Amifostine and Hematologic Effects

CHANTRAPA SRISWASDI, M.D.*,
SAENGSUREE JOOTAR, M.D.**,
FRANCIS J. GILES, M.D.***

Abstract

Amifostine is a protective agent of normal tissue from adverse effects of radiochemotherapy. It is the prodrug that is dephosphorylated by alkaline phosphatase on plasma membrane into the active form named WR-1065. More than 90 per cent of the drug is cleared from plasma in 6 minutes and the peak tissue concentration is 10-30 minutes after intravenous administration. Amifostine has the selective property to protect normal tissue but not cancer cells by mainly scavenging free radicals induced by radiation and chemocytotoxic agents. Both preclinical and clinical studies of this drug provide the significant protection of hematopoietic progentitors from a broad range of cytotoxic agents such as cyclophosphamide, cisplatin, vinblastine, carboplatin, mitomycin-C, fotemustine, doxorubicin, daunorubicin and radiation as well. Moreover, this drug can protect other normal organs or tissues including kidney, salivary gland, liver, heart, lung and small intestine. Amifostine is quite safe, the two major side effects are vomiting and hypotension, and the minor effects are flushing, sneezing, dizziness, chills, metallic taste etc. 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.

Key word : Amifostine, Cytoprotectant

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Investigators and clinicians have attempted to develop cytotoxic agents and regimens to eliminate malignant diseases. The cytotoxic agents affect not only tumor cells but also normal tissues. The nonselective effects influence the quality of life of patients and also limit the dose of chemotherapy

* Department of Medicine, Pramongkutklao Hospital, Bangkok 10400,
** Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Bangkok 10400, Thailand.
*** Department of Leukemia, M.D. Anderson Cancer Center, Houston, Texas 77030, U.S.A.

and radiation. In the last decade, several agents have been developed to protect or rescue normal tissues from these effects such as dexrazoxane (cytoprotectant against cardiotoxicity), mesna (prevent hemorrhagic cystitis), amifostine (broad-spectrum cytoprotectant), leucovorin (rescue agent for high-dose methotrexate), and growth factors (erythropoietin, G-CSF, GM-CSF)[1-3].

The ideal properties of cytoprotectants are : first, selectivity, it can protect healthy or normal tissues from the toxicity of antitumor therapies without protecting the tumor cells; second, broad-spectrum ability, it should protect numerous normal tissues from cytotoxic therapy and have protection against a wide variety of cytotoxic agents; third, no or acceptable side effects[3,4]. One of the cytoprotectants studied extensively is amifostine. Amifostine, originally known as WR (Walter-Reed)-2721, was developed initially during the Cold War by the Walter Reed Army Institute as a radioprotectant[4-6]. This drug was subsequently studied for its potential role in therapeutic radiation, as well as chemotherapy especially in alkylating agents, organoplatinum agents and anthracyclines[1,5,7-9]. This review examines the cytoprotective property of amifostine, particularly its hematologic aspects, mechanism of action, side effects and guidelines for treatment.

Mechanism of action

Amifostine, a phosphorylated prodrug, is rapidly dephosphorylated by alkaline phosphatase (a plasma membrane enzyme) into the free thiol WR-1065 that is its active form[10-12]. WR-1065 is consequently oxidized to the symmetrical disulfide of WR-1065 (WR-33278) or the mixed disulfides with endogenous thiols and thiol containing proteins (Fig. 1)[4,10,13].

This drug is rapidly cleared from plasma, less than 10 per cent of the drug remains in the plasma 6 minutes after intravenous administration[6,11,14,15]. The rapid disappearance of amifostine from the plasma may be due to its rapid conversion into WR-1065 that is also rapidly cleared from the circulation by its fast uptake in normal tissues or its conversion to disulfides[11,16,17].

