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CASE REPORT

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Dendritic cell immunotherapy and topotecan-based metronomic chemotherapy in ovarian cancer — a case study and literature review

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Abstract

Advanced ovarian cancer is associated with an unsatisfactory prognosis. Systemic treatment toxicities adversely affect patient quality of life. Therefore, new, better therapies are needed. We present a case of a patient treated for recurrent ovarian cancer with a sequence of experimental cellular immunotherapy and chemotherapy in both classical and metronomic dosing with satisfactory results. A brief literature review on the subject of metronomic chemotherapy and immunotherapy in ovarian cancer is also provided. The addition of a dendritic vaccine to standard chemotherapy may be a valuable therapeutic option in the group of patients with platinum-sensitive recurrent ovarian cancer. Metronomic chemotherapy is not adequately researched in this setting although it appears to be a noteworthy alternative to classically dosed chemotherapy.

Keywords: ovarian cancer, immunotherapy, metronomic chemotherapy, topotecan, dendritic vaccine

Introduction

Ovarian malignancies currently rank eighth in the world for morbidity and mortality, with a 5-year survival rate in Europe of 23.1% [1]. The multimodal approach including surgery, chemotherapy, and targeted therapy is a standard of care in all stages of the disease [2]. Despite recent advances, currently available systemic treatment regimens still rely heavily on intensive chemotherapy that is characterized by hematological, neurological, cardiovascular, and gastroenterological toxicities that adversely impact patient quality of life (QoL) [3]. Most of these chemotherapy protocols are developed in a way that maximizes the cytotoxic effect by using doses that are very close to the levels that are unacceptably toxic to healthy tissues. Metronomic chemotherapy offers an alternative approach. Altering the dosing regimen so that lower doses are administered more frequently allows the use of noncytotoxic mechanisms of action, thus minimizing side effects and reducing the risk of developing acquired resistance [4]. The obvious benefits of the metronomic approach comprise lower risk of high-grade adverse events, availability to patients unfit for classical cytotoxic regimens, in some cases, the reliance on oral medications, better QoL, and lower cost. Drawbacks include more frequent visits and clinical data limited to few indications [5]. Cancer immunotherapy is based on specific or nonspecific activation or reactivation of selected parts of the immune system to produce a therapeutic effect based on the organism's natural adaptive antineoplastic potential [6]. Although immunotherapy has revolutionized the whole field of oncology in recent years, its utilization in ovarian cancer is still comparatively low.

Case report

A 57-year-old patient was diagnosed with an ovarian mass on abdominal ultrasound performed because of abdominal pain and bloating. She also suffered from obesity, arterial hypertension, and osteoarthritis. Her

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environmental and family history were not significant. After further evaluation, she underwent a radical bilateral oosalpingohysterectomy, with simultaneous omentectomy and appendectomy. Pathological evaluation resulted in the diagnosis of grade 3 adenocarcinoma, a serous papillary subtype, involving both the ovaries and the peritoneum. The initial clinical stage was assessed at III C (according to the classification of the International Federation of Gynecology and Obstetrics, Fédération internationale de gynécologie et d'obstétrique, 1988). Two months after the surgery, she started a typical 6-cycle adjuvant treatment with paclitaxel and carboplatin. After completing treatment, she underwent a typical active follow-up.

Thirty-three months after surgery, a routine computed tomography (CT) scan revealed metastases to the peritoneum, including the surface of the liver. The patient was enrolled in the SOTIO SOV02 clinical trial that tested the efficacy of the DCVAC/ /OvCa dendritic vaccine combined with standard chemotherapy compared to standard chemotherapy alone (NCT02107950). After successful screening, the patient underwent peripheral blood leukocyte apheresis. Separated mononuclear cells were processed in the sponsor's laboratory. Patients' stem cells matured *in vitro* to immature dendritic cells. The dendritic cells were then exposed to standard ovarian cancer cells that had previously been cytolyzed using a method that maximized their immunogenicity. Then, dendritic cells prepared in this way were activated *in vitro* and sent back to the site to be administered to the patient.

During vaccine production, standard-of-care therapy was started. It consisted of six cycles of carboplatin (AUC 5) on day 1, and gemcitabine (1000 mg/m^2) on days 1 and 8, administered every 21 days. Each cycle was administered. The DCVAC/ /OvCa vaccine was initiated 7 weeks after the first dose of chemotherapy. Ten cycles were given at intervals of 4 to 6 weeks. The first 4 doses of the vaccine were administered concurrently with chemotherapy, the next 6 were administered as monotherapy. As olaparib had just received its first approval at the time and was not yet reimbursed, no PARP inhibitor maintenance nor BRCA testing was performed.

