

# Amifostine Plus Carboplatin-Paclitaxel Combination Chemotherapy in Advanced Stage Epithelial Ovarian Carcinoma: Does it Have Any Effect on Therapeutical Benefit and Complications?

*İLERİ EVRE EPİTELYAL OVER KANSERİNDE AMİFOSTİN İLE KARBOPLATİN-PAKLİTAKSEL KOMBİNASYON KEMOTERAPİSİ: TERAPÖTİK FAYDA VE KOMPLİKASYONLAR ÜZERİNDE HERHANGİ BİR ETKİSİ VAR MI?*

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## Summary

**Objective:** The purpose was to detect the impact of amifostine on the adverse effects of platinum-containing chemotherapy regimens and observe its side effects.

**Materials and Methods:** Stage III ovarian cancer patients who first presented to Akdeniz University Obstetrics and Gynecology Department between November 1998 and February 2001 and received paclitaxel/platin regimens in our clinic following tumor debulking and staging were included in the study. Amifostine was administered as a 15-minute iv infusion during the administration of platinum-based chemotherapy to one group. The control group received the standard platinum-based chemotherapy without amifostine.

**Results:** Totally 31 women who received platinum-based chemotherapy at Akdeniz University Obstetrics and Gynecology Department were enrolled in the study. 15 patients received paclitaxel/platin plus amifostine, and the control group consisted of 16 patients. Regarding toxicities, the differences between the two groups were not statistically significant.

**Conclusion:** In this preliminary report, no significant improvement concerning side effects of platinum-based chemotherapy was detected in patients receiving amifostine.

**Key Words:** Amifostine, Ovarian cancer, Chemotherapy

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## Özet

**Amaç:** Amaç, amifostinin platin-içeren kemoterapi rejimlerinin olumsuz etkileri üzerine etkisini belirlemek ve yan etkilerini gözlemlemektir.

**Materyal ve Metod:** Akdeniz Üniversitesi Kadın Hastalıkları ve Doğum Departmanı'na Kasım 1998 ile Şubat 2001 tarihleri arasında başvuran ve kliniğimizde tümör debulking ve evreleme sonrası paklitaksel/platin rejimi alan evre III over karsinomlu hastalar çalışmaya alındı. Bir gruba platin-içeren kemoterapi sırasında 15 dakika intravenöz infüzyon şeklinde amifostin verildi. Kontrol grubu, amifostin almaksızın standart platin-bazlı kemoterapi rejimi aldı.

**Bulgular:** Akdeniz Üniversitesi Kadın Hastalıkları ve Doğum Departmanı'nda platin-bazlı kemoterapi alan total olarak 31 hasta çalışmaya dahil edildi. 15 hasta paklitaksel/platin ile birlikte amifostin alırken, kontrol grubu 16 hastadan oluştu. Toksisiteler açısından, iki grup arasındaki farklar istatistiksel olarak anlamlı değildi.

**Sonuç:** Bu ön çalışmada, amifostin alan hastalarda, platin-bazlı kemoterapinin yan etkileriyle ilgili hiçbir anlamlı iyileşme saptanmadı.

**Anahtar Kelimeler:** Amifostin, Over kanseri, Kemoterapi

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Ovarian cancer continues to be the fourth leading cause of death from cancer in women. Platinum is a primary component of chemotherapy regimens for ovarian cancers. Clinical trials have documented the role of amifostine as a cytoprotectant against cisplatin and cyclophosphamide induced toxicities in patients with ovarian cancer. In these trials, the incidence and severity of many dose-limiting toxicities was reduced significantly by the concomitant administration of amifostine.

Preclinical studies have shown that pretreatment with amifostine provides protection of normal tissues from the cytotoxic effects of alkylating agents, organoplatinums, anthracyclines, taxanes and radiation. Normal tissues protected include bone marrow, kidney, neural tissues, the heart, intestinal crypt cells and pulmonary tissues (1).

