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Response rates to second-line platinum-based therapy in ovarian cancer patients challenge the clinical definition of platinum resistance

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HIGHLIGHTS

- Response to platinum-chemotherapy at recurrence is higher than to non-platinum.
- Patients that recur early (3–6 months) can have improved survival after platinum.
- Biomarkers of platinum-sensitivity are needed to identify potential responders.

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ABSTRACT

Objective. The aim of this study was to compare response rates and survival in women with "platinum resistant" epithelial ovarian cancer (EOC) who received further platinum-based or non platinum chemotherapy for treatment at first relapse.

Methods. Patients with high-grade EOC (including fallopian tube and peritoneal cancer) of all histologies recruited to the Australian Ovarian Cancer Study (AOCS) and treated with platinum-based primary chemotherapy were included. Response to second-line chemotherapy, overall survival (OS) and survival after treatment for first progression (OS2) were determined in all histologies and separately in women with high-grade serous tumors.

Results. Of the 341 patients classified as platinum-resistant by the 6-month threshold, 243 (71%) were treated with chemotherapy at relapse. CA-125 response rates to platinum-based chemotherapy were significantly higher compared to non platinum chemotherapy (51% vs 21%, $P < 0.001$). Among patients with a platinum-free interval (PFI) of 3–6 months, OS2 in patients treated with platinum was significantly longer compared to individuals receiving non platinum-based treatment (median 17.67 months, 95% CI: 14.79–20.75 vs. 10.62 months, 95% CI: 8.02–12.72, $P = 0.022$). The patterns were similar when restricted to patients with high-grade serous histology. In patients with PFI <3 months, there was no significant difference in response or survival according to type of second-line treatment.

Conclusions. Our findings further question the use of a 6-month PFI as an arbitrary threshold for subsequent treatment decision-making. Some patients considered "platinum resistant" still derive clinical benefit from platinum-based chemotherapy. Biomarkers of platinum sensitivity are needed in clinical practice to identify potential responders who should be offered re-treatment with platinum.

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1. Introduction

Most women with epithelial ovarian cancer (EOC) present with advanced disease and are treated with debulking surgery and chemotherapy. The vast majority of patients will still recur [1] and require secondary treatment. Treatment for relapsed disease is mainly guided by the expected response to subsequent chemotherapy. The platinum-free interval (PFI) has been used to categorize relapsed disease as platinum-refractory (progression during therapy or within 4 weeks after last platinum dose), resistant (PFI <6 months), partially sensitive (PFI 6–12 months) and sensitive (PFI >12 months) [2]. These definitions are also commonly used as inclusion criteria in clinical trials of EOC patients [3–5]. However, this categorization is based on small retrospective studies showing that responses to second-line platinum are less likely with shorter time since last platinum-based chemotherapy [6–8]. On the other hand there are anecdotal reports of observed responses to platinum also in patients considered platinum-resistant [9]. There is now substantial evidence that other factors, such as *BRCA1/2* mutation status, affect the response to re-treatment with platinum [10]. In The Cancer Genome Atlas dataset, second-line platinum resulted in longer progression-free survival (PFS) even in patients with short PFI [11]. However, the analysis only included high-grade serous histologies and platinum-resistance was defined broadly as treatment-free interval (TFI) of <18 months. In a recent study of elderly women, platinum combination therapy was associated with decreased risk of death compared to non platinum based therapy also in patients with PFI of 3–6 months [12].

It is crucial to select the most effective treatment for EOC patients at relapse, as single agent non-platinum chemotherapy only yields response rates of 8–21% [3,13–15]. The addition of bevacizumab improves response rates [4], but funding restrictions and concerns about the risk of gastrointestinal side effects in patients with considerable bowel involvement limit its use in patients considered platinum-resistant. This study assessed response to and survival after second-line chemotherapy, comparing platinum- and non-platinum-based chemotherapy in a prospective population-based cohort of EOC patients.

2. Methods

2.1. Patient cohort

Patients were identified in the Australian Ovarian Cancer Study (AOCS), an Australia-wide population-based observational study that prospectively recruited patients between 2002 and 2006. Women with invasive epithelial ovarian, peritoneal, or fallopian tube cancer, aged 18–80 years, were recruited at diagnosis. AOCS was approved by the Human Research Ethics Committees at the Peter MacCallum Cancer Centre, Queensland Institute of Medical Research, and all participating hospitals. In this retrospective analysis we included patients with high-grade carcinomas of all histological subtypes treated with platinum-based chemotherapy in first-line (N = 1086, Fig. 1). Patterns of response to second-line chemotherapy and survival were analyzed according to PFI in all histologies and separately in high-grade serous cases.

