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Impact of neoadjuvant chemotherapy cycles prior to interval surgery in patients with advanced epithelial ovarian cancer

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HIGHLIGHTS

- EOC patients receiving late Interval Debulking Surgery (>4 NAC-cycles) have a poor prognosis compared to patients receiving early IDS.
- The impact of surgical timing is reinforced in the subgroup with complete debulking and remains independent from other prognostic factors.
- The relative contribution of the therapeutic sequence compared to tumor biology and chemotherapy response on prognosis remains controversial.

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ABSTRACT

Objectives. Complete surgery with no macroscopic residual disease (RD) at primary (PDS) or interval debulking surgery (IDS) is the main objective of surgery in advanced epithelial ovarian cancer (EOC). The aim of this work was to evaluate the impact on survival of the number of neoadjuvant chemotherapy (NAC) cycles before IDS in EOC patients.

Methods. Data from EOC patients (stages IIIC–IV), operated on between 1995 and 2010 were consecutively recorded. NAC/IDS patients were analyzed according to the number of preoperative cycles (<4 = group B1; >4 = group B2) and compared with patients receiving PDS (group A). Patients with complete resection were specifically analyzed.

Results. 367 patients were analyzed, 220 received PDS and 147 had IDS/NAC. In group B, 37 patients received more than 4 NAC cycles (group B2). Group B2 patients presented more frequently stage IV disease at diagnosis ($p < 0.01$) compared to groups A and B1. The rate of complete cytoreduction was higher in group B ($p < 0.001$). Patients with no RD after IDS and who had received more than 4 NAC cycles had poor survival ($p < 0.001$) despite complete removal of their tumor (relative risk of death after multivariate analysis of 3 ($p < 0.001$)) with an independent impact from disease stage and WHO performance status.

Conclusions. Patients with advanced EOC receiving complete IDS after more than 4 cycles of NAC have poor prognosis. Despite worse prognostic factors observed in this group of patients, our study reinforces the concept of early and complete removal of all macroscopic tumors in the therapeutic sequence of EOC.

Introduction

Epithelial ovarian cancer (EOC) remains the main cause of gynecological cancer death in developed countries reflecting advanced-stage disease at clinical diagnosis and early propensity for peritoneal dissemination [1]. The standard treatment for advanced EOC consists of optimal cytoreductive surgery associated with a platinum/paclitaxel-based chemotherapy [1]. Despite very high initial chemosensitivity and frequent clinical complete response, the majority of patients relapses and progressively develops resistance to the various chemotherapeutic treatments [2,3]. Over the last decades, retrospective and prospective studies have established that the result of the surgical procedure, defined by the amount of residual disease (RD), was the most important factor impacting on survival [4,5]. It has been now demonstrated that a large improvement in the prognosis of EOC patients is associated with the removal of all macroscopic disease and complete surgery has become the principal goal of the surgical management of advanced EOC [6–10]. Incomplete surgery with any macroscopic RD is associated with a poor survival even with low RD (<1 cm) that appears to give a

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small and limited prognostic impact compared to larger (so-called non-optimal) RD (>1 cm) [10].

Neoadjuvant chemotherapy (NAC) and interval debulking surgery (IDS) have been proposed in the management of advanced EOC to increase the rate of complete surgery while reducing surgical morbidity [9,11]. Initially reserved for unresectable disease or for patients in poor general condition, the prescription of NAC and IDS has increased over the past two decades and the first debulking is now often attempted only after several cycles of chemotherapy. The non-inferiority of IDS after 3 cycles of NAC compared to upfront surgery has been reported by Vergote et al. in a large phase III randomized trial including patients with advanced stages IIIC–IV EOC [9]. Nevertheless, optimal surgical timing and selection criteria for NACT and IDS remain controversial in clinical practice. In parallel, large retrospective studies and meta-analyses have observed a large survival advantage for EOC cancer patients receiving initial and complete removal of all macroscopic tumors prior to initiation of chemotherapy [12]. Furthermore, the quality of surgery was heterogeneous in the EORTC trial with large variations in surgical aggressiveness and complete resection rates among participating centers. This argument has been raised to explain the comparatively low survival observed for patients treated with upfront surgery in this study [12]. Furthermore, retrospective data have also suggested that NAC and IDS compared to primary surgery may increase the risk of developing platinum-resistant disease and less sensitive recurrent disease [13].