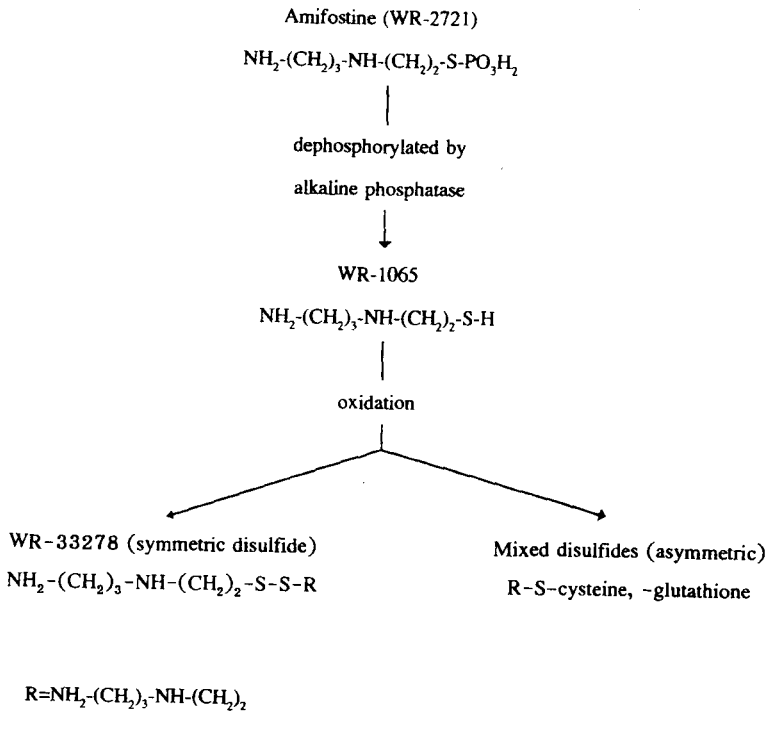

Fig. 1. Amifostine metabolism.

The peak tissue concentration of WR-1065 is achieved 10-30 minutes after injection[15,16].

WR-1065, the active form of amifostine, produces cytoprotective effects by binding and detoxifying directly to the active forms of chemocytotoxic drugs, scavenging free radicals, and donating hydrogen ions for DNA repair[3,4,6,18,19]. Free radicals are thought to be a factor of toxicity induced by radiation and some chemocytotoxic drugs[5-7,9].

Amifostine has the unique ability to protect normal tissues but not tumor cells from radiation or chemotherapy[3,7,10,20-24]. The selective cytoprotection occurs from several mechanisms as follows : first, the concentration of membrane-bound alkaline phosphatase is 275-fold greater in normal than in tumor tissues; second, this drug is absorbed by active transport in normal tissues but passive diffusion in tumor cells; third, the lower blood supply in tumors compared with normal tissues may result in less delivery of the drug to tumor cells; and fourth, the neutral pH of normal tissue results in more uptake of the drug than the acidic environment of tumor tissue[1,3,4,6,25]. The result of these mechanisms causes higher drug concentration in normal organs than in tumor tissue by 50-100 fold, the organs include kidney, salivary gland, bone marrow, liver, heart, lung and small intestine, but has low concentration in brain and spinal cord because of the negligible uptake of amifostine across the blood brain barrier[4,5,7,10,25].

Evidence of hematologic protection

The hematologic toxicity is an important limitation for chemotherapy and radiation therapy. This toxicity is usually manifested as neutropenia and thrombocytopenia. As the hematopoietic growth factors (GM-CSF, G-CSF) reduce the duration of neutropenia, infection event and allow modest escalation of chemotherapy, these agents can not affect the thrombocytopenic problem. Moreover, some data showed that the efficacy of these agents decreased with repeated courses of chemotherapy[2,27,28]. In contrast, both preclinical and clinical studies have shown that amifostine can reduce cytotoxic therapy induced neutropenia and thrombocytopenia[3,4,6,7,26].