The patient suffered chemotherapy toxicity in the form of recurrent cytopenia in all three lines, resulting in a notable reduction in dose intensity. Furthermore, persistent delayed nausea occurred, which was refractory to the standard premedication regimen according to current guidelines [7]. No toxicities attributed to immunotherapy were observed. After the completion of chemotherapy, as vaccine monotherapy continued, all previous toxicities improved, and no new ones occurred. On the follow-up CT scan 10 months after randomization, asymptomatic progression of intraperitoneal implants was discovered.

Second-line chemotherapy was initiated, based on pegylated liposomal doxorubicin at a dose of 50 mg/m^2, administered every 4 weeks. Due to recurrent leukopenia, the dose intensity was again substantially reduced. The follow-up CT scans after 3 and 6 months of treatment showed stable disease. After 6 cycles, there was symptomatic progression of the peritoneal implants, confirmed by CT, 9.5 months after the start of chemotherapy. At the same time, the level of the tumor marker human epididymis protein 4 [(HE4); subfraction 4 of human protein from epididymal epithelial cells] was increasing.

As classical third-line palliative chemotherapy was deemed unfeasible due to the poor tolerance of the previous regimens, it was decided to use metronomic chemotherapy with topotecan in a dose of 1 mg/day per os (p.o.) continuously. Initially, a deep radiological partial response and a two-fold decrease in HE4 levels were achieved. When the level of HE4 increased during treatment, cyclophosphamide was added at a dose of 50 mg/day, also in continuous doses. Modification of the regimen occurred in the absence of clinical or radiological progression. It was dictated by the fact that the preceding episodes of disease progression in the patient had always been preceded by an increase in HE4. The addition of cyclophosphamide caused a 10-fold decrease in HE4 levels. During metronomic chemotherapy, hematological toxicities reoccurred, although with a more manageable intensity, and caused fewer treatment interruptions. The therapy lasted 13 months after which a clinical and radiological progression of the peritoneal lesions occurred.

In the fourth line, weekly paclitaxel chemotherapy was started at a dose of 80 mg/m^2. Only 8 cycles were given. Two months into chemotherapy, a further biochemical and clinical progression occurred.

The last treatment line was chemotherapy with weekly carboplatin (AUC2) in combination with gemcitabine 850 mg/m^2. Treatment was stopped after only 3 cycles due to a severe infusion reaction. The patient refused further treatment and died soon after, with symptoms of cancer progression. Overall survival (OS) for recurrent disease was 45 months.

Discussion

Topotecan works by attaching to the DNA-topoisomerase I complex and inhibiting DNA religation. Effective inhibition of the complex leads to the accumulation of DNA breaks, causing replication inhibition and cell death [8]. Topotecan is also known to have an antiangiogenic effect by inhibiting the transcriptional activity of hypoxia-induced factor 1-α (HIF-1α) [9] and the production of VEGF (vascular endothelial growth factor) [10]. Furthermore, it has been shown that the use of topotecan in metronomic

doses inhibits sympathetic neuroblastoma cell growth with amplification of MYCN (avian myelocytomatosis viral oncogene neuroblastoma-derived homolog viral oncogene of avian myelocytoma), both *in vitro* and *in vivo*, caused by therapy-induced senescence, cell cycle arrest, and DNA double-strand breaks. Metronomic chemotherapy with topotecan applied to ovarian cancer cell lines *in vitro* compared to the maximum tolerated dose (0.5, 1.0, and 1.5 mg/kg/day *vs.* maximum tolerated dose of 7.5 and 15 mg/kg per week) allows achieving a greater reduction in tumor microvessel density; in addition, tumor endothelial cells show a significantly higher sensitivity to topotecan with metronomic dosing [11]. Metronomic chemotherapy with topotecan seems to be a promising research direction, not only because of the possibility of enhancing its antiangiogenic effect, inducing continuous cytotoxicity toward endothelial cells but also because of the potential reduction in the severity of its side effects.

In ovarian cancer, the dose of topotecan recommended by the European Medicines Agency (EMA) is 1.5 mg/m^2 *intravenosus* (iv) daily for 5 days in cycles every 21 days [12]. The reported incidence of key toxicities is grade 4 neutropenia in 81.4%, grade 3/4 anemia in 40.4%, grade 4 leukopenia in 32.7%, and grade 4 thrombocytopenia in 25.4% of patients. More than half (58%) of patients treated this way experience treatment delays, and 30% are forced to have their dose reduced [13]. In the largest study evaluating the efficacy of intravenous topotecan in patients with ovarian cancer, who had failed one platinum-based therapy line for relapsed disease, the objective response rate (ORR) was reported at 20.5%, and median progression-free survival (PFS) was 4.35 months [14].

