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Neoadjuvant Chemotherapy in Ovarian Cancer

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1. Introduction

Ovarian cancer is the second most common gynecological malignancy occurring in about 200,000 women worldwide out of which close to 125,000 die from the disease. In the United States, ovarian cancer is detected in about 21,000 women resulting in about 14,000 deaths (Parkin, Bray et al. 2005; Sankaranarayanan and Ferlay 2006; Jemal, Siegel et al. 2009). The majority of women diagnosed with ovarian cancer, are usually diagnosed in the advanced stage of the disease (Yancik 1993). This chapter highlights major developments that have led to emergence of neoadjuvant chemotherapy (NAC) as a useful strategy for managing advanced ovarian carcinoma.

For many years, primary cytoreductive surgery (PCS) followed by adjuvant chemotherapy with a platinum based agent has been the standard of care for management of advanced ovarian cancer (Griffiths 1975; 1994; Hoskins, McGuire et al. 1994; Curtin, Malik et al. 1997; Berek, Trope et al. 1999; Bristow, Tomacruz et al. 2002; Kyrgiou, Salanti et al. 2006). The Gynecologic Oncology Group (GOG) defines optimal cytoreduction as leaving residual disease less than one centimeter in maximum tumor diameter. Residual disease after cytoreduction is a known risk factor for disease recurrence and poor survival. In a GOG study, compared to patients with microscopic residual disease, patients with 0.1 to 1.0 cm and >1.0 cm residual disease had an increased risk of recurrence (HR = 1.96; 95% CI, 1.70 to 2.26; and HR = 2.36; 95% CI, 2.04 to 2.73, respectively) and death (HR = 2.11; 95% CI, 1.78 to 2.49; P<.001; and HR = 2.47; 95% CI, 2.09 to 2.92, respectively) (Winter, Maxwell et al. 2007).

However, there are recent studies challenging this GOG definition of optimal cytoreduction. These studies have shown even better survival rates when post surgical tumor size is reduced to no visible disease. A retrospective study divided the cohort of 465 patients undergoing surgery into no visible residual disease, residual tumor size <0.5 centimeter, 0.6-1 centimeter, 1-2 centimeter or greater than 2 centimeter. The survival outcomes of the above five cohorts were 106 months, 66 months, 48 months, 33 months and 34 months respectively. The overall survival rate was significantly better in the group cytoreduced to no visible disease. The group with residual tumor size <1 cm had better survival outcomes compared to group of patients with >1cm residual disease (Chi, Eisenhauer et al. 2006).

Another study comparing patients that had been cytoreduced to no visible disease to patients cytoreduced to less than 1 cm versus more than 1 cm concluded that the former group had better overall (OS) and progression free survival (PFS) as well as lesser platinum resistance (Eisenhauer, Abu-Rustum et al. 2008).

Debate exists as to whether the observed survival benefits for cytoreducted patients are a function of tumor biology or surgical effort. Hientz et al observed that cytoreduction is easier to obtain in young patients with low grade tumor, smaller sized metastases and no

ascites (Heintz, Van Oosterom et al. 1988). One study also showed that women who could not be optimally debulked had higher frequency of pelvic and paraortic lymph node metastases (Burghardt, Girardi et al. 1991). Hacker et al reported that presence of extensive metastatic disease was by itself a poor prognostic marker despite optimal cytoreduction (Hacker, Berek et al. 1983). Friedlander reported that the size of largest residual tumor was not an independent prognostic factor when newer variables such as DNA ploidy were included in multivariate analysis. (Friedlander, Hedley et al. 1988)

2. Neoadjuvant chemotherapy: Role in ovarian cancer

Neoadjuvant chemotherapy is defined as chemical cytoreduction occurring prior to any significant attempt at surgical reduction of the tumor. On the other hand, interval debulking surgery (IDS) refers to secondary surgical cytoreduction in patients who could not be optimally cytoreducted in the first surgical attempt. This involves administrating chemotherapy after primary surgery and then repeating the surgical procedure in hopes of achieving optimal cytoreduction. An EORTC study that randomized 319 patients who had residual disease of more than 1 centimeter after primary surgery and received three cycles of cyclophosphamide and Cisplatin to undergo either debulking surgery or no surgery. Progression free survival and overall survival were both significantly higher in the group that underwent interval debulking surgery. However, a large prospective GOG trial showed that this approach did not improve progression free survival or overall survival when compared to post operative chemotherapy alone (Rose, Nerenstone et al. 2004).
Neoadjuvant chemotherapy has been proposed for patients with advanced ovarian cancer where the disease extent would deem optimal cytoreduction extremely difficult or impossible (Ledermann 2010). Studies have shown that neoadjuvant chemotherapy can improve quality of life in patients over an extended period of time. One study analyzing quality of life of patients receiving neoadjuvant chemotherapy using EORTC quality of life questionnaire as a tool assessing global health, symptom improvement and functional status reported that life overall quality of life improved after neoadjuvant chemotherapy and continues to improve up to a period of 12 months. (Chan, Ng et al. 2003).