To date, timing of surgery in the therapeutic sequence of EOC and the selection of patients who will benefit from primary surgery or NAC-IDS remain controversial. In the case of NAC and IDS, high disparities also exist as to how many cycles of NAC should be given prior to IDS, ranging from three to six or more. For advanced or unresectable disease, some authors have recently proposed to increase the number of NAC cycles with the aim of improving the rate of complete resection [14]. Preliminary reports have mentioned that IDS could be delayed after 6 or more cycles without detrimental consequences for long-term survival [15,16]. The purpose of the present study was to evaluate the impact on survival of the number of NAC cycles before the first cytoreductive surgery in a large cohort of advanced EOC patients treated in a specialized center.

Patients and methods

Patients

All of the patients diagnosed with an advanced primary epithelial EOC operated on at our institute between 1995 and 2010 were recorded in a prospective database. Patients with stage IIIC or IV, undergoing primary (PDS) or interval debulking surgery (IDS) were included consecutively. All patients were classified at diagnosis according to the WHO performance status. Patients with incomplete clinicopathological data, non-epithelial ovarian cancers, or stages IIIC without abdominal peritoneal carcinomatosis (retroperitoneal positive nodes only) and patients receiving their first debulking surgery in other institutions were systematically excluded from this study.

Surgery

Surgical staging was defined according to the International Federation of Obstetricians and Gynecologists (F.I.G.O.) staging system. The initial extent of the disease at the start of each surgical procedure was quantified using the peritoneal cancer index (PCI), derived from Jacquet and Sugarbaker [17]. Surgery was considered complete when all visible tumors were removed (no macroscopic RD) at the end of the intervention. Two groups were formed according to the time of the first cytoreductive surgery in the therapeutic sequence. Group A consisted entirely of patients who had their first debulking surgery before any chemotherapy (PDS). Group B consisted of patients receiving their first debulking after their initial NAC (IDS). Some patients in this group may have undergone an initial exploratory laparotomy in a different hospital or an exploratory laparoscopy followed by chemotherapy before IDS at our institution. Group B was divided according to the number of NAC cycles received prior to IDS (group B1 received 4 or less NAC cycles and group B2 received more than 4 cycles before surgery). In the different groups, patients with complete resection were specifically identified and analyzed.

Chemotherapy

All patients were treated with a first-line platinum-based chemotherapy in combination with paclitaxel for 6–8 courses, every 3 weeks, as specified by the different ongoing protocols during the years of study. Since inclusion of patients in the current study ended in 2010 before publication of the GOG-218 and the ICON-7 trials, no patient received antiangiogenic treatment (i.e. bevacizumab) in association with this first-line chemotherapy.

Observation

Individual data for all patients were prospectively collected: age at diagnosis, WHO performance status, dates of surgery and chemotherapy, the presence of ascites, stage, tumor grade, histology, extent of the disease and PCI at each laparotomy, RD after primary or interval surgery, CA-125 levels before and after surgery and chemotherapy. For patients in group B, the number of cycles and the response to NAC were also recorded. Tumors were defined as refractory in the case of progressive disease during the initial therapeutic sequence and resistant when recurrence was observed in the first 6 months after the end of the initial chemotherapy. Mortality and morbidity defined by death and complications within the first 30 days after each surgical procedure were also recorded. Treatment Free Interval (TFI) corresponded to time between the end of the first-line chemotherapy and the start of a second line in the case of recurrence.

Follow-up

All patients were regularly evaluated at the end of the treatment for evidence of disease recurrence. Clinical examinations, tumor markers assay (CA-125) and CT-scans were performed every 4 months. The date of progression was determined by CT scan and/or CA-125 levels on two consecutive assays.

Statistical analysis

Statistical analysis was performed with the log-rank and χ^2 tests to compare univariate prognosis factors. The Cox proportional hazard regression model was used to determine the independent contributions of the prognostic variables in a multivariate analysis. Survival curves were performed with the Kaplan–Meier method. Progression-free survival (PFS) and overall survival (OS) were calculated from the date of diagnosis. Differences were considered statistically significant at $P < 0.05$. STATA 10 statistical software (Stata Corporation, College Station, Texas, USA) was used for the analysis.

Results

Patients and tumors (Table 1)

Three hundred and sixty seven patients at stage IIIC (n = 301) or IV (n = 66) advanced EOC underwent primary surgical exploration or IDS at our institution during the indicated period and were eligible for inclusion in our study. The median age at diagnosis was 59 years (range: 21–89) and the average follow-up duration was 82 months (range: 9–203 months). Group A, B1 and B2 patients and tumors' characteristics