Review Article

Neoadjuvant chemotherapy in gynecological cancers

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Summary

Neoadjuvant chemotherapy in gynecological cancers is an approach that is shown to have positive effects on survival. It increases the rate of resectability in ovarian and cervical cancers and thus contributes to survival. However, there are studies reporting that despite increasing operability, the approach does not make any changes in terms of survival. Nevertheless, no negative effects have been reported in studies conducted till today. Prospective and randomized well-designed studies that encompass a high number of cases and parameters, including cost-effectiveness, are needed in both types of cancers. Until the results of such studies are obtained, neoadjuvant chemotherapy may be taken into consideration as an alternative when conventional methods do not suffice. The number of studies concerning endometrial, vulvar and vaginal cancers are few in the area of neoadjuvant chemotherapy.

Key words: Gynecologic cancer; Chemotherapy; Neoadjuvant chemotherapy; Ovarian cancer; Cervical cancer; Vulvar cancer; Endometrial cancer.

Introduction

Failure in the treatment of advanced stages and/or recurrent genital cancers in women points out the need for research on different treatment modalities. The fact that use of chemotherapy in addition to surgery and/or radiotherapy particularly in ovary and cervix cancers has been demonstrated to considerably contribute to the extension of life-spans of the concerned patients has drawn attention to this field. Chemotherapy in gynecological cancers is applied in adjuvant, concomitant or neoadjuvant forms. Recently, there have been many studies on neoadjuvant chemotherapy in gynecological cancers in parallel to the other applications and the results are optimistic.

Neoadjuvant chemotherapy refers to the use of chemotherapy for three to six cycles before surgery of tumors that are confirmed by biopsy and deemed unsectable. The use of chemotherapy during the period before secondary cytoreduction following suboptimal surgery is known as induction chemotherapy. Although unresectable tumors are common in both conditions they are different entities. Suboptimal surgery is performed in the second and therefore should be considered separately. Neoadjuvant chemotherapies in gynecological cancers will be discussed but other areas of application for chemotherapy will not be addressed.

Neoadjuvant chemotherapy in ovarian cancer

Primary treatment of epithelial ovarian cancers has for a long time been cytoreductive surgery aimed at total excision of the tumor. Cytoreduction, which maximally reduces the tumor load, is the key point of treatment for ovarian cancer. The result of a meta-analysis demonstrated that there was a positive correlation between the rate of cytoreduction and median survival and a negative one between the former and the amount of residual tumor [1]. Therefore, the standard mode of treatment that is currently considered acceptable in advanced-stage and/or high-risk patients is cytoreductive surgery followed by chemotherapy [2]. Standard adjuvant chemotherapy is a combination of paclitaxel and carboplatinum [3]. Prognosis is poor in cases where optimal cytoreduction can not be performed and in those with residual tumor [4]. However, despite the advances in surgical methods, total excision of the tumor or excision within the limits of optimal cytoreduction in advanced ovarian cancers is not always possible. The neoadjuvant chemotherapy approach has been developed as a concept that offers the opportunity for optimal cytoreduction in such cases. Neoadjuvant chemotherapy in ovarian cancers is applied after histopathologic diagnosis. Following several cycles of chemotherapy interval cytoreduction is performed. Biopsy material is obtained in several different ways: laparatomy, laparascopy and open laparascopy.

The benefits hoped to be reaped from this chemotherapy application are reduction of the tumor so as to allow surgery and to obtain the infrastructure required to improve the patient's performance. Surgery is the indispensable mode of treatment in ovarian cancers and thus all these modifications in chemotherapy aim at paving the way for optimal cytoreduction.

