Outcome of patients with advanced ovarian cancer who do not undergo debulking surgery: A single institution retrospective review

Claudia Marchetti[a,b], Rebecca Kristeleit[a], Mary McCormack[c], Tim Mould[d], Adeola Olaitan[d], Martin Widschwendter[d], Nicola MacDonald[d], Jonathan A Ledermann[a*].

[a]UCL Cancer Institute and UCL Hospitals, London , UK
[b] Department of Gynecological and Obstetrical Sciences and Urological Sciences, University "Sapienza", Rome, Italy
[c]Cancer Division, University College Hospital, UCL Hospitals, London, UK
[d] Departments of Gynaecological Oncology, Women's Health University College Hospital, UCL Hospitals, London, UK

corresponding author

Correspondence to:

Jonathan A Ledermann,

UCL Cancer Institute and UCL Hospitals, 90 Tottenham Court Rd., London W1T 4TJ, United Kingdom

Phone: 44-20-7679-9874

Fax number: 44-20-7679-9899

E-mail: j.ledermann@ucl.ac.uk

Abstract

OBJECTIVE: To assess the outcome of patients with advanced ovarian cancer (OC) who were treated without surgery, having received upfront chemotherapy and no interval debulking surgery (IDS).

METHODS: Retrospective analysis of medical and chemotherapy records of consecutive patients with OC between 2005 and 2013 at UCL Hospitals London, UK who received neoadjuvant chemotherapy (NACT) and were then found to be unsuitable for IDS following review by the multidisciplinary team.

RESULTS: Eighty-three patients (18%) out of 467 receiving NACT did not undergo IDS. Median age was 70 years (range 33–88); 51.8% presented with stage IV disease. Forty-three patients received carboplatin and paclitaxel (CP) (51.8%) and 37 received carboplatin alone (C) (44.6%); 3 (3.6%) patients received other platinum-based combinations. Reasons for not proceeding to surgery were: poor response to chemotherapy after 3-4 cycles of NACT (61/83, 73.5%); comorbidities (12/83, 14.5%); patient decision (4/83, 4.8%). Six patients (7.2%) received < 3 cycles of NACT due to a worsening clinical condition. The median overall survival (OS) for patients not undergoing IDS was 18 months (95% CI 10–20 months). Forty-four (53%) patients received > 2 lines of chemotherapy. In a univariate analysis CP, age < 70 years, and absence of comorbidities were factors influencing OS. In a multivariate analysis only having received CP remained independently associated with OS (HR 0.49, 95% CI 0.29-0.84).

CONCLUSIONS Chemotherapy alone can provide reasonable disease control in patients unsuitable for IDS and CP should be used if possible.

Key words: advanced ovarian cancer, surgery, chemotherapy, neoadjuvant, debulking, carboplatin, paclitaxel

INTRODUCTION

Epithelial Ovarian Carcinoma (EOC) is the leading cause of death from gynecological cancer in the Western World. For women presenting with advanced disease the 5-year survival rate is approximately 30%[1]. Survival of women with epithelial ovarian cancer has improved partly as a consequence of more aggressive surgery to achieve optimal cytoreduction, the use of platinum-based treatment and better treatment of recurrent disease [2]. Nonetheless, approximately 80% of patients who present with advanced disease develop progression or relapse and die within 5 years from diagnosis[3].

Optimal primary debulking surgery followed by platinum-based chemotherapy [3] is the recommended treatment for advanced ovarian cancer (FIGO III–IV). Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) can be considered an alternative first-line treatment for patients in whom primary cytoreductive surgery is not possible or contraindicated due to co-morbidity [4-6]. Recent studies have shown similar outcome to primary surgery when interval

debulking surgery (IDS) is performed after three cycles of neoadjuvant chemotherapy followed by three post-IDS cycles of chemotherapy [4-6].

It has been estimated that in 10-25 % [6-8] of patients surgical debulking may be not feasible even after NACT, due to poor response to chemotherapy, poor or worsening of performance status, significant co-morbdities, or patients desire to avoid extensive surgery that might require bowel resection.

For these women chemotherapy is the primary treatment. It is usually given with palliative intent but little is known about the outcome of these patients

The aim of this retrospective study was to understand the natural history of patients with advanced stages of EOC, treated with chemotherapy alone.

MATERIALS AND METHODS

All women with a diagnosis of invasive EOC who were treated between January 2005 and December 2013 at UCL Hospitals, London UK were included in this audit. Data were collected between October and November 2014 by reviewing the medical records, radiological imaging, chemotherapy prescriptions and outcome information.

The inclusion criteria were as follows: (1) histologically confirmed diagnosis of epithelial ovarian cancer; (2) not suitable for primary or interval debulking surgery; (3) having received primary chemotherapy and (4) availability of medical records.