## Materials and Methods

The patient population consisted of Stage III ovarian cancer patients who first presented to Akdeniz University

**Table 1.** Demographic characteristics of patients

	Amifostine group(n:15)	Control group(n:16)
Mean age	56.08 (39-70)	55.3 (33-72)
Mean gravida	4.3 (2-7)	3.56 (0-10)
Mean parity	3.4 (2-7)	3.06 (0-10)

Obstetrics and Gynecology Department between November 1998 and February 2001 and received paclitaxel / platin regimens in standard doses in our clinic following surgery for tumor debulking and staging. All the patients had undergone optimal cytoreduction before starting chemotherapy. The patients were randomly assigned into two groups, informed of the addition of amifostine to their regimens. Amifostine (Ethyol; Alza Pharmaceuticals, Palo Alto, CA/US Bioscience, West Conshohocken, PA), was administered with platinum based chemotherapy in 15 patients and was not in 16 patients.

After the administration of paclitaxel at the dose of 175 mg/m<sup>2</sup> in three hours, amifostine at the dose of 910 mg/m<sup>2</sup> was administered as a 15-minute iv infusion to patients in supine position. Within 15 minutes of the completion of the amifostine infusion, carboplatin at the dose of AUC 6 in 2000cc %0.45 saline solution was administered. The dose of carboplatin was calculated via Calvert's formula. Antiemetics consisted of 48 mg intravenous dexamethasone given in two divided doses 12 and 6 hours before initiation of therapy. Other antiemetics such as metoclopramide, ondansetron, granisetron were used as needed. The patient's blood pressure was measured just before the amifostine infusion, once during the amifostine infusion, and once when the amifostine infusion ended. The treatment regimen was repeated every 21 to 28 days.

After the end of 6 cycles of chemotherapy, 9 of the amifostine-receiving patients and 11 of the control group

underwent second look laparotomy to observe the response to chemotherapy. Statistical analysis was performed by Mann Whitney U test and Fisher's exact test, and p values smaller than 0.05 were considered to be statistically significant.

## Results

Table 1 demonstrates that there were no statistically significant differences in the demographic characteristics of the study population when the two groups were compared. Thirty-one patients were included in the study. Fifteen patients, receiving 90 cycles of chemotherapy, were administered amifostine. Sixteen patients receiving a total of 117 cycles did not receive amifostine. Complete remission was higher in the amifostine group, without statistical significance.

During treatment, blood counts were obtained to monitor hematological toxicities. Every patient had a blood count the day before she received chemotherapy, and in the middle of two cycles, which corresponded to the 10<sup>th</sup> day after receiving chemotherapy. The current study compares the hematological parameters of the two groups. Average values of blood counts before and after chemotherapy are given in Table 2. No significant differences were noted between the thrombocyte and hemoglobin levels of the two groups neither before nor after each chemotherapy cycle (Table 2). Among the amifostine receiving patients, one patient had thrombocyte count below 100000 before and after receiving her chemotherapy course, in two of her six chemotherapy courses. Other than this patient who later developed chronic thrombocytopenia, only four courses of the 90 amifostine-containing ones were complicated by thrombocytopenia (below 100000/mm<sup>3</sup>). These were a count of 51000/mm<sup>3</sup> after the fifth course, and a 88000/mm<sup>3</sup> following the second course in another patient. The third patient who faced thrombocytopenia had a count of 36000/mm<sup>3</sup> after the third course and a 20000/mm<sup>3</sup> after

**Table 2.** Hematological parameters measured before administering chemotherapy and after a 10 day interval following chemotherapy

	Amifostine group (n:90)	Control group (n:117)	P
Mean thrombocyte count before chemotx(/mm <sup>3</sup> )	270000 (10000-690000)	264000 (16000-475000)	NS
Mean thrombocyte count after chemotx(/mm <sup>3</sup> )	212000 (51000-561000)	204000 (105000-376000)	NS
Mean hemoglobin level before chemotx(mg/dl)	10.9 (8.3-13.4)	11.3 (9.0-14.0)	NS
Mean hemoglobin level after chemotx(mg/dl)	10.6 (7.0-13.0)	11.1 (9.0-13.0)	NS
Mean leukocyte count before chemotx(/mm <sup>3</sup> )	5940 (2860- 14000)	6435 (2600- 13900)	NS
Mean leukocyte count after chemotx(/mm <sup>3</sup> )	3620 (980- 13000)	4285 (1660- 11900)	NS
Mean antiemetic dose	48 mg dexamethasone 6 mg granisetron	48 mg dexamethasone 6 mg granisetron	NS
Mean TA (Systolic/Diastolic)	123.5 / 70.4	122 / 72	NS

