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Case series

Nivolumab use for *BRCA* gene mutation carriers with recurrent epithelial ovarian cancer: A case series

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ABSTRACT

Tumors deficient in DNA mismatch repair are known to display increased susceptibility to immune checkpoint inhibitors due to accumulation of DNA damage and increased neoantigen load. This suggests that deficiency in the *BRCA*-related DNA repair mechanism may also be a surrogate marker for immunotherapy response. The aim of this study was to examine the efficacy of the immune checkpoint inhibitor, nivolumab, in women with *BRCA* gene mutations and recurrent müllerian cancer. This retrospective case series followed six *BRCA* carriers who received nivolumab monotherapy (3.0 mg/kg, intravenous, day 1 and 15, every 4 weeks) as salvage therapy for recurrent epithelial ovarian ($n = 5$) and fallopian tubal ($n = 1$) cancers. Toxicity, treatment response, and survival were examined. Median age was 57 (range 51–64). *BRCA*1 and 2 mutations were equally distributed. All had high-grade serous histology, and all but one had advanced-stage disease at initial diagnosis. The majority had platinum-resistant disease ($n = 4$). All received salvage therapy prior to nivolumab therapy (median 3 lines), including PARP inhibitors ($n = 3$). The median number of nivolumab treatment cycles was 9, including 2 women receiving 18 cycles. Three women developed nivolumab-related toxicities, most commonly grade 2 hypothyroidism ($n = 2$). Median follow-up time was 13.4 months, and there were 3 complete responses, 1 partial response, and 2 patients with progressive disease. Objective response rate was 67% (4 out of 6). In conclusion, our study suggests that nivolumab monotherapy is well-tolerated and may be an effective salvage therapy for *BRCA* mutation carriers with recurrent epithelial ovarian, fallopian tubal, and primary peritoneal cancers.

1. Introduction

In 2018, ovarian cancer remains the most deadly gynecologic malignancy in the United States (Siegel et al., 2018). The vast majority of patients ultimately recur, after which systemic chemotherapy plays a pivotal role. The currently available effective approaches for recurrent ovarian cancer include cytotoxic chemotherapy and biological targeting, such as anti-angiogenic and DNA repair inhibition. Recently, studies have shown that immunotherapy can be another effective treatment modality for recurrent disease.

In high-grade serous ovarian carcinoma, the most common histological type of ovarian cancer, nearly 15% of women harbor germline *BRCA* mutations, and nearly half of tumors have alterations in the homologous recombination pathway (Liu and Konstantinopoulos, 2017). A recent study has shown that BRCA-mutated high-grade serous ovarian carcinomas have a high mutational load and more tumor-specific neoantigens (Strickland et al., 2016). In general, tumors with a high mutation burden have increased levels of neoantigens, which play a major role in the activity of immunotherapy (Hamanishi et al., 2016; Schumacher and Schreiber, 2015). These neoantigens recruit tumor-infiltrating T lymphocytes, resulting in a compensatory upregulation of the programmed cell death protein 1 (PD-1) pathway and suppression of the host immune system. PD-1 is a cell surface receptor that interacts with its ligand (PD-L1) to downregulate T cell activity (Ishida et al., 1992). Thus, targeting the PD-1 pathway with a checkpoint inhibitor is an attractive approach in hyper-mutated tumors.

A recent clinical trial has shown anti-tumor activity with immune checkpoint inhibitors against tumors with mismatch repair deficiencies (Le et al., 2017; 2015). This proof-of-principal study led to the theory that inhibiting the PD-1/PDL-1 pathway may be effective in sustaining

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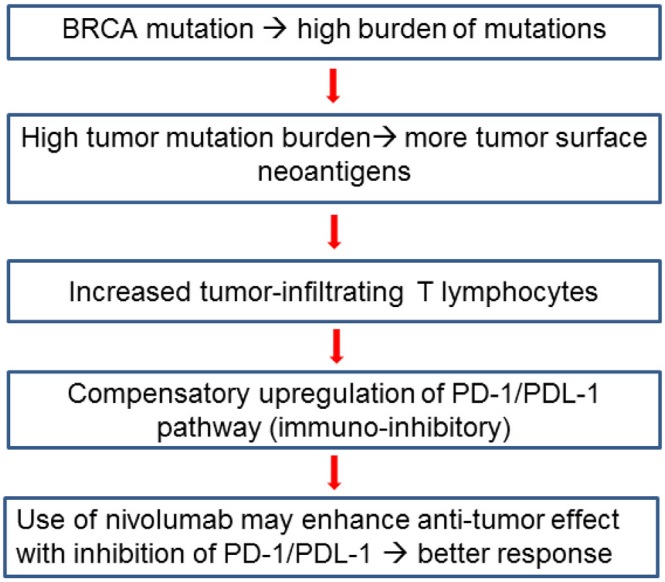

Fig. 1. Schema for proposed rationale of the study.

T lymphocyte activity against BRCA-mutated tumors.

