Case Report

The Use of Antioxidants with First-Line Chemotherapy in Two Cases of Ovarian Cancer

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Objective: Because of poor overall survival in advanced ovarian malignancies, patients often turn to alternative therapies despite controversy surrounding their use. Currently, the majority of cancer patients combine some form of complementary and alternative medicine with conventional therapies. Of these therapies, antioxidants, added to chemotherapy, are a frequent choice.

Methods: For this preliminary report, two patients with advanced epithelial ovarian cancer were studied. One patient had Stage IIIC papillary serous adenocarcinoma, and the other had Stage IIIC mixed papillary serous and seromucinous adenocarcinoma. Both patients were optimally cytoreduced prior to first-line carboplatinum/paclitaxel chemotherapy. Patient 2 had a delay in initiation of chemotherapy secondary to co-morbid conditions and had evidence for progression of disease prior to institution of therapy. Patient 1 began oral high-dose antioxidant therapy during her first month of therapy. This consisted of oral vitamin C, vitamin E, beta-carotene, coenzyme Q-10 and a multivitamin/mineral complex. In addition to the oral antioxidant therapy, patient 1 added parenteral ascorbic acid at a total dose of 60 grams given twice weekly at the end of her chemotherapy and prior to consolidation paclitaxel chemotherapy. Patient 2 added oral antioxidants just prior to beginning chemotherapy, including vitamin C, beta-carotene, vitamin E, coenzyme Q-10 and a multivitamin/mineral complex. Patient 2 received six cycles of paclitaxel/carboplatinum chemotherapy and refused consolidation chemotherapy despite radiographic evidence of persistent disease. Instead, she elected to add intravenous ascorbic acid at 60 grams twice weekly. Both patients gave written consent for the use of their records in this report.

Results: Patient 1 had normalization of her CA-125 after the first cycle of chemotherapy and has remained normal, almost 3½ years after diagnosis. CT scans of the abdomen and pelvis remain without evidence of recurrence. Patient 2 had normalization of her CA-125 after the first cycle of chemotherapy. After her first round of chemotherapy, the patient was noted to have residual disease in the pelvis. She declined further chemotherapy and added intravenous ascorbic acid. There is no evidence for recurrent disease by physical examination, and her CA-125 has remained normal three years after diagnosis.

Conclusion: Antioxidants, when added adjunctively, to first-line chemotherapy, may improve the efficacy of chemotherapy and may prove to be safe. A review of four common antioxidants follows. Because of the positive results found in these two patients, a randomized controlled trial is now underway at the University of Kansas Medical Center evaluating safety and efficacy of antioxidants when added to chemotherapy in newly diagnosed ovarian cancer.

INTRODUCTION

Ovarian cancer remains one of the most lethal of all gynecologic malignancies, accounting for more deaths than cervical and uterine cancer combined [1]. In the last decade, an estimated 26,700 new cases of ovarian cancer were diagnosed per year, with approximately 14,800 women dying of this disease per year [2]. Unfortunately, women with advanced stage disease have dismal five-year survival rates, despite the development of new chemotherapeutic treatments.

Despite attempts to improve survival rates in patients with malignancies, living with the diagnosis of cancer is an ongoing

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Table 1. Patient 1

Month	DX	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Pathology	Papillary serous adenocarcinoma IIIc																																								
CA-125	999	119	9.7	15	11.1	12.3	11.1	11.9		10.6	10.5	15.3	9.2	7.4		8.4	6.9	8.7	8.1		8.9		7.8	7.5			7				9.6			9.8	11.8		12	14.4		8.8	
Antioxidants																																									
Oral		*Oral prior to chemo–continues to date																																							
IV (60 grams in 500cc D5W)						2×/Week→						1×/Week→												→Every 10–14 Days→																	
Toxicity				**	***																																				
Imaging Studies											†								CAT Scan-neg.																			CAT Scan-neg.				
Chemotherapy		Paclitaxel/Carboplatin ×6— Paclitaxel Consolidation × 6→																																							

* Vit. E (1200 IU), Coenzyme Q-10 (300 mg), Vit. C (9000 mg), B carotene (25 mg), Vit. A (10,000 IU).

** Numbness/tingling–feet & hands (neurontin without benefit).

*** Shortness of breath, fatigue, peripheral edema- tricuspid/aortic valve regurgitation related to chemotherapy.

† CAT Scan-Question of new pelvic mass (12/21/99)—Endovag US-Negative for new mass (12/23/99).

and difficult experience. Because of the pervasive feeling of sadness, fear, anxiety, anger, and the potential for mortality, patients often turn to complementary and alternative therapies [3,4]. It is reported that the use of complementary and alternative medicine is increasing among cancer patients [5–8].

