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Primary and acquired platinum-resistance among women with high grade serous ovarian cancer

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HIGHLIGHTS

- Primary (PPR) and acquired (APR) platinum-resistant patients have a poor prognosis.
- Survival is related to the number of biologic agents received in PPR patients.
- Stage and clinical trial participation predicts survival in APR patients.

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ABSTRACT

Objective. Women with primary platinum resistant (PPR) high grade serous ovarian cancer (HGSOC) are known to have a poor prognosis. Less is known regarding outcomes in patients with acquired platinum resistance (APR). The goal of this study was to evaluate survival in both PPR and APR patients.

Methods. A retrospective review of HGSOC patients diagnosed between 2000 and 2010 was performed. Descriptive statistics summarized clinical characteristics and demographics. The Kaplan-Meier method estimated progression free survival (PFS) and overall survival (OS). The association of OS and clinical factors was modeled using Cox proportional-hazards.

Results. Of the 330 patients identified, 81 (25%) had PPR. Of the remaining women, 55 (22%) developed APR. Median PFS of PPR patients was 4.2 months and median OS was 17.8 months. On multivariate analysis, the number of biologic agents received was the only predictor of OS. Patients with APR had a median PFS of 14.2 months and a median OS of 56 months. OS from the date of platinum resistance was 21.9 months, though this was not different than PPR patients ($p = 0.19$). Multivariate analysis found cancer stage and clinical trial participation to be associated with OS.

Conclusions. Platinum resistance confers a poor prognosis in the APR and PPR setting. The number of biologic agents received is the strongest predictor of OS among women with PPR. Cancer stage and clinical trial participation predicts OS in patients with APR. Providing opportunities to participate in clinical trials, especially those involving targeted therapy, should be a priority in these populations.

1. Introduction

Though ovarian cancer only accounts for approximately 3% of cancer cases among women, it is one of the most deadly. In 2015, it is estimated that there will be approximately 21,000 new ovarian cancer cases, and more than 14,000 women will die from the disease [1]. Though most patients will achieve remission with front-line platinum-based chemotherapy, up to 80% of these women will recur [2].

Upon relapse, ovarian cancer patients are classified according to the length of time since they last received a platinum agent. Patients who relapse within six months of completing initial platinum therapy are primary platinum-resistant. These women carry a poor prognosis, with response rates to subsequent lines of therapy ranging from 7 to 20%. Patients who relapse more than 6 months following primary platinum therapy are considered to be platinum-sensitive. In contrast to platinum-resistant patients, women who are platinum-sensitive can expect response rates of 30–90% to additional platinum agents, with higher response rates noted in patients with a longer platinum-free interval. Unfortunately, almost all platinum-sensitive patients will eventually develop resistance, at which point they are considered to have acquired platinum-resistance [3–6].

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The poorer prognosis of platinum-resistant ovarian cancer as compared with platinum-sensitive ovarian cancer is well-documented. However, there is no published data evaluating outcomes in the acquired platinum-resistant population. The purpose of this study is to describe survival among women with acquired platinum-resistance as compared with women with primary platinum-resistance in a cohort of patients with high grade serous ovarian cancer.

2. Materials and methods

A retrospective review was conducted of women with high grade serous ovarian cancer treated at The University of Oklahoma Health Sciences Center between January 2000 and December 2010. Approval was obtained from the Institutional Review Board (IRB) prior to initiating the study. As no data was collected prospectively, a waiver of informed consent was granted by the IRB. Women were excluded from the study if there was no histologic confirmation of their diagnosis, the status of platinum sensitivity could not be determined, or they had inadequate data in the medical record.

Clinical data was abstracted from the medical record. Treatment outcomes were recorded based on Response Evaluation Criteria in Solid Tumors (RECIST) and serum CA-125 levels [7,8]. Biologic agents were defined as any non-cytotoxic drug that was prescribed as a treatment for the patient's cancer and included medications used within or outside of a clinical trial. Patients were categorized as primary platinum-resistant if they recurred within six months of the conclusion of primary platinum chemotherapy. Platinum-sensitive patients who then progressed or recurred within six months of receiving additional platinum were deemed to have acquired platinum-resistance.

Progression free survival (PFS) was defined as the time from the last day of the initial chemotherapy to the first recorded evidence of progression. Without progression, survivors were censored at last follow-up and non-survivors were censored at the date of death. Overall survival (OS) was defined as the time from the last day of the initial chemotherapy to death (all causes), unless noted otherwise. Survivors were censored at last follow-up.

