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Clinical outcome of neoadjuvant chemotherapy for advanced ovarian cancer☆

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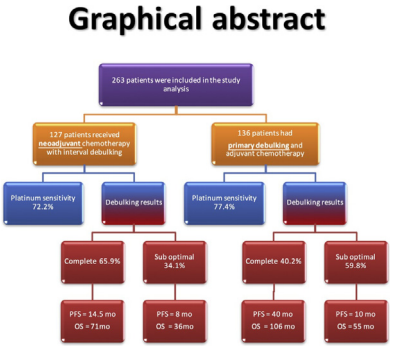
HIGHLIGHTS

- Neoadjuvant chemotherapy (NACT) does not increase "platinum resistance".
- Complete debulking after NACT has better outcome than residual disease after primary debulking.
- Inability to achieve complete surgical resection should be identified so that NACT may be offered.

GRAPHICAL ABSTRACT



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ABSTRACT

Objective. To evaluate clinical outcome in patients selected to receive neoadjuvant chemotherapy (NACT) compared to primary debulking surgery (PDS).

Methods. Retrospective study including all consecutive patients diagnosed and treated for advanced (stages III-IV) ovarian cancers between the years 2003–2015.

Results. 263 women were included in the study, of these, 127 patients were selected to receive NACT and 136 were treated with PDS followed by adjuvant chemotherapy.

PDS was associated with longer OS in stage IIIc disease (median OS: 60.2 vs. 48.8 months; *p*-value 0.039) compared with NACT.

Patients achieved higher rates of complete cytoreduction in the NACT group compared to the PDS group (65.9% vs. 40.2%; $p = 0.001$). Patients attaining complete cytoreduction after PDS had the best survival, (median OS 106 months) followed by those with complete cytoreduction after NACT (median OS 71 months), followed by those with residual disease after PDS (median OS 55 months). Patients with residual disease following interval debulking after NACT had the worst outcome (median OS 36 months).

Platinum sensitivity following first line and second line chemotherapy was similar whether patients received neoadjuvant chemotherapy or not.

Conclusion. PDS was associated with improved outcome. NACT appears to improve survival outcome in patients that would have had residual disease after PDS, and attain complete cytoreduction at the time of interval cytoreduction. This treatment option can be used in selected patients that are not candidates for complete cytoreduction at PDS.

☆ The authors report no conflict of interest.

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1. Introduction

The standard treatment for patients with ovarian cancer has been primary cytoreduction surgery followed by platinum based chemotherapy [1], except in those who are not considered fit to undergo surgery. The definition of optimal cytoreduction has evolved over the years and it has become evident that complete cytoreduction with no visible residual macroscopic disease is the goal to impact outcome [2]. Recently, molecular characteristics of the tumor and its micro-environment correlated with the ability to attain complete cytoreduction, suggesting that some factors related to the biology of the disease in conjunction with the skills of the surgeon dictate whether the disease is amenable to complete debulking [3–5].

For the patients in whom it is not expected that complete cytoreduction can be attained during primary debulking surgery (PDS), some have advocated to reduce the tumor burden by neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) [6–9]. This alternative approach of treating patients with primary NACT has gained momentum in the last two decades. Two randomized controlled studies evaluating the outcome have been published. In 2010, Vergote et al. published an international trial that randomized patients with advanced stage cancer (IIIC-IV) to either primary debulking surgery (PDS) followed by adjuvant chemotherapy or NACT followed by IDS and adjuvant therapy. No difference was found in overall survival (OS) with lower rates of adverse events in the NACT group [10]. Limitations of that study include the use of non platinum combination therapy in around 10% of patients and the inclusion of patients with advanced disease only. The CHORUS study was the second randomized controlled study published recently, with overall similar results, showing NACT to be non-inferior to PDS [11]. It is important to note that in both studies low rates of complete cytoreduction were reported. Given the results of these studies, as well as several retrospective studies [6–8,12] NACT has gained momentum but controversy remains. While 82% of SGO (U.S. Society of Gynecologic Oncology) members did not consider the available evidence sufficient to justify NACT [13], 70% of the ESGO (European Society for Gynaecological Oncology) members believed there was sufficient evidence to use NACT followed by IDS for the treatment of stage IIIC and IV ovarian cancer [14]. Some have also raised concerns regarding increased platinum resistance in patients treated with NACT [15,16].