Revised manuscript accepted for publication June 19, 2005

Neoadjuvant chemotherapy preceding surgery may provide a significant reduction in tumor load and facilitate optimal cytoreduction. In a study by Mazzeo *et al.* [5] optimal cytoreduction was achieved after neoadjuvant chemotherapy in 53% of cases whose tumors were primarily considered unresectable. Survival of these cases was longer than for those in whom optimal cytoreduction could not be performed (41 months versus 23 months). Similarly, Vrscaj *et al.* reported in a study with Stage IIIC and IV cases that radicalism of cytoreduction increased significantly in those patients who received neoadjuvant chemotherapy [6].

In a study including advanced stage (FIGO Stage III and IV) ovarian cancer cases who were referred after initial laparotomy and biopsy and matched in terms of FIGO stage, age, grade and histological type, Jakob JH *et al.* compared cases who had cytoreduction by immediate reexploration and those who had interval cytoreduction after 2-4 cycles of neoadjuvant chemotherapy. Optimal cytoreduction to less than or equal to 2 cm could be performed in 77% of cases who had interval cytoreduction while the rate in those who had immediate-reexploration was 39%. Survival of cases who had optimal cytoreduction was longer in comparison to those who did not have optimal cytoreduction (18.1 months vs 7.5 months) [4].

When it comes to the possibility of optimal cytoreduction a number of aspects should be again revised. These include the definition of optimal cytoreduction and the experience of the surgeon and the center where optimal cytoreduction is performed. In a number of different studies optimal cytoreduction is defined differently depending on the residual tumor diameter, which can range from 0.5 cm to 2 cm [7]. Vergote *et al.* reported in their study that total residual tumor volume was more important than the diameter of the largest residual tumor. In the concerned study, optimal cytoreduction was defined as residual tumor volume less than 1 x 1 cm or 1 g [8].

Experience of the center and the surgeon is very important in the success of optimal cytoreduction. While the rate of optimal debulking of advanced-stage tumors in multi-center studies is reported to be 50% or lower, the same rate rises to 75-90% when the same procedure is applied to similar cases at experienced centers by a gynecological oncologist [9]. Life-threatening postoperative complications are rarer when primary surgeries are performed in specialized departments. However, this depends on the aggressiveness of the surgery apart from the experience of the center and the surgeon. The higher the degree of optimal cytoreduction, the higher the rate of postoperative complications [10]. In this respect, neoadjuvant chemotherapy may decrease postoperative complications at experienced centers by reducing the need for aggressiveness in surgery.

Neoadjuvant chemotherapy offers cases that are inoperable because of low-performance status the survival advantage of cytoreduction. Schwartz *et al.* [11] compared patients who were treated by conventional methods (primary surgery and adjuvant chemotherapy) and those who had neoadjuvant chemotherapy followed by cytoreductive surgery, and found that there was no difference in terms of progression-free survival and overall survival although the cases who received neoadjuvant chemotherapy were older and had poorer performance status. In addition, intraoperative blood loss and the period of stay in the intensive care unit and the hospital were significantly lower in those who were given neoadjuvant chemotherapy. Moreower, in another study by Schwartz *et al.*, there was again no difference between the two groups in terms of progression-free survival and overall survival [12].

In a study with cases who had FIGO Stage IIIC tumor and acid volume over 500 ml, Kuhn et. al. compared neoadjuvant chemotherapy (3 cycles of platinum/taxane-based chemotherapy followed by interval debulking surgery) and conventional treatment (tumor debulking surgery followed by 6 cycles of platinum/taxane-based combination chemotherapy) in terms of tumor resection rate, need for blood transfusion, morbidity, mortality, duration of surgery and median survival. Tumor resection rate was found significantly higher in those receiving neoadjuvant chemotherapy than those who had conventional treatment. Median survival was also found significantly higher in the neoadjuvant chemotherapy group (42 months vs 23 months). However there was not any difference between groups regarding need for blood transfusion, morbidity, mortality and the period of surgery [13].