Staging was performed radiologically and defined in accordance with the FIGO (International Federation of Gynecology and Obstetrics) classification for ovarian cancer. All patients had previously undergone histological review by a specialist in gynaecological pathology. Patients with a borderline tumor or a non-epithelial tumor were excluded.

All patients were treated with platinum-based chemotherapy and underwent radiological evaluation after 3 or 4 cycles of chemotherapy. They were assessed for surgery by the Multidisciplinary Team.

Criteria for a poor response and consequently unsuitability for surgery were defined as follows: diffuse deep infiltration of the root of the small bowel mesentery, widespread bowel serosal involvement, multiple parenchymatous liver metastases, infiltration of the duodenum and/or pancreas and/or the large vessels of the hepatic-duodenal ligament, celiac trunk or behind the porta hepatis, multiple lung metastases.

The medical charts were reviewed to obtain information on the reason for not undergoing surgery, the type of first line chemotherapy, dates of treatment and the reasons for dose reductions and delays. The Charlson Comorbidity index (CCI) score [9] was used retrospectively to assess co-morbidity.

Response was assessed by physical examination, serial measurement of CA125, and computed tomographic imaging. Response at the end of treatment was assessed by CA125 according to GCIG criteria [10] and radiological assessment (computed tomographic scan). Progression was defined by clinical or radiological findings and the time to progression was taken as the date of radiological evidence of progression. Further treatments were recorded and overall survival was calculated from the date of primary diagnosis to date of death or to last follow-up visit for the patients still alive. Median follow-up period was measured from the date of primary diagnosis to the time of last follow-up visit.

Chi-square or Fisher's exact test was used for comparison of categorical variables. A logistic regression model was applied to determine the effect of independent variables (age, grading, presence of comorbidities (CCI)/ pulmonary embolism, stage, and histology) on the choice of chemotherapy. Survival was calculated using the Kaplan–Meier method. Log-rank test was used to compare survival between groups. Multivariate analysis for prognostic factors was performed by Cox's proportional hazards regression model. All P values were two-sided, and the p-value was set at 0.05. All statistical calculations were carried out using SPSS for Mac version 22.0 (SPSS Inc., USA).

RESULTS

During the study period primary chemotherapy was given to 467 patients with ovarian cancer and 83 patients (18%) did not proceed to surgery, and are the subject of this study.

The median age was 70 years (range 33–88 years). Two age categories were defined: 70 years old or younger, and greater than 70 years old: the median age was 61 years (range 33–70) in the former, and 79 years (range 71–88) in the latter. Clinical and pathological characteristics of patients are described in table 1. Ten patients (12%) had previous history of other cancers. Patients in the older group were more frequently affected by comorbidities (according to CCI), 65.9% compared to 45.2% in the younger patients; Forty-three patients (51.8%) had stage IV disease and 10 patients (19.3%) presented with a pulmonary embolism (PE), or developed a PE during chemotherapy (5 patients).

Paclitaxel and carboplatin were given to 43 patients (51.8%) and 37 received carboplatin alone (44.6%); three patients (3.6%) received other platinum –based combinations. The median number of cycles given was 6 (range 1-8), and 24% of patients received less than 6 cycles. Five patients also received bevacizumab (6.3%). Patients older than 70 years (OR 0.31, CI95% 0.10-0.93, p= 0.007) and those presenting with at least one comorbidity (OR 0.31, CI95% 0.10-0.90, p= 0.016) were more likely to receive carboplatin alone treatment rather than carboplatin plus paclitaxel.

Six patients (7.2%) received less than 3 cycles of chemotherapy, stopping because of a worsening clinical condition, and were therefore not assessable for IDS (table 2).

Sixty-one patients (73.5%) out of the whole group were judged to be unsuitable for optimal surgical debulking on the basis of a poor response to chemotherapy. Other reasons for having not having surgery were patient decision (4/83, 4.8%) and the presence of comorbidities in 12/83, 14.5%). The

comorbidities were severe cardiovascular disease (CVD) (7 patients), a cerebrovascular accident (CVA) (1 patient) and significant worsening pulmonary embolus (8 patients), including 4 patients with CVD or CVA.

At the end of chemotherapy 53 patients (63.8 %) had a partial response on CT imaging, 12 (14.4%) had stable disease and ten (12%) patients had disease progression. In 2 patients radiological information was absent (2.4 %) and 6 patients were not assessable for IDS, as stated above. According to CGIG criteria, among the 59 patients whose CA125 measurements were available and evaluable, 50 (84.7%) had a response, including 17 (28.8%) with a complete response, whilst there were 6 (10.1%) who did not achieve any response and 3 were not evaluable (CA 125 below normal range at diagnosis).