2.1 Patient selection

Several studies have tried to define the group of patients in whom, due to the advanced and unresectable nature of their disease, primary surgery would be difficult or have a suboptimal result. These patients could potentially benefit from neoadjuvant chemotherapy (Markman 2010; Weinberg, Rodriguez et al. 2010). Nelson et al. were the first to study CT imaging criteria to define cytoreducibility by primary surgery. Forty two patients with epithelial ovarian carcinoma underwent preoperative CT scan. Primary tumor was scored as non cytoreducible if the following characteristics were present: attachment of omentum to spleen, >2 centimeter of disease in mesentery, liver, gallbladder fossa, diaphragm, paraaortic suprarenal lymph nodes, and pericardial nodes, pulmonary or pleural involvement. This study concluded that CT scan was a sensitive tool to predict optimal cytoreduciblity (sensitivity= 92.3 percent) with specificity being 79.3 percent. Addition of Ca-125 to upper limits of 36 units/ml, 65 units/ml or 100 units/ml did not enhance CT prediction of accuracy (Chi, Franklin et al. 2004).
Preliminary studies indicate that higher Ca-125 levels (>2000 U/ml) may be a risk factor for suboptimal cytoreduction and hence may prompt initial cytoreduction before proceeding with primary surgery. In a retrospective review of 314 patients, 94 patients who received neoadjuvant chemotherapy had more advanced disease ($p<0.001$) and had higher CA-125

levels (p<0.001). Optimal cytoreduction rate was significantly higher in the neoadjuvant chemotherapy group (81.9% vs. 50%, p<0.001) but progression free survival was similar in both groups. However, in patients with CA-125 levels >2000 U/ml, progression free survival was significantly higher in neoadjuvant chemotherapy group. (HR= 0.62, 95% CI = 0.24-0.96, P=0.037)(Kang, Kim et al. 2011).

Recently, RNA microarray analysis has been used to identify gene expression associated with optimal debulking. After looking at more than 22,000 genes in forty four study patients by the means of RNA microarray analysis, Berchuck et al were able to identify a set of 32 genes which are potentially strong predictors of optimal or suboptimal debulking (Berchuck, Iversen et al. 2004).

2.2 Outcomes

Neoadjuvant chemotherapy followed by surgery has shown to improve perioperative outcomes such optimal cytoreduction, decrease blood loss, and reduce length of hospitalization. (Fanfani, Ferrandina et al. 2003; Milam, Tao et al. 2011)

Several small studies of patients with advanced ovarian cancer have demonstrated that neoadjuvant chemotherapy is associated with same progression free survival and overall survival as the patients treated conventionally.(Giannopoulos, Butler-Manuel et al. 2006) (Chambers, Chambers et al. 1990; Schwartz, Chambers et al. 1994) However, there are also some studies which show significantly improved survival with neoadjuvant chemotherapy.(Hou, Kelly et al. 2007) (Kuhn, Rutke et al. 2001)

The cost of caring for patients who have had an extensive but suboptimal surgery may be greater than those treated with neoadjuvant chemotherapy. (Schwartz, Chambers et al. 1994) These studies also demonstrate that neoadjuvant chemotherapy is associated with lesser surgical morbidity such as blood loss, shorter operative times and shorter length of hospital and ICU stay.(Lawton, Redman et al. 1989; Chambers, Chambers et al. 1990; Jacob, Gershenson et al. 1991; Lim and Green 1993; Schwartz, Chambers et al. 1994; Vergote, De Wever et al. 1998; Schwartz, Rutherford et al. 1999) One retrospective study of 116 patients showed worse outcomes with neoadjuvant chemotherapy with greater survival in primary surgery group (53% vs. 30%, p=0.03). However, in this study, patients in the neoadjuvant chemotherapy group were significantly older (p<0.001), had higher grade of disease (p<0.005) and when adjusted for age and grade, patients there was no difference in overall survival (p=0.95) (Steed, Oza et al. 2006).