In a French study including Stage IIIC and IV cases, optimal cytoreduction was successfully performed in 91% of cases who were considered unresectable at the first surgery. It was reported in the same study that neoadjuvant chemotherapy could be useful in distinguishing chemo-sensitive patients and that aggressive surgery could be avoided in chemo-resistant cases who are known to have poor prognoses despite everything [13]. Another, recent study reported that the use of neoadjuvant chemotherapy led to an improvement in functional status and overall quality of life of the patients who had advanced stage ovarian tumors [15].

As a result, studies concerning the use of a neoadjuvant chemotherapy approach in advanced stage ovarian tumors have hitherto reported that this approach enabled interval cytoreduction, increased the rate of optimal cytoreduction, and as a result extended survival and elevated the quality of life. However, the use of different chemotherapy protocols (and at different dosages), cytoreduction with various definitions, the surgical experience of the centers, initial staging procedure and performance status of the patients are not standardized. Therefore, well designed, prospective, randomized studies are needed. Until the results of such studies are obtained neoadjuvant chemotherapy may be employed as an alternative after getting histopathologic confirmation in cases of advanced stage patients (FIGO Stage IIIC and VI), total metastatic tumor load greater than 1,000 g, poor performance status, presence of unresectable tumor, and presence of uncountable plaque-shaped peritoneal metastases [7].

Neoadjuvant chemotherapy in cervical cancer

Primary treatment in cervical cancers is surgery, radiotherapy or a combination of the two. However, results obtained with these treatments are not satisfactory and thus the possibility of using chemotherapy regimes that are used extensively in many types of cancer was put on the agenda. At the end of years of research, several studies were published in the last decade showing that chemotherapy regimes could be utilized in patients with cervix cancer. At present chemotherapy in cervical cancer has three areas of use. These are primary treatment, radiation sensitizer and neoadjuvant chemotherapy treatments (16). In this part, neoadjuvant chemotherapy given before surgery will be discussed.

As known, numerous studies concerning neoadjuvant chemotherapy have reported that it increased surgical resectability and survival in early, recurrent and advanced cervical cancers. Panici *et al.* gave neoadjuvant chemotherapy including cisplatinum, bleomycin and methotrexate to locally advanced cervical carcinoma cases with FIGO stage between IB and III and obtained 50% complete and 68% partial response. When pretreatment characteristics were analyzed in the response given to neoadjuvant chemotherapy, it was found that the response was poorer in case of bilateral parametrial affection and tumor diameter larger than 5 cm. Three-year survival rates of cases who responded to neoadjuvant chemotherapy were apparently better than the rates of those who did not respond. In these cases the average number of excised lymph nodes was 60 and lymph node affection incidence was lower than expected. Twenty out of 62 operated cases had recurrence. The prognostic factors for recurrence were found to be parametrial affection and cervical infiltration deeper than 5 mm. Three-year disease-free survival rates for Stage IB-IIA, IIB and III were 89%, 73% and 43%, respectively. The same rates in operated cases were 100%, 81% and 66% [17].

Namkoong *et al.* compared in their study 92 locally-advanced, Stage IB, IIA and IIB cervical cancer patients who had neoadjuvant chemotherapy before radical surgery with patients who had the same status but had radical surgery without neoadjuvant chemotherapy. In this study an 87% response to neoadjuvant chemotherapy was obtained in squamous cell carcinoma. Pelvic lymph node metastasis (34% vs 17%) and recurrence (35.5% vs 18.5%) were higher and disease-free survival was shorter in those who did not receive neoadjuvant chemotherapy. All these differences were significant [18].

Sardi *et al.* investigated the effects of administering three courses of neoadjuvant chemotherapy including 50 mg/m^2 cisplatinum, 1 mg/m^2 vincristine and 25 mg/m^2 bleomycin on survival. Stage IB patients were divided into two groups: Group I included 103 patients, 56 of whom had bulky (4 cm and over) tumor and were treated with surgery (Wertheim-Meigs) and adjuvant radiotherapy. One hundred and two patients (61 bulky) in Group II were given neoadjuvant therapy before these treatments; 67-month (31-102 months) median follow-up showed that there was no difference (77% vs 82%) between survival and disease-free survival of 2-4 cm tumors whereas the difference in bulky tumors (80% vs 60%) was significant. Operability in cases of bulky tumors given neoadjuvant therapy was 100%, while the rate in those who did not receive neoadjuvant therapy was 85%. Recurrence was found significantly lower in those receiving neoadjuvant therapy. The authors suggested in this study that with a free-survival margin neoadjuvant chemotherapy can improve survival in bulky tumors due to increased operability and reduced pathological risk factors [19].