Thirty-nine out of 83 patients (46.9%) received only one line of chemotherapy; 24 (28.9%) patients received a second line of chemotherapy following disease progression. Subsequently, 15 patients (18%) received 3 lines, 2 patients (2.4%) received 4 lines, 1 patient (1.2%) received 5 lines and 2 patients (2.4%) received 6 lines of chemotherapy. Overall, 44 (53%) patients received > 2 lines of chemotherapy.

The median follow-up period was 18 months. The median OS of the overall population was 18 months (95% CI 10–20 months).

Analysing OS according to type of chemotherapy received in the overall population (Fig. 1), women who underwent carboplatin plus paclitaxel had better median OS of 27 (95% CI 20–33 months) months compared with 15 (95% CI 14–19 months) months for patients who received carboplatin alone (log rank: p=0.002; HR 0.45, 95% CI 0.27- 0.75).

In a univariate analysis (table 3), type of chemotherapy (carboplatin vs. carboplatin plus paclitaxel) and age (> or $\leq$ 70 years), and absence of comorbidities were factors influencing OS. However, in the multivariate analysis (table 3) only treatment with the combination of carboplatin plus paclitaxel was independently associated with OS (log rank: p=0.002; HR 0.49, 95% CI 0.29-0.84).

DISCUSSION

Debulking surgery to remove all residual disease remains the cornerstone of ovarian cancer treatment [11]. Nonetheless, even in clinical trials of NACT in patients with potentially operable disease, 10-25% are not able to undergo debulking surgery [6,7]. There is little information about the outcome of this group of women. The key finding was that 18% of all patients in our institution undergoing primary chemotherapy do not undergo surgery and their median survival was 18 months. A poor response to chemotherapy was the main reason for failure to proceed to surgery and in 27% the decision was made not to operate because of co-morbidity or patient choice. However, 68.8% patients achieved a partial response to chemotherapy, 53% received a further line of chemotherapy, and 24 % had 3 or more lines of treatment.

The median age of our population was 70 years, higher than the population median age of EOC at diagnosis [3]. Co-morbidity is more common in older patients so they are more likely to receive single agent carboplatin chemotherapy. Both age ≥70 years and CCI score ≥1 were independent predictors of single agent chemotherapy. This is in accordance with other experiences [12]. Although carboplatin and paclitaxel are considered as standard of treatment for stage II–IV ovarian cancer [13], single agent carboplatin compares well to a carboplatin plus paclitaxel combination [14] and it has been proposed that it is an acceptable standard treatment for older patients [15].

We found that receiving the combination of carboplatin and paclitaxel is independently associated with better survival, even after adjusting for age and comorbidities. This underlines the importance of identifying which factors should preclude the use of paclitaxel in elderly patients.

Approximately half of our patients received two or more lines of treatment. Whilst surgery plays a key role in the management of ovarian cancer, patients unable to undergo surgery should still be

considered for active management as in some of them, multiple lines of treatment are able to control the disease for many months. In our series, though we did not have information on symptom control or quality of life, the administration of several lines of chemotherapy contributed to the finding of a median OS of 18 months, which compares favourable to other reported series in which the median OS was in the range of 8-11 months [8,14-17] for patients unsuitable for surgery. Shalowitz et al recently reported a shorter OS for those who only received systemic treatment (12 months), and an even shorter OS for those who did not receive any treatment (1.4 months); unfortunately data about treatment administered and number of chemotherapy lines are lacking and further comparisons are not possible. Overall, we might speculate that the availability of different combinations of treatment we described can provide some of these women with the opportunity of extended palliation without surgery as they can receive several lines of treatment in the absence of surgery.

The present study was a single institution retrospective investigation. Whilst consecutive patients were included, a selection or referral bias could have occurred, and this might have influenced the analyses, particularly the comparison of single agent and combination therapy. Nonetheless we believe that our findings provide useful and relevant information to decision-making about surgery for clinicians treating patients with neoadjuvant therapy. Cytoreductive surgery remains the cornerstone of treatment of advanced EOC but when it cannot be performed chemotherapy provides good palliation and disease control for many patients.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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Conflict of interest statement

The authors declare that they have no competing interests.

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291 **LEGEND**

292 **TABLES**

293 Table 1: Patients Pathological and Clinical characteristics.

294 Table 2: Characteristics of patients receving less than 3 cycles.

295 Table 3: Univariate and multivariate analysis of prognostic factors.

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297 **FIGURE**

298 Figure 1 : Overall survival of patients receiving carboplatin alone (37 patients) or carboplatin plus
299 paclitaxel (43 patients) (log rank: p=0.003)

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