A survey of breast cancer patients determined that the interest in megavitamin and herbal therapies was 47.4% and 37.1% respectively, and their use was 25% and 14% respectively [5]. This was compared to the use of megavitamin and herbal therapies in the general population at 2% and 3%. This same study found that 80% of these patients never attempted to abandon conventional therapy, but continued to use their conventional treatments along with the alternative therapies. In fact, the only patients who reported that they might abandon their conventional therapy (1%) were those with the gravest prognosis [5].

Other reports place the prevalence of use of complementary and alternative medicine by cancer patients in an estimated range of 7% to 64% [6–8]. At the present time, many cancer patients combine some forms of complementary and alternative therapy with their conventional therapies [7–8]. A recent survey of patients in a comprehensive cancer center placed the use of vitamin and minerals at 62.6%; of these patients, 76.6% combined the use of vitamins and minerals with conventional chemotherapy [8]. The majority of these patients are adding megavitamin and mineral therapies without the knowledge of the treating physician [7–8].

Patients use complementary and alternative therapies for a variety of reasons [6,7]. Patients use these therapies to improve quality of life (77%), improve immune function (71%), prolong life (62%) or relieve symptoms (44%) related to their disease [6]. Only 37.5% of the survey patients expected complementary and alternative therapies to cure their disease. Whatever the reasons, alternative therapy use is on the rise and this includes megavitamin and mineral cocktails during chemotherapy administration.

Megavitamin and mineral cocktails include antioxidants such as the commonly consumed antioxidants vitamin E (mixed tocopherols and tocotrienols), vitamin C, β-carotene (natural mixed carotenoids) and vitamin A. Controversy exists about the use of antioxidants with chemotherapy, but increasing evidence suggests a benefit when antioxidants are added to chemotherapy [9–16]. We are reporting two cases of advanced ovarian cancer where antioxidants were added adjunctively to chemotherapy without adversely effecting outcome or survival.

METHODS

Both patients gave verbal and written consent for the use of their records in this report.

Case 1

A 55 year-old female was evaluated for increasing abdominal girth. On examination, she was found to have a large pelvic mass, which extended into the abdominal cavity. This was confirmed on CT scan. Her baseline CA-125 was 999.

She underwent surgical exploration and was found to have disseminated disease involving the diaphragm, small and large bowel, peritoneum, mesentery and omentum with extension to the spleen. The patient was optimally cytoreduced. Final staging and pathology was consistent with a Stage IIIC papillary serous adenocarcinoma of the ovary.

Postoperatively, the patient received standard carboplatin (AUC 6) and paclitaxel (175 mg/m2) chemotherapy for a total of six cycles (Table 1). Her CA-125 fell to <35 after the completion of her first cycle of chemotherapy. Her CT scan was negative for measurable disease. Consolidation paclitaxel (175 mg/m2) was given for an additional 6/12 intended cycles. Prior to the first cycle of chemotherapy, the patient elected to start daily oral antioxidants, which included vitamin E (1,200 IU), coenzyme Q10 (300 mg), vitamin C (9,000 mg), beta-carotene (mixed carotenoids, 25 mg), and vitamin A (10,000 IU). At the completion of the first course of chemotherapy, but prior to initiation of consolidation chemotherapy, the patient began parenteral ascorbic acid. To prevent the possibility of hemolysis, G6PD status was assessed prior to intravenous ascorbic acid and found to be normal.

The ascorbic acid infusions were begun at 15 grams and increased to 60 grams per infusion given twice weekly. The 60-gram dose was tailored to the pre- and post-infusion ascorbate level, which maintained plasma ascorbate levels above 200 mg/dL. At this plasma level, ascorbic acid is reported to promote neoplastic cell cytotoxicity [9–10].

The 60-gram ascorbic acid infusions were given two times per week during the six cycles of consolidation chemotherapy, after which the patient continued the 60-gram ascorbic acid infusions once per week. This dose and schedule was continued for one year, after which the patient chose to reduce the frequency of the infusions to every 10 to 14 days.

The patient is currently over 40 months from initial diagnosis and remains on ascorbic acid infusions. She has had several CT scans, as well as a PET scan, all of which remain negative for disease. Her CA-125 remains normal at a value of 8.8.

Case 2

A 60-year-old, gravida 0 para 0, post-menopausal woman presented with increasing abdominal girth. Ascites and a 13×8×9.6 cm complex pelvic mass were identified on ultrasound. Her initial CA-125 was 81. At laparotomy, the patient was found to have a large exophytic mass filling the pelvis and attached to the omentum. She was optimally cytoreduced. Pathology was consistent with a mixed papillary serous and seromucinous adenocarcinoma of the ovary, FIGO (International Federation of Gynecology and Obstetrics) stage IIIC.