In a prospective randomized clinical study, including 192 squamous cell carcinoma, Stage Ib-IIb cases, Napolitano *et al.* administered 106 cases three courses of neoadjuvant chemotherapy containing cisplatinum, vincristine and bleomycin and treated 86 cases with conventional radiotherapy or surgery. Five-year survival rates in Stage Ib-IIa cases were 78.6% in those who received neoadjuvant therapy and 73.2% in those who had conventional treatment; the rates in Stage IIb patients were 68.7% and 64.3%, respectively. There was no significant difference between groups. As for 5-year disease-free survival, the rate in Stage Ib-IIa cases was 77.1% in those who had neoadjuvant therapy and 64.3% in those who had conventional treatment. The difference between the two was significant. The rates in Stage IIb cases were 56.2 and 57.1%, respectively, the difference being insignificant [20].

Chank *et al.* divided Stage IB-IIA cervical cancer patients with bulky tumors (4 cm and over) into two groups. One of the groups was given neoadjuvant chemotherapy and then subjected to radical hysterectomy; the other group received only primary radiotherapy. Cisplatinum 50 mg/m^2 and vincristine one mg/m^2 for one day and bleomycin 25 mg/m^2 was used in three cycles as neoadjuvant chemotherapy. The 39-month median follow-up did not show a significant difference regarding disease-free survival and overall survival [21].

A study by Hung *et al.* reported the results of 162 patients with Stage IB-IIA early phase bulky cervical cancer. The patients were given three cycles of neoadjuvant chemotherapy containing cisplatinum, vincristine and bleomycin and after that they underwent radical hysterectomy and pelvic lymphadenectomy. Rates of overall survival and relapse-free survival in the whole series were reported as 69% and 65%, respectively [22].

Neoadjuvant chemotherapy is studied less in cervical adenocarcinomas. Most of the present studies are about squamous cell carcinomas. There are a number of studies concerning adenocarcinomas, though not many. In one of these, neoadjuvant therapy in the form of intraarterial cisplatinum and doxorubicin was given to 16 cervical adenocarcinoma cases (Stage IIa-IIIb), who had not received any treatment before, and significant changes in mean tumor volume were obtained. Clinical response was found to be 58.3% in this study [23]. In another study on cervical adenocarcinoma 25% complete response was obtained in Stage Ib-III cases with neoadjuvant chemotherapy. A reduction of 50% in volume was seen in all cases [24].

As a result, neoadjuvant chemotherapy provides significant increases in the survival and disease-free survival of cervical cancer patients within tolerable limits of toxicity.

Neoadjuvant chemotherapy in vulvar cancer

Vulvar squamous carcinomas make up 4-8% of all gynecological cancers. When the diagnosis is given, 40% of the patients are at advanced stages like Stage III and IV [25]. Patients are treated primarily with surgery, radiotherapy or a combination of the two and about 25% of the patients treated develop recurrence [26]. Traditionally, the most important aspect investigated for vulvar cancer is how to reduce the radicalism of the surgery. For this purpose radiation, chemo-radiation and less radical surgical modalities have been used before surgery. One of the preoperative regimes used on this basis is neoadjuvant chemotherapy. The number of studies on this modality is fairly limited. Considering the encouraging results obtained from neoadjuvant chemotherapy in local advanced-stage cervical cancers, Benedetti *et al.* tried neoadjuvant chemotherapy in advanced stage vulvar cancers. In their study they used a neoadjuvant chemotherapy regime including cisplatinum, bleomycin and methotrexate and applied radical surgery for operable patients – 21 vulvar cancer cases in Stage IVa (TNM: 6 cases T2N2MO; 11 cases, T3N2MO; 4 cases, T4N2MO). Operability rate was found to be 90% and pathological down stage 33% in this study; 68% of operated cases showed recurrence in 3-17 months while 50% showed more remote recurrence [27].

