Long-Term Tumor-Free Survival in a Patient with Stage IV Epithelial Ovarian Cancer Undergoing High-Dose Chemotherapy and *Viscum album* Extract Treatment: A Case Report

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ABSTRACT

Introduction: Epithelial ovarian cancer (EOC) has a poor prognosis in advanced stages. High-dose chemotherapy (HDC) was pursued in the 1990s but was not found to improve survival of patients with EOC in larger studies. Many patients with cancer use *Viscum album* extracts (VAE). Also called European mistletoe, *Viscum album* can lead to improved quality of life and reduced chemotherapy side effects and may have synergistic cytotoxic and proliferation-inhibiting effects when used together with chemotherapy.

Case Presentation: A high-grade serous epithelial ovarian carcinoma with peritoneal, adrenal, and hepatic metastases (FIGO Stage IV) was diagnosed in a 50-year-old premenopausal woman. Tumor and metastases were surgically removed in cytoreductive surgery, and the patient received adjuvant chemotherapy, without experiencing side effects from treatment. After a second-look surgery revealed lymph node metastases, HDC and autologous hematopoietic stem cell transplantation were performed. Additionally, the patient opted for treatment with VAE, which she continuously received. The patient remained tumor-free in follow-up examinations and has enjoyed good health for 20 years after initial diagnosis.

Discussion: Treatment with VAE in this case might have contributed to the reduction of side effects from HDC and may have acted synergistically with HDC in tumor control. Cases of VAE in EOC should be carefully documented and reported to further illustrate the influence of VAE on this cancer presentation.

INTRODUCTION

High-grade serous carcinoma is presumed to originate from the fallopian tube and is part of the group of epithelial ovarian cancers (EOCs) that share many similarities regarding behavior and clinical course.[1] EOCs have a fair prognosis in early stages but a poor prognosis in advanced stages, with a 5-year survival rate of 92% and 27%, respectively. Most EOCs are diagnosed at an advanced stage.[2] Risk factors include a family history of gynecologic cancers, especially when associated with a *BRCA* gene mutation, which is a positive prognostic factor. Lower cancer stage, young age, low-grade and nonserous histology of the tumor, and patient's unrestricted performance status are further predictors of a more favorable outcome.[2,3] Advanced EOC is treated with surgical cytoreduction and adjuvant chemotherapy. Combination therapy of platinum- and taxane-based regimens show the best results regarding survival.[4] High-dose chemotherapy (HDC) with stem cell transplantation was developed in the 1980s to overcome drug resistance and prevent recurrence,[5] but it did not prove to be effective in EOC regarding overall survival.[6]

Viscum album extracts (VAE) are made from European mistletoe (*Viscum album* L), a hemiparasitic shrub growing on different host trees (eg, apple, pine, elm, oak). Several commercial VAE preparations are used as supportive therapy in patients with cancer. They are administered parenterally, usually subcutaneously, in an increasing, individually adapted dose.[7] VAE contain a variety of active ingredients[8]; the lectins, in particular, have strong cytotoxic and apoptogenic effects and show synergistic effects with radiotherapy and chemotherapy. Downregulation of a variety of cancer genes involved in tumor progression has been shown, as well as a reduction of cell migration, interference with tumor angiogenesis, and selective cyclooxygenase-2 inhibition.[8-10] With its compounds, VAE show immune-modulating effects and reduce tumor-induced immunosuppression.[11,12] Clinical trials have shown an improved quality of life of patients with cancer[13,14] and a promising effect on survival,[13,15] whereas tumor remissions have been reported only in small trials and case reports, usually after high-dose and local VAE application.[16-22] Side effects include frequent dose-dependent local skin reactions and flulike symptoms and occasional pseudoallergic reactions, but otherwise VAE therapy appears safe, even at higher doses.[23]

To our knowledge, no data on the combination of VAE and HDC have been published. We herein report a case involving this combination treatment.

CASE PRESENTATION

Presenting Concerns

A 50-year-old premenopausal white woman received a diagnosis of EOC with peritoneal, adrenal, and hepatic metastases (FIGO [International Federation Gynecology and Obstetrics] Stage IV). She was of healthy weight; enjoyed physical activities, especially hiking, in her spare time; had had 2 pregnancies and 2 births; breastfed each child for several months; and did not use contraceptives. Several relatives of the patient had gynecologic and other cancers: Breast cancer in 2 sisters and a cousin; probable ovarian cancer in her mother and a maternal

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aunt; cancer without further specification in her maternal grandmother; and oto-rhinolaryngologic cancer in her paternal grandfather. Informed consent was received from the patient for the publication of this report.

Therapeutic Intervention and Treatment

After diagnosis, the patient underwent bilateral ovariectomy and adnexectomy, hysterectomy, omentectomy, cholecystectomy, resection of carcinomatous nodes, metastasectomy of liver metastases (segments VI-VII), and resection of the right suprarenal gland. In pathologic investigation, a high-grade serous carcinoma was diagnosed; molecular testing was negative for *BRCA-1* and *BRCA-2* mutations. After surgery, she was treated with 6 cycles of carboplatin and cyclophosphamide. After termination of chemotherapy, a computed tomography scan showed suspicious-appearing lymph nodes in the pancreaticolienal region.

