to improve the prognosis of ovarian cancer are still being debated.

At our institution, we give neoadjuvant chemotherapy under the following circumstances:

1. patients who are considered medically unfit for primary surgery,
2. patients with a large pleural effusion,
3. patients with parenchymal liver metastasis and
4. patients with peritoneal carcinomatosis.

The authors believe that after the results of two randomized, prospective, multicenter trials become available, the use of neoadjuvant chemotherapy followed by debulking surgery may be accepted as a standard procedure for the treatment of advanced ovarian cancer. Until the results of these studies are known, this approach should be regarded as experimental and must not be used as standard therapy.

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