Reducing the dose of cytotoxic drugs used in metronomic chemotherapy has the potential to improve QoL by minimizing toxicity [4]. There is a body of preclinical evidence on low-dose metronomic topotecan impeding the activity of crucial pathways involved in sustained proliferative signaling and neoangiogenesis [11, 15]. Several works investigated the clinical utility of such regimens in ovarian cancer. In a phase II Canadian trial, 63 pretreated ovarian cancer patients were randomized to topotecan 1.5 mg/m^2 iv daily for 5 days repeated every 21 days, or topotecan 1.75 mg/m^2 as a 24-hour infusion once a week for 4 weeks repeated every 6 weeks. The response rates were 22.6% *vs.* 3.1% ($p = 0.026$); the toxicity was significantly lower for the weekly regimen and survival data were similar between arms [16]. In a subsequent dose escalation study, 41 patients with pretreated ovarian cancer were treated with continuous weekly topotecan at a starting dose of 1.5 mg/m^2, escalated in 0.5 mg/m^2 increments of 0.5 mg/m^2 every 21 days up to a maximum dose of 4.0 mg/m^2. The toxicity profile was favorable: 17% of patients had grades 3–4 neutropenia and 22% had grades 3–4 fatigue with no grade 4 thrombocytopenia or anemia reported. The response rate was 24% with a clinical benefit ratio of 66% and the median time to progression (MTTP) was 3.6 months [17, 18]. An Israeli phase II single-arm study investigated 23 pretreated patients, treated with 4 mg/m^2 administered weekly for 3 weeks in a 28-day cycle. The toxicity profile was favorable with 4.3% of grade 3 neutropenia, 4.3% of grade 3 anemia, and grade 3 thrombocytopenia that required a dose reduction in 17.4% of cases. The ORR was 47.8% and median PFS was 4.9 months [19]. Another study of 69 women with a pretreated disease investigated a topotecan dose of 3.75 mg/m^2 administered iv, on days 1, 8, and 15 of a 28-day cycle. The toxicity profile was again favorable. The ORR was 20.3%, and median PFS was 5.7 months [20]. Although there were studies that showed a similar activity of high-dose, 3-weekly intravenous topotecan to high-dose, 3-weekly oral topotecan [21, 22], there is surprisingly little evidence on the metronomic approach using the oral formulation that is readily available and well suited for a continuous low-dose approach. A study of 72 patients treated with metronomic oral topotecan alone or with oral cyclophosphamide for standard refractory relapsed ovarian cancer (median of 2 previous lines and 18.3 months of prior treatment) was recently published. The authors reported a radiological response rate of 27.2% and a disease control rate of 86.3%. They evaluated that median PFS was 3.65 months in the general population and 10.7 months among the responders. G3–4 neutropenia occurred in 32.8% of patients; G3–4 thrombopenia in 3.8%, and G3–4 anemia in 25.9%. These results, although preliminary, show promise and warrant further studies of metronomic topotecan dosing [23].

There were studies searching for possible immune checkpoint regimens to treat ovarian cancer, specifically concentrated around the ligand of programmed cell death protein 1 (PD-L1)/programmed cell death protein 1 (PD-1) blockade. The use of antibodies such as nivolumab (anti-PD-1) and avelumab (anti-PD-L1) has not shown an improvement in PFS or OS in patients with platinum-resistant ovarian cancer [24, 25]. The phase II multicohort KEYNOTE-158 study with previously treated advanced microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers showed that pembrolizumab (anti-PD-1) generated an ORR in 40.9% (95% CI 20.7–63.6%) of 25 ovarian cancer patients enrolled in the study. This supports the use of pembrolizumab in dMMR/MSI cancer patients [26].

