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Original Article

The Neoadjuvant Approach in the Treatment of Patients with Advanced Epithelial Ovarian Carcinoma

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ABSTRACT:
Aims: **Ovarian cancer has a very poor prognosis, with 5-year survival rates of 5–20% for advanced-stage disease. This work was designed to verify whether the neoadjuvant approach had an effect on survival in patients with advanced-stage ovarian cancer.**
Materials and methods: **Patients with stage III or IV disease who received neoadjuvant platinum-based chemotherapy (group 1) were compared with a group of conventionally treated patients (group 2).**
Results: **Most of the patients in group 1 (76%) had partial tumoral responses after chemotherapy. Patients from group 1 ($n = 42$) had a median survival that was not different from that in patients from group 2 ($n = 348$). Patients who received platinum-based chemotherapy with taxanes had the same survival of patients who received no taxanes.**
Conclusions: **Our results showed similar responses and survival rates for patients with stage III or IV ovarian cancer treated with neoadjuvant platinum-based chemotherapy, when compared with patients who underwent primary suboptimal cytoreductive surgery. Our data therefore support the ongoing trials to determine the optimum timing of surgery for ovarian cancer. Rosa, D. D. *et al*. (2007). *Clinical Oncology* 19**, 125–128

Key words: Advanced ovarian cancer, interval surgery, neoadjuvant chemotherapy, ovarian cancer

Introduction

Ovarian cancer has a very poor prognosis, with 5-year survival rates of 5–20% for advanced-stage disease (International Federation of Gynaecology and Obstetrics [FIGO] stages III and IV). The standard therapy for patients with advanced disease is debulking surgery followed by platinum-based chemotherapy. Unfortunately, radical debulking surgery allows for optimal cytoreduction in less than 50% of patients with advanced ovarian cancer [1]. Despite controversies in published studies [2–5], the addition of taxanes to the chemotherapeutic regimen has been recommended as the first choice for these patients. In spite of efficient chemotherapeutic regimens, the prognosis of patients with residual tumour masses larger than 1–2 cm in diameter after debulking surgery is very poor, with 5-year survival rates around 20% [6,7].

Neoadjuvant chemotherapy has been proposed as an alternative approach to primary cytoreductive surgery as the initial management of bulky ovarian cancer with the aim of improving surgical efficiency, quality of life and, perhaps, survival [8,9]. In this study we compared the neoadjuvant approach with the conventional treatment of primary debulking surgery followed by chemotherapy for patients with FIGO stage III or IV ovarian cancer. As published studies are controversial considering the benefits of the neoadjuvant treatment, our main objective was to evaluate the effect of this approach on overall survival.

Materials and Methods

We retrospectively analysed two cohorts of patients with stage III or IV large volume disease from our database. For the last 7 years we have recorded clinical data on all patients coming through the ovarian cancer clinic. We analysed patients treated in our institution from 1997 to 2006. Patients in group 1 had received neoadjuvant platinum-based chemotherapy followed by cytoreductive surgery. The neoadjuvant treatment was recommended in patients with stage IV disease or to those with stage III disease around nerves or vessels, or including the bile ducts, that would preclude optimum cytoreduction; all patients received surgery after chemotherapy. All surgery was carried out by gynaecological oncologists. Patients in group 2 were treated with primary cytoreductive surgery that was suboptimal, that is, it had left residual disease of 2 cm or more in the abdomen. This group received platinum-based

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chemotherapy after surgery. Responses were evaluated after surgery for group 1 and after postoperative chemotherapy for group 2. Informed consent was obtained from each participant from group 1 and the study was approved by the Ethics Committee.

Pearson's chi-squared test was used to compare differences in qualitative variables. The Mann—Whitney test was used for the comparison of quantitative variables, assuming that these variables did not follow a normal distribution. For all hypothesis tests, a two-tailed alpha value < 0.05 was considered statistically significant. Univariate survival analyses from the date of diagnosis were executed using the Log-rank test and Kaplan—Meyer curve. Data analysis was carried out with SPSS software 11.5.0.

Results

We analysed 42 patients in group 1 and compared this patient population with 348 conventionally treated patients in group 2. The median follow-up was 20 months (range 2—91 months). There were no significant differences in the baseline characteristics between the two groups of patients (Table 1). Group 1 patients received a median of five cycles of chemotherapy (range one to nine) before undergoing surgical cytoreduction; most of these patients (76%) had partial tumoral responses after chemotherapy and before surgery. Seven patients out of the 42 received postoperative chemotherapy. No patient received consolidation with radiotherapy.

There were no differences in survival between groups 1 and 2 (Table 2, Fig. 1). Analysing the tumoral response, there were also no differences between the two groups (Table 2).

Both groups were stratified according to the type of chemotherapy (platinum based with or without taxanes). There were no differences in survival among patients in groups 1 and 2 when analysing the type of chemotherapy received.

The a posteriori calculus of the power for this retrospective review was 73%. To perform this calculus, we considered a difference of 20% in survival between the two groups, with a bicaudal alpha of 0.05 and a beta of 0.20.

Discussion

The role of neoadjuvant treatment for patients with advanced-stage ovarian cancer is controversial [10,11]. Hitherto there is no conclusive evidence for a survival advantage of the neoadjuvant approach compared with conventional treatment. Our retrospective review showed that patients submitted to neoadjuvant chemotherapy had a median survival that was not different from that of patients submitted to suboptimal debulking surgery. Therefore, these findings are in accordance with several retrospective studies and non-controlled clinical trials that have suggested that patients with an unsuccessful attempt at initial tumour-reductive surgery benefit from surgery after initial chemotherapy, with no difference in survival between these two treatments [10—17]. However, it should be noted that the retrospective nature of our study did not allow us to obtain data on toxicity, which is considered an important end point in the evaluation of the neoadjuvant approach in patients with advanced ovarian cancer.

Platinum plus taxane-based chemotherapy is considered standard for patients with advanced-stage ovarian carcinomas after primary radical tumour debulking [18]. Four studies have assessed the effect on progression-free survival and overall survival when paclitaxel was added to either cisplatin or carboplatin in the adjuvant setting [2—5]. Two showed that combination chemotherapy with paclitaxel prolonged both progression-free and overall survival in patients with advanced disease as compared with regimens that did not contain taxanes [2,3]. The inclusion of paclitaxel in first-line therapy seemed to result in a 30% reduction in the risk of death [2]. The other two studies, however, showed no superiority in survival with the addition of paclitaxel [4,5]. In our study, the addition of a taxane to the chemotherapeutic scheme had no effect on survival for patients who received chemotherapy in the neoadjuvant or adjuvant setting.

In conclusion, our results showed similar responses and survival rates for patients with stage III or IV ovarian cancer treated with neoadjuvant platinum-based chemotherapy, when compared with patients who underwent primary

Table 1 — Baseline characteristics of the patients*

	Group 1 (neoadjuvant; $n = 42$)	Group 2 (suboptimal debulking; $n = 348$)
Median age in years (range)	66 (38—86)	61 (23—88)
Stage of ovarian cancer		
III	29 (69%)	254 (73%)
IV	13 (31%)	94 (27%)
Performance status†		
100%	17 (41%)	194 (56%)
80—90%	19 (45%)	108 (31%)
60—70%	6 (14%)	46 (13%)
Chemotherapy regimen		
Platinum based	42 (100%)	348 (100%)

*There were no differences between the groups. †According to the Karnofsky scale.