Postoperatively, the patient was felt to be GOG (Gynecologic Oncology Group) performance status 2. In the months following surgery, the patient was admitted to the Intensive Care Unit (ICU) on two separate occasions and placed on ventilatory support secondary to a respiratory arrest and supraventricular tachycardia. After she was discharged from the ICU, she was started on oral megace (80mg/BID) and tamoxifen (20mg/day). The patient had evidence for progression of disease with ascites and an elevated CA-125 to 127.

Three months after her primary cytoreductive surgery the patient began front-line chemotherapy, consisting of carboplatinum (AUC 6) and paclitaxel (135mg/m^2) for six cycles (Table 2). Prior to beginning chemotherapy, the patient began oral daily antioxidants, consisting of oral ascorbic acid (3,000mg/day), vitamin E (1,200 IU/day) and beta-carotene (25mg/day) and vitamin A (5,000 IU/day). The CA-125 normalized after the first cycle of carboplatin/paclitaxel chemotherapy.

After the completion of her first course of chemotherapy, the patient was found to have disease in the pelvis. An MRI identified a heterogeneous 8 cm mass in the pelvis and a new 2 cm × 2 cm retroperitoneal mass felt to be metastases. The patient declined consolidation chemotherapy, instead opting for continuation of oral antioxidants and initiation of parenteral ascorbic acid infusions. After normal G6PD status was confirmed, ascorbic acid infusions were begun at 15 grams and increased to 60 grams per infusion. The dose was adjusted by a pre- and post-ascorbic acid infusion to maintain plasma levels at above 200mg/dL. The patient had daily 60-gram ascorbic acid infusions for one week and then began twice weekly infusions, which continues to date 36 months post-diagnosis. Although further diagnostic imaging was declined, physical examination has remained normal. Her most recent CA-125 is 5, and she is over three years out from diagnosis.

RESULTS

In the first patient, CA-125 levels fell to a normal range after surgery and remain normal to date. Positron emission tomography and CAT scans remain without evidence of recurrence.

Patient 2 had a co-morbid condition that prevented her from receiving first line chemotherapy until three months after diagnosis. Prior to institution of chemotherapy, patient 2 had evidence for progression of disease with ascites and an elevated CA-125 at 108 and 127 onto separate evaluations. The CA-125 normalized after the first cycle of carboplatin/paclitaxel chemotherapy. After completion of the six cycles of chemotherapy as noted above, the patient was found to have disease in the pelvis. The patient declined further consolidation chemotherapy, but instead elected to continue with oral antioxidants and parenteral ascorbic acid infusions. CA-125 levels remain normal to date over three years after diagnosis.

Table 2. Patient 2

Month	DX	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38
Pathology	Mixed papillary serous and seromucinous adenocarcinoma IIIc																																						
CA-125	81	127	108	25	26	28	27	19							6				7							Normal							6				5		
Antioxidants																																							
Oral			*Oral-prior to chemo-continues to date																																					
Intravenous C (60 grams in 500cc D5W)													Daily/2× Weekly																										→
Complications			**		***																																		
Toxicity																																							
Imaging Studies					†				††																														
Chemotherapy									Paclitaxel/carboplatin ×6— ‡																																

* Vitamin C (3,000 mg p/day); Multi-vitamin/Min→ β-carotene, Vitamin A, Vitamin E (1200 IU).
** GOG Performance Status 2, Respiratory Arrest ICU.
*** SVT Respiratory Arrest ICU.
† Pleural Effusions CXR, Ascites US.
†† MRI-Residual Pelvic Mass + 2×2 Retroperitoneal Mass.
‡ Refused Consolidation Chemotherapy.

Both patients were monitored for toxicity, and neither patient had grade three or four toxicity that limited completion of six cycles of front-line chemotherapy. Both patients had mild, self-limited nausea. Patient 1 noted the onset of numbness and tingling of both hands and feet during the first course of chemotherapy, but prior to the institution of parenteral ascorbic acid. Patient 1 also complained of the onset of fatigue, increased shortness of breath and peripheral edema during the first course of chemotherapy, but prior to the introduction of intravenous ascorbic acid. Subsequent evaluation by an echocardiography identified tricuspid and aortic valve regurgitation. The patient is well controlled on aldactone and lasix.

Neither patient demonstrated hematologic toxicity, including neutropenia or thrombocytopenia. Neither patient required colony-stimulating factors. There was no evidence for febrile neutropenia or infection. Neither patient demonstrated elevated renal or liver enzymes.