A phase II study carried out by Wagenaar *et al.* included vulvar cancer patients in whom resection with standard radical vulvectomy was impossible (n:12) or who showed recurrence after incomplete resection (n:13). The patients were given a chemotherapy regime containing bleomycin, CCNU, and methotrexate, and resectability was investigated in cases who responded to chemotherapy. Two cases gave complete and 12 gave partial responses. In the 8-month median follow-up 18 cases died due to disease, two due to drug toxicity and two due to other diseases with only two patients surviving. Staging in this study was made according to clinical and radiological findings. Of the two surviving patients one was FIGO Stage II and the other III. Median survival was 7.8 months and progression-free survival 4.8 months with one-year survival reaching 32% [28].

As a result, the number of studies reporting neoadjuvant chemotherapy in vulvar cancer are few and results are not promising. Although there are studies reporting that response to neoadjuvant chemotherapy was noted, studies conducted with different chemotherapy regimes and different patient groups are not sufficient to give the last word on this topic.

Neoadjuvant chemotherapy in endometrial cancer

Endometrial cancer is the most common type of female genital cancer. Standard treatment is surgery at early stages as well as adjuvant radiotherapy depending on the pathological findings. There are very few studies on neoadjuvant chemotherapy in endometrial cancers. Chemotherapy is generally evaluated at advanced stages or in case of recurrence as an alternative to surgery or radiotherapy [29].

In their study on neoadjuvant chemotherapy Fujiwaki *et al.* administered neoadjuvant therapy in the form of intraarterial cisplatinum and doxorubicin to 16 endometrial cancer cases (Stage Ia-III) who had not received any treatment before. They evaluated the change in tumor volume using magnetic resonance imaging; 87.5% of cases showed clinical response and 12.5% showed complete response with tumor diameter showing a significant reduction in all cases [23]. Similarly, there are case reports demonstrating complete remission with neoadjuvant chemotherapy [30].

Uterine papillary serous carcinoma, an aggressive variant of endometrial cancer, was treated with neoadjuvant therapy in the form of carboplatinum and paclitaxel combination, and two cases were reported to show significant response [31, 32].

Neoadjuvant chemotherapy in vaginal cancer

Vaginal cancer is a very rare type among female genital cancers. Primary treatment at early stages is surgical excision preserving vaginal integrity. In addition, radiotherapy is the standard mode of treatment at early and advanced stages. The number of studies on the use of neoadjuvant chemotherapy in vaginal cancers is fairly limited [33].

In their study Long *et al.* administered neoadjuvant chemotherapy containing methotrexate, vinblastine, doxorubicin and cisplatinum to three advanced stage vaginal cancer cases who had not received any treatment before, and obtained objective regression [34]. In addition, there are case presentations in the literature reporting remission in cases who were given neoadjuvant chemotherapy before surgery [35, 36].

Conclusion

Use of neoadjuvant chemotherapy in gynecological cancers has been shown to have positive effects on survival in ovarian and cervical cancers. Neoadjuvant chemotherapy may be regarded an alternative, particularly in advanced-stage ovarian cancer cases where conventional approaches are insufficient. There are many studies demonstrating the positive effect of neoadjuvant chemotherapy on survival in cervical cancer. It is an important aspect of neoadjuvant chemotherapy to increase resectability especially in advanced stage and/or bulky tumors. Experience regarding the use of neoadjuvant chemotherapy in other gynecological cancers is fairly limited.

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