In extensive preclinical studies, amifostine has shown the significant protection of hematopoietic progenitors from a broad range of cytotoxic agents,including daunorubicin, mitoxantrone, paclitaxel, cisplatin, doxorubicin, diaziquone, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, mitomycin-C, BCNU, 5-FU and radiation as well[4, 8,29-35]. In 1981, Wasserman et al[30] demonstrated the cytoprotective effects of amifostine against mouse bone marrow colony forming units from cytotoxic agents and radiotherapy. They showed the dose-modifying factors (the ratio that was determined from the CFU survival curve, it has protection if the ratio is greater than 1) for bone marrow protection it was 4.6, 3.2, 2.4, 1.5, 2.7, 2.4 for nitrogen mustard, cisplatinum, cyclophosphamide, BCNU, 5-FU and radiation, respectively. List et al showed multilineage cytoprotection of amifostine *in vitro*[8]. It was able to protect CFU-GEMM against cytotoxicity from daunorubicin, mitoxantrone and paclitaxel, and also protect BFU-E against toxicity from doxorubicin, mitoxantrone, paclitaxel, cisplatin and diaziquone[8]. Van Laar et al evaluated the cytoprotective effect of amifostine on the combination of carboplatin and 5-FU in an animal trial by intraperitoneal injection of 200 mg/kg amifostine 5 minutes prior to the chemotherapy administration, they found that this drug had a protective ability against carboplatin and 5-FU induced thrombocytopenia[33].

According to the previous preclinical studies, the results have influenced further clinical trials of amifostine as a cytoprotective agent.

Phase I study was conducted by Kligerman et al[36] to determine a maximum tolerated dose or an acceptable tolerated dose and side effects of amifostine. One hundred twenty-one patients with advanced malignancies received a single dose of amifostine (escalated from 25 to 1,330 mg/m^2) before cyclophosphamide, nitrogen mustard, cisplatin or radiation. From this study, it was found that a maximum tolerated dose had not been reached but an acceptable tolerated dose was 740 mg/m^2. The most serious and life-threatening side effect was hypotension, however, only 5 per cent of patients had serious hypotension (drop in systolic blood pressure more than 20 mmHg for at least 5 minutes). The second important side effect was emesis. Both hypotension and emesis caused incomplete infusion of amifostine in about 6 per cent of the total patients. There was no death related toxicity. Kligerman et al did a further phase I trial of multiple doses of amifostine before protracted fractionated radiation therapy[37]. They concluded that the maximum tolerated dose of this drug for fractionated radiation was 340 mg/m^2.

Glick et al conducted phase I controlled trials of amifostine and cyclophosphamide[38]. In this study, fifteen patients received amifostine 450-1,100 mg/m^2 prior to cyclophosphamide 1,200-1,800 mg/m^2 and 4 weeks later (after full hematologic recovery), they were subsequently treated with cyclophosphamide alone. With amifostine pretreatment, eleven of fifteen patients (73%) had improved nadir WBC counts (p=0.008) and seven of eleven (64%) who had nadir differential counts performed had improved nadir granulocyte counts (p=0.05). The mean WBC nadir with combined drugs was 2,700/mm^3 and 1,800/mm^3 in cyclophosphamide alone (p=0.008). The mean granulocyte nadir with these combinations was 1,274/mm^3 compared to 765/mm^3 with cyclophosphamide alone.

Constine et al[39] provided data from a phase I/II trial. They showed that patients with amifostine given prior to hemibody irradiation (HBI) had a more rapid and complete return of WBC than the control group (HBI alone) and no life-threatening toxicity in the amifostine group compared to 2 life-threatening events in the control group. However, there was no difference in the platelet nadir and platelet recovery in the groups. From this study, the authors suggested that the appropriate dose of amifostine was 750-900 mg/m^2[39].

In multiple phase I studies, the dose of amifostine was established at 740-910 mg/m^2 in a single dose regimen and 340 mg/m^2 in a multiple dose regimen[37-41]. Amifostine not only has hematologic protection but also other organ protection from cytotoxic agents such as nephrotoxicity and peripheral neuropathy from cisplatin, and mucositis from cisplatin plus radiation[41,42]. The results of preclinical and phase I trials suggest that this drug is quite safe and has potential broad spectrum cytoprotection against many cytotoxic agents.