The largest randomized control trial to analyze the role of neoadjuvant chemotherapy in advanced stage ovarian carcinoma was performed by Vergote et al. In this study, 718 patients with stage IIIc or IV ovarian carcinoma were randomized to primary debulking surgery or neoadjuvant chemotherapy. Primary debulking surgery group had attempt at cytoreduction in the beginning followed by 3 cycles of platinum based chemotherapy, followed by interval debulking if needed, followed by 3 additional cycles of chemotherapy. 704 patients were required in order to show noninferiority with respect to survival between primary debulking surgery and neoadjuvant chemotherapy, with a one-sided type I error of 0.05 and a power of 80%. The expected median survival in the primary debulking surgery arm was 31 months. The expected optimal debulking rate (≤ 1 centimeter) was 50% in the primary debulking surgery. It was found that percentage of patients with large size metastases (>10 centimeter and >2 centimeter) was fewer in the group that received neoadjuvant chemotherapy. 53 percent of patients in neoadjuvant chemotherapy group had no residual disease after interval debulking while the corresponding number in primary debulking surgery group was 21 percent only. Optimal

cytoreduction defined as residual tumor <1 centimeter could be obtained in 82 percent of patients in neoadjuvant chemotherapy group and 46 percent patients in primary debulking surgery group. There was lower incidence of post operative mortality and morbidity (hemorrhage, fever, fistula formation) in neoadjuvant chemotherapy group. Both the groups had similar progression free (12 months) and overall survival (29 months for primary debulking surgery vs. 30 months for neoadjuvant chemotherapy, HR 0.98 (95% C.I. 0.85-1.14)). There did not seem to be a subgroup based on stage III or IV, age, WHO performance, histological type, countries with high or low optimal debulking rate for which primary debulking surgery or neoadjuvant chemotherapy followed by interval debulking surgery result in better survival. In multivariate analysis, optimal debulking was the strongest independent prognostic factor for overall survival ($p<0.0001$). Hence, it can be concluded from this study that optimal debulking should remain the goal of every surgical effort but the timing of this procedure (primary debulking surgery or interval debulking surgery) does not seem to affect outcomes. Due to the lower morbidity of interval debulking surgery compared with primary debulking surgery and the similar survival, neoadjuvant chemotherapy can be considered a preferred treatment in these patients with stage IIIC/IV ovarian cancer. Interval cytoreductive surgery is also currently a subject of the Chemotherapy or Upfront surgery in Ovarian Cancer Patients (CHORUS) study in Canada and the United Kingdom.

One possible arguement against neoadjuvant chemotherapy is that it deprives potential candidates of intraperitoneal chemotherapy. Studies (Smith, Moon et al. 2009), *Barnett abs. SGO 2007)* have shown that intraperitoneal therapy can be successfully incorporated post-operatively in patients that are able to be optimally debulked following neoadjuvant chemotherapy. Intraperitoneal therapy was well tolerated in these studies.(Tiersten, Liu et al. 2009)

Though there are no standard predictors of response to neoadjuvant chemotherapy, reduction in volume of ascites and decreasing Ca-125 values are the most studied parameters. A randomized phase 2 multicenter trial evaluated early response criteria and surgical outcomes in patients with advanced stage (stage IIIC or IV) ovarian carcinoma with large volume ascites treated with neoadjuvant chemotherapy. Patient were randomized into receiving 2/6 vs. 3/6 cycles of carboplatin and docetaxel preoperatively and response was measured by assessing residual ascites volume and CA-125 levels. It was found that reduction in ascites volume to <500ml and CA-125 to <50% of initial value, were predictors of good response (Polcher, Mahner et al. 2009).

Neoadjuvant chemotherapy followed by cytoreductive surgery has shown to yield better results in advanced ovarian cancer then compared to chemotherapy only approach. Another retrospective study of 129 patients with stage IV ovarian cancer showed that patients who were treated with neoadjuvant chemotherapy followed by cytoreductive surgery had a median survival of 45.5 months, which was significantly better than patients who did not have cytoreductive surgical procedure (15.1 months) ($p<0.01$)(Rafii, Deval et al. 2007).

A phase two study to assess the safety and efficacy of neoadjuvant chemotherapy (four cycles of carboplatin and paclitaxel) followed by debulking surgery followed by four more cycles of chemotherapy for mullerian carcinoma was done in Japan. Out of the fifty-three patients who received neoadjuvant chemotherapy, 47 underwent interval debulking surgery (89%). Twenty two (42%) patients achieved complete clinical remission which was also the primary endpoint. Complete resection of tumor could be performed in 55% (29/53) patients. Median overall and progression free survival was 45 and 14 months respectively. Main toxicity of chemotherapy regimen was neutropenia (grade 4 in 70% patients) and anemia (Onda, Kobayashi et al. 2009).