In this study we analyzed the outcome of patients that were selected to one or the other approach based on the evaluation of the gynecologic oncology tumor board, whether complete cytoreduction was attainable at primary surgery, and if NACT influenced the development of platinum resistance.

2. Materials and methods

2.1. Study population

The study population was composed of all consecutive patients who were diagnosed and treated for International Federation of Gynecology and Obstetrics (FIGO) stages III-IV ovarian cancer, since the initiation of the division of Gynecologic Oncology, at the McGill University-affiliated Jewish General Hospital in 2003, until 2015. Patients were diagnosed with stage IV if they had A - pleural effusion with positive cytology, B - hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs, including inguinal lymph nodes and lymph nodes outside of the abdominal cavity. Patients with low stage disease were excluded from the study. The Institutional Review Board (in accordance with the Helsinki declaration) approved the study, protocol #15-070.

2.2. Study design

Data for the study was collected retrospectively from a prospective computerized database. For each patient, we extracted information regarding age, body mass index (BMI), histological type and grade, FIGO stage, extent of cytoreductive surgery and residual disease, administration of neoadjuvant chemotherapy (NACT), type of chemotherapy used in first line, CA 125 levels, and response to treatment. Patients were presented to the tumor board if primary complete cytoreduction did not appear feasible. NACT was advocated in the presence of diffuse carcinomatosis on imaging, metastases to liver parenchyma or porta-hepatis, and lesions involving the base of the mesentery. These recommendations did not change over time as the rule in the department has remained that only patients who are not expected to safely undergo complete cytoreduction undergo NACT. All cytoreductive surgeries were performed by one of four fellowship trained gynecologic oncologists, with the intent to reach complete cytoreduction. The extent of cytoreduction was defined as complete, only if no macroscopic disease was observed at the end of the operation. First line platinum combination therapy was used in all patients.

During the surveillance period, routine follow-up examinations included CA125 levels and clinical examinations at intervals of 4 months during the first two years from diagnosis, followed by every 6 months for up to 5 years, and then yearly thereafter. Imaging was performed when clinically indicated, either by symptoms, clinical findings, or increase in CA125. Overall survival (OS) was defined as the time from diagnosis to either last follow-up or death. In patients who had recurrence, progression free survival (PFS) was defined as the time from the last cycle of treatment to either the diagnosis of recurrence or death.

2.3. Statistical analysis

Statistical analysis was performed using the STATA 12 (StataCorp, College Station, TX). Statistical significance was calculated using the chi square test for differences in qualitative variables and the Student *t*-test for differences in continuous variables.

Kaplan-Meier survival curves were used to calculate survival estimates (PFS and OS), log rank test was used in order to quantify survival differences according to different variables. Proportional hazard regression models were used to estimate the relative rate of survival for different clinical variables including NACT. For this model we used clinical factors that are known to be correlated with outcome of patients with ovarian cancer. These variables include stage, grade, surgical outcome, treatment protocol (treated as categorical variables) and age (treated as a continuous variable).

Given the proportional distribution of patients to each of the treatment groups and assuming equal HR for events between the PDS and NACT group, the sample size for this study gives >80% power to detect survival differences. However, whereas the utility of prospective power analysis in experimental design is universally accepted, the usefulness of retrospective techniques is controversial. Different retrospective analyses can yield substantially different information. In the case of this study the goal is to quantify our certainty in the findings of the study, in which case calculating a confidence interval about the observed effect size was selected.

2.4. Results

During the study period, 263 women were diagnosed with stages III-IV ovarian cancer. Of these, 127 patients underwent NACT with interval debulking surgery (IDS) followed by adjuvant chemotherapy (NACT group), and 136 were treated first with PDS and then adjuvant chemotherapy (PDS group). Carboplatin and Paclitaxel combination was used in all patients except four patients in the PDS group and five in the NACT group who received single agent Carboplatin. In the NACT group, the median number of cycles before IDS was three (range 1–6). Overall the median number of cycles was 6 in the PDS group and 7 in the NACT group

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