DISCUSSION

The use of antioxidants during chemotherapy remains a matter of controversy. The prevailing opinion is that antioxidants may reduce the effectiveness of chemotherapy by interfering with reactive oxidant neoplastic cytotoxicity. In addition, Golde's group at Memorial Sloan-Kettering Cancer Center has implicated vitamin C in tumor growth [17]. However, there is increasing evidence that antioxidants may improve efficacy of chemotherapy and inhibit neoplastic cell growth selectively [9–13,15,16,18–20].

One of the most controversial therapies is the use of high-dose ascorbic acid [9,10,19,21–24,17]. Riordan *et al.* have shown that vitamin C in doses many times over the RDA is a potent immunomodulator and has been found to be preferentially cytotoxic to neoplastic cells [9,10]. Vitamin C enhances the activity of natural killer cells *in vivo* and also enhances both B and T cell activity [25,26]. At doses in the gram range, it has been demonstrated to increase survival time of patients with malignancies [9,10,19,23].

Roomi *et al.* investigated the underlying critical features for toxic activity of ascorbic acid on neoplastic cells [27]. The investigators manipulated the structure of ascorbic *in vitro* to maximize its cytotoxic effect on tumor cell growth. It was found that the cytotoxic activity was not apparently related to the metabolic or vitamin activity at the cellular level. The cytotoxic activity was a result of direct cell killing by ascorbate.

Benade described a tenfold to hundredfold greater content of catalase, the enzyme that reduces hydrogen peroxide to water and oxygen, in normal cells when compared to tumor cells [28]. Increased intracellular hydrogen peroxide generation by vitamin C coupled with a lack of catalase activity in neoplastic cells results in preferential cytotoxicity to tumor cells. Yet, little toxicity has been demonstrated to normal host cells

[9,10,19,29]. When vitamin C is given intravenously to maintain plasma levels above 200mg/dL, cytotoxicity is induced in tumor cells with negligible toxic effects to the host [9,10]. One potential concern is hemolysis in G6PD deficiency that has been reported with high-dose intravenous ascorbic acid and all patients should be pre-screened prior to high dose infusion [9–10].

Teicher suggests a role for carotenoid supplementation in conjunction with cytotoxic therapies in established malignant disease [30]. However, other studies have found a negative correlation between the use of β-carotene and tumor regression or development [31,32]. These conflicting results are most likely related to the use of high-doses of a single antioxidant in the study design and its negative effect on redox buffering. When taken alone in high doses, synthetic β-carotene suppresses uptake of other carotenoids and acts as a prooxidant [15]. Natural mixed carotenoids, in doses up to 20–40 mg/day, were found to be without toxicity and to act synergistically with cisplatin [13].

Vitamin E has a very important impact on the phenotype of dedifferentiated malignant cells by causing differentiation, most likely indirectly through the effects of adenylate cyclase [33]. This has been shown to result in an increase and release of transforming growth-factor β, which acts as a growth inhibitory signal for malignant cells [15]. Vitamin E has been shown to decrease the toxicity of chemotherapy without reducing its effectiveness [13].

The precise mechanism of vitamin A actions on inhibition of cancer growth is unknown; however, it seems to increase inhibitory levels of specific signaling pathways in neoplastic cells. Examples of vitamin A actions include inhibition of protein kinase C activity in cancer cells and reduction of expression of *c-myc* and *H-ras* oncogenes and other cellular genes in cell culture [11,13,15]. Vitamin A also induces cell differentiation in some tumors of epithelial origin and appears to work synergistically with chemotherapeutic agents [11]. Animal studies also show an inhibition of transplanted tumor growth when high doses of vitamin A are administered; this is associated with the absence of toxicity to normal tissues [13,34,35]. In addition, vitamin A combined with the biological response modifier interferon α2a has been shown to be effective in the treatment of squamous cell carcinoma of the cervix [11]. Although significant benefits are demonstrated when combined with chemotherapy, there is no evidence for the reduction of effectiveness of chemotherapy when vitamin A is added in therapeutic doses [13].

In summary, human, animal and *in vitro* studies have shown that antioxidants inhibit neoplastic cell growth by complex mechanisms. These include increases in neoplastic cell differentiation, increases in apoptosis, inhibition of protein kinase C activity, adenylate cyclase activity and other mechanisms. Despite the fact that chemotherapy-induced formation of free radicals is well demonstrated, chemotherapy-induced cytotoxicity in general does not seem to depend on formation of reactive oxygen species; thus, the concept that antioxidants are contraindicated during most chemotherapy regiments is no longer valid [11–16,36]. In fact, as demonstrated with the reported cases, antioxidants when added adjunctively to chemotherapy may improve the efficacy of chemotherapy and may prove to be safe. Because of the positive results found in the two reported patients, a randomized controlled trial is now underway at the University of Kansas Medical Center to further evaluate safety and efficacy of antioxidants when added to chemotherapy in newly diagnosed ovarian cancer.

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