Although, ability of neoadjuvant chemotherapy to help achieve optimal cytoreduction is an important end point in most of the above trials, it is important to note that significance of achieving optimal surgical cytoreduction is still unclear. Some studies define it to be one of the most important indicators of prognosis (Eisenkop, Spirtos et al. 2003; Aletti, Dowdy et al. 2006; Chi, Eisenhauer et al. 2006), others have demonstrated less benefit. A meta-analysis of fifty eight studies analyzing about 6900 patients demonstrated that maximal cytoreduction in advanced ovarian cancer led to only a modest improvement in outcomes, however, it was the use of platinum based chemotherapy which had the most pronounced effect (Hunter, Alexander et al. 1992).
The results of various studies analyzing the outcomes of neoadjuvant chemotherapy in advanced ovarian cancer are summarized in table 1.

Study type	Author	# Patients	Stage	Optimal cytoreduction (NAC VS. PDS)	OS (NAC VS. PDS)
Randomized control trial	Vergote et al (Vergote, Trope et al. 2010)	670	IIIc-IV	82% vs. 46% (p= NS)	30m vs. 29m (p=0.98)
Randomized control trial	Kumar et al	128	IIIc- IV	83% vs. 13% (p<0.001)	41m vs. 42 m (p=ns)
Prospective non randomized	Kuhn et al (Kuhn, Rutke et al. 2001)	63	IIIc	More in NAC group (p=0.004)	42m vs. 23m (0.007)
Retrospective	Steed et al (Steed, Oza et al. 2006)	116	IIIb-IV	48% vs. 14% (p<0.01)	P=0.95 when adjusted for age and grade
Retrospective	Hou et al (Hou, Kelly et al. 2007)	172	IV	95% vs. 71% (p<0.001)	31m vs. 20m (p<0.01)
Retrospective	Ansquer et al (Ansquer, Leblanc et al. 2001)	54	IIIc- IV	91% vs. 82%	Higher in NAC group (p<0.01)
Non randomized prospective trial	Giannopoulos et al (Giannopoulos, Butler-Manuel et al. 2006)	64	IIIc-IV	82.9% vs. 62.1% (p=0.061)	Not calculated
Retrospective	Schwartz, chambers	29	IIIc-IV	Not calculated	P= 0.26
Retrospective	Schwartz, Rutherford	265	IIIc-IV	Not calculated	1.09y vs. 2.18y (P=0.1578)

Table 1. Studies comparing primary debulking surgery (PDS) to interval debulking after neoadjuvant chemotherapy (NAC), OS: overall survival

2.3 Number of cycles of NAC

In an analysis of patients treated with neoadjuvant chemotherapy, 18 patients were operated after three cycles of neoadjuvant chemotherapy and 32 patients received six cycles of neoadjuvant chemotherapy. There was no significant difference in survival after three and six cycles of chemotherapy (20 vs. 15 months, p = 0.27). The main factors influencing treatment results were optimal cytoreduction and tumor grade. The side effect frequency and profile was also similar in the two groups (Bidzinski, Danska-Bidzinska et al. 2005).

3. Conclusion

There is reasonable evidence to suggest that neoadjuvant chemotherapy has a role in carefully selected group of patients with advanced ovarian cancer, in whom primary

surgery will be impossible or suboptimal due to existing comorbidities or extent of the disease. It has also been documented that patients undergoing neoadjuvant chemotherapy followed by surgery have a much better quality of life and require a shorter time to return to baseline. Moreover, neoadjuvant chemotherapy demonstrates clear benefit in terms of shorter hospital stays and lesser post-operative morbidity. Although, the landmark trial investigating the role on neoadjuvant chemotherapy in advanced ovarian cancer did not show a survival advantage, it does demonstrate that neoadjuvant chemotherapy increases chances of optimal cytoreduction. In such patients, primary chemotherapy followed by surgical resection is an acceptable management option.

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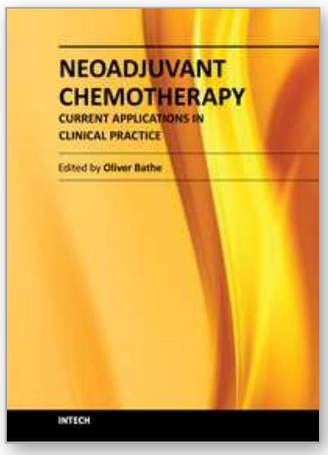

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The most significant advances in cancer therapy in recent years have involved the development of systemic therapeutics. With improvements in response rates in solid tumors, opportunities have arisen to enhance the effectiveness of surgery. Administration of systemic therapy prior to surgery - neoadjuvant chemotherapy - represents one approach by which clinicians have successfully reduced the extent of surgery and, in some instances, positively impacted on clinical outcomes. This collection of works by expert clinicians from a variety of disciplines represents an exploration of the current knowledge of the role of neoadjuvant chemotherapy in diverse tumor types.

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