Descriptive statistics were used to summarize patient demographics and clinical characteristics. Wilcoxon rank-sum tests were used to compare skewed continuous variables between groups. Survivor curves were estimated using the Kaplan-Meier method and compared using log-rank tests. The Cox proportional-hazards models were used to assess the association of demographic and clinical characteristics with OS. Variables considered included age at diagnosis, stage, BMI, primary treatment, bevacizumab usage with cytotoxic agents, number of biologic regimens, residual disease, and participation in clinical trial. Hazards ratios (HR) with their 95% confidence intervals (CI) were computed. Two-way interactions were assessed in building the final model. All statistical evaluation was performed using the SAS software version 9.2 (SAS Institute, Cary, NC). All reported p-values were 2-sided, and $p < 0.05$ was considered statistically significant.

3. Results

Of the 330 women included in the study, the majority presented with stage III (72.4%) or stage IV (15.8%) disease. In total, 81 (25%) women were primary platinum-resistant. Of the remaining 249 patients, 55 (22%) developed acquired platinum-resistance during the study period. Demographic and clinical characteristics of these groups are summarized in Table 1.

Table 1
Demographics and clinical outcomes.

	Primary platinum resistant (n = 81)	Acquired platinum resistant (n = 55)
Age in years	67	61
Median	(17–88)	(31–87)
(Range)		
Race % (n)	87.7 (71)	94.4 (51)
White	4.9 (4)	3.7 (2)
African-American	2.5 (2)	1.9 (1)
Native American	2.5 (2)	0 (0)
Asian	2.5 (2)	0 (0)
Hispanic		
BMI	26.6	25.1
Median	(13.7–46.7)	(17.3–61.3)
(Range)		
Stage % (n)	1.2 (1)	9.1 (5)
II	71.6 (58)	76.4 (42)
III	23.5 (19)	14.6 (8)
IV	3.7 (3)	0 (0)
Unstaged		
Primary treatment %	7.4 (6)	1.8 (1)
(n)	13.6 (11)	7.3 (4)
Chemotherapy only	79.0 (64)	90.9 (50)
Neoadjuvant chemo/surgery		
Surgery/adjuvant chemo		
Debulking % (n)	61.7 (50)	83.6 (46)
Optimal	30.9 (25)	14.6 (8)
Suboptimal	7.4 (6)	1.8 (1)
N/A or unknown		
Number of treatment	3	5
regimens	(1 − 10)	(3 − 11)
Median		
Range		
Number of cytotoxic	3	4
agents	(1–8)	(2–8)
Median		
Range		
Number of biologic	60.8 (48)	34.6 (19)
agents % (n)	30.4 (24)	41.8 (23)
0	8.9 (7)	23.6 (13)
1		
≥2		
Clinical trial	50.6 (41)	54.6 (30)
participation % (n)		
Follow-up time in	22.3	50.7
months	(0.8–88.8)	(12.1–173.2)
Median		
Range		
PFS in months (95% CI)	4.2 (3.6–4.7)	14.2 (11.1–21.3)
OS in months (95% CI)	17.8 (13.8–23.3)	56.0 (40.2–76.3)

3.1. Primary platinum resistance

Primary platinum-resistant women had a median age of 67 years (range 17–88), a median BMI of 26.6 kg/m^2, and the majority of patients had stage III disease (71.6%). Upon diagnosis, 79.0% (n = 64) of women underwent primary cytoreductive surgery followed by adjuvant platinum-based chemotherapy. While 13.6% (n = 11) of patients were dispositioned to neoadjuvant chemotherapy followed by interval cytoreductive surgery, only 7.4% (n = 6) were treated with platinum-based chemotherapy alone. In all, 29.6% of primary platinum-resistant patients (n = 24) had a complete response (CR), 54.3% had stable disease (SD) or a partial response, and 16.1% (n = 13) had disease progression at the conclusion of primary therapy.

The median number of treatment regimens for primary platinum-resistant patients was 3 (range 1–10). When this was evaluated by type of treatment received, the median number of cytotoxic agents was 3 (range 1–8), while the median number of biologic agents was 0 (mean 0.58, range 0–7). Of the 79 women with evaluable data, 48 (60.8%) received no biologic agents, 24 (30.4%) had 1 biologic agent, and 7 (8.9%) had ≥2 biologic agents.

With a median follow up of 22.3 months, primary platinum-resistant patients had a median PFS for front-line therapy of 4.2 months (95% CI 3.6–4.7) and a median OS of 17.8 months (95% CI 13.8–23.3). When calculated from the date that the patient was determined to be primary platinum-resistant, OS was 15.1 months (95% CI 12.5–23.3). Of interest,