2.2. Clinical and pathologic data

Assessment of medical records, histopathology, data on progression and follow-up have been described previously [10,16]. Chemotherapy data in first- and second-line and response assessments, including CA-125 levels and imaging results, were obtained from medical records through AOCS. Cases were reviewed by a panel of gynecologic pathologists.

2.3. Clinical definitions

Response to second-line treatment was assessed using Gynaecological Cancer InterGroup (GCIG) CA-125 definitions [17]. Briefly, ≥50% reduction in CA-125 from an elevated pretreatment level, maintained for at least 28 days was considered a response. All other evaluable cases were categorized as "No response". Response by CA-125 was not evaluable if (1) CA-125 was ≤2× upper normal limit (UNL) prior to second-line treatment or (2) there was no CA-125 reading on or after second-line treatment or (3) only one reduced CA-125 reading was available after start of second-line.

PFS was the time interval between the dates of diagnosis and disease progression, based on GCIG criteria [17]. When CA-125 was not evaluable or progression preceded a CA-125 increase, date of first progression was based on imaging, deterioration in health status attributable to disease, or death. PFI was defined as the time between the dates of last dose of platinum-based chemotherapy given in first-line and progression.

Overall survival (OS) was the time interval between the dates of diagnosis and death from any cause, or last follow-up. OS2 was defined as the time interval between dates of first dose of second-line chemotherapy to death from any cause, or last follow-up.

2.4. Statistical analysis

Descriptive statistics were used. Comparisons between groups were performed using *t*-tests, Fisher's exact tests or Cochran-Armitage test as indicated. Differences in survival were determined using Kaplan-Meier curves with log rank test. *P*-values <0.05 were considered statistically significant and all tests were two-sided. Analyses were performed with STATA, version 12.0 (Stata Corp LP, Texas, USA).

3. Results

3.1. Clinical characteristics

Of the 1086 women included, 882 progressed (81.2%) and 828 died (76.2%) with a median follow-up of 10 years. Baseline characteristics are listed in Table 1 and the cohort description is shown in Fig. 1. Among women who progressed, most patients (n = 541, 61.3%) had a PFI of >6 months, 228 (25.8%) between 6 and 12 months and 313 (35.5%) >12 months. Of those with a PFI of ≤6 months (38.7%, 341/882), 190 (21.5%) had a PFI of 3–≤6 months and 151 (17.1%) had a PFI of 0–≤3 months. Second-line treatment for all patients according to PFI is listed in Table 2 and Supplementary Table S1.

Patients with longer PFI were more likely to be re-treated with platinum-based chemotherapy ($P < 0.001$) (Supplementary Fig. S1) and longer PFI was associated with longer OS ($P < 0.001$) and OS2 ($P < 0.001$) (Fig. 2A and B).

3.2. Responses to platinum-based therapy associated with PFI

Baseline characteristics of patients with PFI ≤6 months according to the type of second-line treatment regimen are shown in Table 1. Of these 243 patients, 24% (n = 58) received platinum-based chemotherapy, either with platinum-combination (n = 38) or single-agent platinum (n = 20). The majority of patients with PFI ≤6 months (n = 185, 76%) received non platinum-based chemotherapy. The most commonly administered non platinum agents were pegylated liposomal doxorubicin (PLD) (n = 130), weekly taxol (n = 24), doxorubicin (n = 10) or topotecan (n = 8). Patients treated with platinum were more likely to undergo third line chemotherapy at the time of progression when compared to patients treated with non platinum (46/58, 79% (after platinum) vs 107/185, 58% (after non-platinum), respectively, $P = 0.003$).

Overall, 486/654 (74.3%) patients who received second-line chemotherapy were evaluable by CA-125 (Fig. 1). Response rates to platinum-based chemotherapy were higher than to non-platinum, and response to both platinum- and non-platinum-based treatment increased with increasing PFI (Fig. 3A and B). Among patients with a PFI ≤6 months, the response to platinum-based chemotherapy was significantly higher

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