Therapeutic vaccines are designed to eliminate cancer cells by stimulating a specific immune response. The main mechanism of the activity of anticancer vaccines is generation of antigen-specific CD8+ T-lymphocytes, which stimulate the formation of cytotoxic T lymphocytes capable of eliminating cancer cells. An additional desired effect of such a vaccine is the generation of long-term memory CD8 + T cells, which will prevent tumor recurrence. A critical step in vaccination is successful presentation of tumor antigens to T lymphocytes [27]. Dendritic cells are the most efficient antigen-presenting cells [28], and as such, they are being investigated as a therapeutic target. Dendritic cells recognize pathogens, tissue damage signals, and tumor antigens. Then they migrate to secondary lymphatic organs, where they present antigens with the participation of Major Histocompatibility Complex I and II (MHC I/II) molecules to activate T CD4 + and T CD8 + lymphocytes [28]. Neoplastic cells can inhibit dendritic cell maturation and induce modification of their phenotype to activate Th17 or regulatory T lymphocytes. The mechanisms mentioned above are conducive to the failure of the immune system in the fight against cancer [29]. The patient described here was treated with a vaccine containing expanded, activated, autologous dendritic cells that had been loaded *ex vivo* with tumor antigens. The source of neoplastic antigens was standardized allogeneic ovarian cancer cells killed by high hydrostatic pressure. The results of the step-by-step analysis of the SOV02 study published in 2016 revealed only a non-significant trend towards an improvement in OS in the DCVAC/OvCa group, with no difference in PFS or other endpoints. The final analysis published in 2021 showed a significant difference in OS, in favor of the DCVAC/OvCa group, with a reduction in the risk of death of 62% compared to chemotherapy alone. The authors of the study concluded that the used vaccine induced a delayed but sustained antitumor immune response that stabilized the disease in the long term and slowed its progression, resulting in increased survival [30]. This activity pattern with a significant OS benefit, contrasting with little to no benefit in terms of immediate activity signals (i.e. ORR and PFS), has been reported before for a similar immunotherapeutic [31]. Despite the promising results of the SOV02 clinical trial in which the patient participated, the study is formally negative. There are no other positive studies on the use of dendritic vaccines in ovarian cancer; therefore, none of the drugs in this class are currently approved as a treatment option for these patients.

We identified 3 clinical studies (including the SOV02 study) recruiting the same population (first-line patients with recurrent platinum-sensitive ovarian cancer) conducted over a timeframe similar to our patient [30, 32, 33]. Table 1 [30, 32, 33] shows OS reported in these studies in patients treated with standard platinum-based two-drug chemotherapy in combination with targeted drugs. Our patient achieved OS of 45 months from the disease relapse, which is notably above average as compared to the results presented in the cited clinical trials.

The most studied markers associated with ovarian cancer are Cancer Antigen 125 (CA125) and HE4. HE4 is used to monitor patients with ovarian cancer and has several advantages over CA125. In patients with relapse, the level of HE4 can increase several months earlier than the level of CA125, and in some cases, HE4 is the only marker whose level increases before relapse [34, 35]. Our patient achieved satisfactory survival during the treatment of an advanced form of poor prognosis neoplasm. In our opinion, this case study illustrates the importance of giving cancer patients access to clinical trials. It is also another piece of evidence on the favorable activity and toxicity profile of the metronomic topotecan dosing regimen and is a reminder that Ca125 is not the only circulating tumor marker useful in the treatment of ovarian cancer.

Table 1. A selection of results of clinical trials in do-novo ovarian cancer, reflecting the expected prognosis in patients who were clinically similar to the one presented

	Kathleen N. Moore et al. 2019 NCT02092363 [32]	**David Cibula et al. 2021 NCT02107950 [30]**	**Jacobus Pfisterer et al. 2020 NCT01837251 [33]**
Study type	A phase Ib dose escalation study	A randomized, open-label, phase II trial	A randomized, open-label, phase III trial
Patients	37	71	682
Intervention	Ipafricept + carboplatin + + paclitaxel	Carboplatin + gemcitabine *vs.* DCVAC/OvCa + carboplatin + + gemcitabine	Bevacizumab + carboplatin + + gemcitabine *vs.* bevacizumab + + carboplatin + pegylated liposomal doxorubicin
mOS [months]	33	22.1 *vs.* 35.5	27.8 *vs.* 31.9
95% OS confidence interval	23.4–NR	Not reported	25.5–30.2 *vs.* 28.5–34.8

mOS — median overall survival; NR — not reached; OS — overall survival

Article Information and Declarations

Ethics statement

Article have been conducted according to the principles stated in the Declaration of Helsinki.
All authors have read and agreed to the published version of the manuscript.
None of the data reported in Sotio SOV02 trial has been used in this report.

Author contributions

P.M: formal analysis, investigation, resources, data curation, writing — original draft preparation; M.R.-S.: investigation, resources, writing — original draft preparation; P.M.P.: Conceptualization and patient selection, methodology, formal analysis, investigation, resources, data curation, writing — original draft preparation.

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Conflict of interest

P.M., M.R.-S.: declare that they have no conflicts of interest.
P.M.P.: received compensation from Sotio for participation in an SOV02 and SOV03 trials.

Supplementary material

None.

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