Based on this mechanism (Fig. 1), we hypothesized that the immune checkpoint inhibitor, nivolumab, may be effective against recurrent epithelial ovarian cancer in women harboring a *BRCA* gene mutation. The objective of the study was to describe the effectiveness of an immune checkpoint inhibitor, nivolumab, on patients with recurrent ovarian cancer and a *BRCA* mutation in a retrospective case series.

2. Patients and methods

2.1. Eligibility criteria

Upon obtaining Institutional Review Board approval at the University of Southern California (USC), an institutional database was utilized to retrospectively identify eligible cases between January 2016 and December 2017 at Los Angeles County USC Medical Center and USC Keck Medical Center. The inclusion criteria were women with germline *BRCA* 1/2 mutations and recurrent epithelial ovarian, fallopian tubal, or primary peritoneal carcinoma who received nivolumab as salvage therapy. Patient demographics, tumor characteristics, treatment and response details, adverse events, and survival outcomes were abstracted from medical records.

2.2. Clinical information

Patient demographics included age at nivolumab treatment, race/ethnicity, and *BRCA* mutation type. Tumor characteristics at initial diagnosis included cancer type, stage, histology, and platinum sensitivity status. Treatment history included previous utilization of poly ADP ribose polymerase (PARP) inhibitors, lines of salvage chemotherapy prior to nivolumab, and the details of nivolumab therapy (dose, schedule, and number of cycles administered). Treatment response included objective response rate and clinical benefit rate. Adverse events during nivolumab therapy were also collected. Survival outcomes included progression-free survival and overall survival.

2.3. Study definition

Cancer stage was based on the 2014 International Federation of Gynecology and Obstetrics (FIGO) criteria. Treatment response was assessed *via* the immune-related Response Evaluation Criteria in Solid Tumor (iRECIST, version 1.0) (Seymour et al., 2017). Objective response rate was defined as either complete response or partial response. Clinical benefit rate was defined as complete/partial responses and stable disease. Treatment-related toxicity was assessed with the National Cancer Institute's Common Terminology Criteria for Adverse Event (CTC-AE, version 5.0). Progression-free survival was defined as the time interval between the initiation of nivolumab and the first progression of disease or death. Overall survival was defined as the time interval between the initiation of nivolumab and death from disease any reason (all-cause). Women with the above survival events were censored at the last follow-up.

2.4. Statistical consideration

Continuous variables were assessed for normality, expressed with mean and standard deviation or median and range as appropriate. Categorical variables were expressed with number and percent proportion. Standard descriptive analysis was performed for this case series.

3. Results

Six women met the inclusion criteria and their demographics are summarized in Table 1. The median age at initiation of nivolumab treatment was 57 years (range 51–64), and the majority were younger than 60 years of age (n = 4, 67%). Race/ethnicity varied (Caucasian, non-Hispanic n = 2, 33%, Asian n = 2, 33%, and Hispanic n = 1, 17%). *BRCA* mutations were equally divided between *BRCA1* (n = 3, 50%) and *BRCA*2 (n = 3, 50%).

Tumor characteristics are shown in Table 2. High-grade serous ovarian carcinoma constituted the majority of cases (n = 5, 83%). All but one woman had advanced-stage disease at diagnosis (stage III-IV n = 5, 83%). All women received a platinum and taxane doublet as initial therapy. Prior to nivolumab initiation, all women received salvage chemotherapy: 4 (67%) women received 3 or fewer regimens, and 2 (33%) women received > 6 regimens. The majority of the study population had platinum resistant disease (n = 4, 67%). Three (50%) women were previously treated with a PARP inhibitor.

Treatment type is shown in Table 3. Treatment dose for nivolumab was 3.0 mg/kg, intravenously, day 1 and 15, every four weeks in all patients. A median of 9 (range 3–18) cycles were administered. Three (50%) women received > 10 cycles. Three (50%) women achieved a complete response, one (17%) had a partial response, and two (33%) experienced progressive disease. These statistics indicate that both objective response rate and clinical benefit rate were 67%.

Toxicity profile related to nivolumab therapy is shown in Table 3. There were three (50%) women who developed toxicity related to nivolumab (all were grade 2). The most common toxicity was hypothyroidism (median time to onset, 3 months), all cases of which were successfully treated with oral levothyroxine. One patient (Case 3) opted to hold nivolumab treatment due to thyroid lab abnormalities. Despite cessation, the treatment response has been maintained after nine months off the drug. In another patient (Case 2) nivolumab treatment was held due to developing lichen planus after 18 cycles, and she

Table 1
Patient demographics.

No.	Age	Race/Ethnicity	Cancer type	Gene	Mutation
1	64	Asian	PPC	*BRCA2*	c.3744_3747delTGAG
2	63	Other	HGSOC	*BRCA1*	c.5444G > A
3	52	Caucasian	HGSOC	*BRCA1*	Deletion exons 1–7
4	59	Caucasian	HGSOC	*BRCA2*	c.5946delT
5	55	Asian	HGSOC	*BRCA2*	c.276dupA
6	51	Hispanic	HGSOC	*BRCA1*	c.4327C > T

Abbreviations: HGSOC, high-grade serous ovarian carcinoma; and PPC, primary peritoneal carcinoma

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