NS: Nonsignificant

**Table 3.** Average blood counts after each chemotherapy course

	Amifostine group			Control group		
	Hemoglobin level (mg/dl)	White blood cell count (/mm <sup>3</sup> )	Platelet count (/mm <sup>3</sup> )	Hemoglobin level (mg/dl)	White blood cell count (/mm <sup>3</sup> )	Platelet count (/mm <sup>3</sup> )
After course 1	10.8 (9.1-12.4)	4394 (2250-13500)	222000 (118000-444000)	11.2 (10.5-13)	3772 (2890-8580)	255000 (119000-357000)
After course 2	11.0 (7.9-12.3)	4335 (2220-8410)	268000 (88000-485000)	11.6 (9.2-12.0)	4612 (2680-7740)	233000 (126000-435000)
After course 3	10.8 (9.1-12.0)	3300 (1240-6210)	201000 (36000-560000)	11.3 (9.8-12.9)	6817 (2380-11900)	235000 (161000-376000)
After course 4	11.1 (9.6-12.4)	3869 (2020-5300)	186000 (20000-420000)	10.9 (9.4-11.6)	5110 (2190-5510)	225000 (112000-327000)
After course 5	11.0 (7.8-12.0)	3268 (1380-5440)	170000 (51000-282000)	11.3 (8.5-11.5)	5203 (2190-12000)	179000 (105000-327000)
After course 6	10.7 (8.8-12.8)	3051 (980-5930)	155000 (16000-315000)	11.1 (8.9-12.4)	4970 (2180-5400)	199000 (146000-252000)

the fourth course. All of these resolved spontaneously, only in one course was thrombocyte transfusion necessary. Among the 90 courses of Paclitaxel-Carboplatin combination with Amifostine treatment, thrombocytopenia was observed in 6.67%, whereas no thrombocytopenia occurred in patients treated with Paclitaxel-Carboplatin combination only. The median platelet nadir values were 115000 and 126000 in the amifostine-receiving and control groups respectively. Requirements of platelet and red blood cell transfusion were not reduced in the group that received amifostine. Among 31 patients, one developed chronic thrombocytopenia after six cycles of Paclitaxel-Carboplatin+Amifostine. In three courses of the 90 (3.33%), the leukocyte count after chemotherapy was below 1500 (average 1200). None of the treatment cycles were delayed because of low blood count, and none of the 31 patients necessitated a reduction in the dose of chemotherapeutics due to toxicity. The average levels of blood counts taken 10 days after each course of chemotherapy are given in Table 3.

Amifostine pretreatment did not affect the antitumor effects of paclitaxel-carboplatin as assessed by response determined at second-look surgery (Table 4).

The incidence and severity of peripheral neuropathy were not reduced in the group that received amifostine.

Considering the hypotensive effect of amifostine, none of the patients had a significant fall of blood pressure during the administration of amifostine.

### Discussion

At least one third of all patients receiving cisplatin experience neurotoxicity, ototoxicity, and/or nephrotoxicity. Although carboplatin is significantly less toxic than cisplatin, it can cause cumulative bone marrow damage, manifested by chronic thrombocytopenia in 20% to 25% of patients who receive six or more therapy courses (2). Furthermore, when platinum agents are combined with paclitaxel, myalgias and arthralgias may become dose and course limiting (3).