In a second-look surgery, the mesenteric lymph nodes were excised, after which they were histologically diagnosed as lymph node metastases from the EOC. Chemotherapy was changed to high-dose carboplatin and paclitaxel. The precise dosage could not be verified but we assumed it to be 6 cycles of carboplatin/paclitaxel as follows: Carboplatin, 6 mg, target area under the free carboplatin plasma concentration vs time curve; paclitaxel, 175 mg/m^2, over 3 hours at 21-day intervals (as described by Sabatier et al[24]). The patient subsequently underwent autologous hematopoietic stem cell transplantation.

After the initial diagnosis, the patient went to a physician (RK) specializing in oncology and with additional training in anthroposophic medicine[25] and was treated with subcutaneous VAE in slowly increasing dosages (Table 1). Initially, fermented aqueous VAE from pine tree hosts was used (containing 0.75 ng/mg mistletoe lectin and 0.35 μg/mg viscotoxin). After termination of chemotherapy, VAE from apple tree hosts was used (containing 39.5 ng/mg mistletoe lectin and 1.4 μg/mg viscotoxin).

No other cancer-specific treatment was used. Additional anthroposophic medicine[26] remedies were provided for this patient. Naja comp was given for treatment of phlebitis; *Aurum* D8 and *Antimon arsenicosum* D8 were given for relief of emotional distress. The patient also took food supplements: Vitamin D, Curcuma preparation, papaya preparation, and pineapple preparation. She fasted 1 day per week as well as for 2 days before intravenous chemotherapy treatment. Furthermore, she followed a diet of reduced sugar and dairy products. Table 1 and the supplemental Figure 1 (available at www.thepermanentejournal.org/files/2018/18-025-Fig1.pdf), show timelines of the case.

Table 1. Timeline of the case of a 50-year-old patient with epithelial ovarian cancer

Time	Intervention/Treatment
Initial diagnosis	
Year 0 - month 0	Surgical removal of tumor and metastases
Phase 1	
Month 0 - 6	6x carboplatin + cyclophosphamide; VAE pini 1 mg - 20 mg subcutaneous 3/wk
Month 8[a]	Second-look surgery with removal of positive nodes and splenectomy
Phase 2	
Month 9 - 13	High-dose carboplatin + paclitaxel; VAE pini 1 mg - 20 mg, subcutaneous 3/wk
Month 13	Autologous hematopoietic stem cell transplantation
Phase 3	
Month 13 - year 3	VAE mali 20 mg, subcutaneous 3/wk
Year 3 - present (y 20)	VAE mali 20 mg, subcutaneous 3/wk, with treatment breaks: 1 m out of 3

[a] Patient has been tumor-free since the surgery in month 8.
VAE mali = *Viscum album* extract from host apple tree; VAE pini = *Viscum album* extract from host pine tree.

Follow-up and Outcomes

The patient reported that the treatment with chemotherapy—even the HDC—was well tolerated, and apart from short, self-limiting periods of nausea, she showed no adverse effects. In regular follow-up examinations, no signs of recurrence or other tumor appearance have been detected. As of this writing, the patient has been tumor-free for 20 years and is in good health and enjoying good quality of life. This case report was prepared following the CARE Guidelines.[27]

DISCUSSION

We describe a woman with advanced and metastatic high-grade serous carcinoma who was treated with surgery, HDC, and VAE and reported no serious side effects from cytotoxic treatment and has had an extraordinarily long-term tumor-free survival in good health and without any restrictions. Because prognosis in advanced EOC is poor, we presume that VAE treatment contributed to this positive outcome.

However, other factors may have played a role in the course of our patient. Long-term survival in patients with advanced EOC stages has been described, but characteristics leading to long-term survival in patients with advanced tumor stage have not been conclusively detected until now.[2] Furthermore, HDC might have positively affected the course of our patient. Although HDC could not be proved to influence survival and is therefore not generally recommended, it may have some beneficial effect in younger patients (aged < 50 years) and in carriers of *BRCA* mutations.[24]

In the case presented here, the patient, aged 50 years at diagnosis, had negative prognostic characteristics such as the advanced tumor stage with metastases in the liver, renal gland, and peritoneum as well as the histologic subtype of a high-grade serous carcinoma. Nonetheless, the tumor-free survival time of our patient is extraordinarily long (20 years, still ongoing and with good health as of this writing). The patient tolerated chemotherapy well, even HDC.

Because antitumoral effects of VAE have been documented in a broad variety of preclinical studies,[8,11,28] and because prolonged survival of patients with other types of cancer[15] as well as reduced chemotherapy side effects[13] have been reported with use of VAE, we presume that the

adjunct VAE treatment and the anthroposophic treatment setting may have contributed to the favorable outcome.

Our case adds to preliminary positive results of 2 small randomized and 2 nonrandomized VAE trials in the setting of EOC.[28] Together, these results warrant the conduct of rigorous, further investigations of the influence of VAE treatment on tumor behavior, survival, and quality of life in patients with EOC. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Author Contributions

Paul G Werthmann, MD, contributed to case report design, collected and provided data, was the principal author of the paper, and is the guarantor of the paper and all data. Robert Kempenich, MD, contributed to case report design, was the physician-in-charge for the case, and collected and provided data. Gunver S Kienle, MD, contributed to case report design and supervised the report and the publication process.

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