**Table 4.** Findings at second look laparoscopy or laparotomy

	Amifostine group(n:9)	Control group (n:11)	P
Complete remission	5 (%55.5)	4 (%36)	NS
Incomplete remission	4 (%44.4)	7 (%63.6)	

Amifostine is a phosphorylated aminothiols prodrug that is dephosphorylated at the tissue site by membrane-bound alkaline phosphatase to its active metabolite, the free thiol, WR-1065. WR-1065 is the form of drug that is taken up into cells, wherein the thiol detoxifies cisplatin by binding to acuated platinum (4).

The reduction in cyclophosphamide and cisplatin related toxicities manifest as a decrease in the incidence and severity of neutropenia-related fever and sepsis and in the number of patients with ovarian cancer who discontinue therapy before completion of treatment, thus improving the tolerability of this antineoplastic regimen. In our series, neutropenia was not encountered in any of the patients, and none of the patients discontinued therapy.

The drug was approved by the FDA of U.S.A. for use as a cytoprotectant in cyclophosphamide and cisplatin treatment for advanced ovarian cancer and non small cell lung cancer. The basis for the selective cytoprotection of normal tissue by amifostine is explained by its unique systemic and tissue distribution pharmacokinetics. Following drug administration, the drug is rapidly cleared from blood. Ninety percent of the drug is cleared from the plasma within 6 minutes and the amount of the prodrug that is bioconverted to the free thiol in the systemic circulation relative to that occurring in normal tissues is small (5).

Thrombocytopenia is a dose-limiting toxicity for carboplatin. With the demonstration that granulocyte (G-CSF) and granulocyte-macrophage colony-stimulating factors (GM-CSF) could reduce the rate of hospitalization for neutropenic fever, a variety of cytokines have been investigated

for their effects on chemotherapy-induced thrombocytopenia. IL-1 has been found to reduce thrombocytopenia associated with carboplatin-based chemotherapy (6,7). However, due to its significant adverse effects such as fever, headache, tachycardia, further clinical investigation of IL-1 for protection against thrombocytopenia was abandoned. Use of IL-6 was also limited due to such constitutional symptoms. IL-11 was found to reduce the need for platelet transfusions in patients who had previously experienced chemotherapy-induced thrombocytopenia. Noted side effects with IL-11 were predominantly related to fluid retention (8,9).

A phase I study of WR-2721 and carboplatin suggested that WR-2721 at a dose of 740 mg/m<sup>2</sup> might increase the maximum tolerated dose of carboplatin from 400 to 500 mg/m<sup>2</sup> (10). Among the early experiences with amifostine in a carboplatin-containing chemotherapy regimen is a non-randomised, sequential cohort trial of therapy with the combination of carboplatin and cisplatin, either alone or with amifostine (11). Significant reductions in grade 2-4 granulocytopenia and thrombocytopenia were observed in patients receiving amifostine. No treatment delays were necessary in the group receiving amifostine. Effects of amifostine on the thrombocytopenia produced by carboplatin-containing combination chemotherapy regimens are being investigated by randomized trials (12).

The two major randomized studies are in patients with solid tumors (13,14) and with nonsmall-cell lung cancer (15). Data indicate that platelet recovery is more rapid in amifostine-treated patients (14), that is, it reduces the severity and duration of thrombocytopenia caused by carboplatin. The study by Budd et al (14) showed that median platelet nadir values were reduced in amifostine-treated patients, however according to Betticher et al (15), the median platelet nadirs did not differ between the two arms. In our study, the median platelet nadir values did not differ statistically between the two groups as well.

In the study by Budd et al (14), nausea and vomiting were more severe in amifostine-treated patients. Hypotension was generally noted to reverse within 5 minutes of interrupting the amifostine infusion. This was similar in our study as well, and no dosage reduction below 910 mg/m<sup>2</sup> had been necessary.

The ability of amifostine to demonstrate multilineage bone marrow protection is an advantage compared to currently available growth factors, as it provides a reduction in the need for platelet transfusions and helps to maintain the desired chemotherapy dose intensity (16). Future clinical trials will be helpful in demonstrating the optimal dosing regimen with amifostine and carboplatin, and further defining the role of amifostine as a multilineage bone marrow protectant in carboplatin-containing combination chemotherapy regimens.

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