Aviles et al[23] conducted a clinical trial of amifostine with intermediate doses of cyclophosphamide. Forty patients with previously untreated high-risk diffuse large cell lymphoma were randomly assigned to four groups (10 patients in each group). The group 1 patients received amifostine 910 mg/m^2 prior to cyclophosphamide 1,500 mg/m^2 for two cycles. Group 2 and group 3 patients received amifostine/cyclophosphamide only on one cycle and cyclophosphamide alone on the other cycle (their own control). The last group of patients received cyclophosphamide alone on two cycles. The patients who were treated with amifostine had fewer days of severe granulocytopenia (grade III or IV). No infection related to granulocytopenia was observed in amifostine plus cyclophosphamide compared to four in cyclophosphamide alone. The mean delay to treatment was 0.8 days in amifostine plus cyclophosphamide and 6.3 days in cyclophosphamide alone[23]. Glover et al[43] reported data from a phase II trial of the effect of amifostine on cyclophosphamide-induced hematotoxicity. Twenty-one patients with diverse malignancies were treated initially with 1,500 mg/m^2 of cyclophosphamide alone and 4 weeks later, after complete hematologic recovery, patients received 740 mg/m^2 of amifostine intravenous infusion over 15 minutes, then followed 15 minutes later by the same dose of cyclophosphamide. The mean WBC nadir was 1,760/mm^3 and 2,500/mm^3 in cyclophosphamide alone and amifostine plus cyclophosphamide, respectively (p<0.0005). The mean granulocyte nadir was also lower in cyclophosphamide alone compared to amifostine pretreatment (541/mm^3 *vs* 1,247/mm^3, p<0.0005). Although thrombocytopenia was found only in patients with cyclophosphamide alone (9.5% *vs* 0%), this difference was not statistically significant[43].

Amifostine has been shown to decrease both the degree and duration of granulocytopenia in cyclophosphamide therapy, and also decreases non-hematologic toxicities in cisplatin therapy such as nephrotoxicity, and neurotoxicity[44-46]. The results led to development of phase III trials of amifostine in protection against toxicities induced by a combination of these drugs[21]. Kemp et al[21] randomized 242 women with advanced ovarian cancer to receive six cycles of cyclophosphamide 1,000 mg/m^2 and cisplatin 100 mg/m^2 (CP) every 3 weeks with or without amifostine 910 mg/m^2 given prior to chemotherapy. One hundred and twenty two patients were randomized to receive amifostine plus CP and 120 patients were randomized to receive CP alone. The two groups were well matched with respect to age, race, FIGO stage, extent of residual disease and performance status. The amifostine plus CP group had a significant decrease in treatment discontinuation due to hematologic toxicity (p = 0.016). Pretreatment with amifostine reduced the incidence of neutropenia associated with fever and/or infection requiring antibiotics (p=0.005), days in hospital (p=0.019) and days on antibiotics (p=0.031). Additionally, pretreatment with amifostine resulted

Table 1. Clinical trails in Amifostine.

Study design	Disease	Regimen	Hematologic protection	Other organ protection	Reference
Controlled trial	Diverse neoplasm	Cyclophosphomide 1,500 mg/m^2 Amifostine 740/ mg/m^2	↓ granulocytopenia (p<0.0005) ↓ thrombocytopenia - NS	-	43 (1986)
Controlled trial	NHL	Cyclophosphomide 1,500 mg/m^2 Amifostine 910/ mg/m^2	↓ granulocytopenia, ↓ infection event	-	23 (1997)
Multicenter randomized controlled trial	Advanced ovarian cancer	Cyclophosphomide 1,000 mg/m^2 Cisplatin 100 mg/m^2 amifostine 910/ mg/m^2	WBC protection (p<0.005) Platelet protection (p=0.169) RBC protection (p=0.23) Required antibiotic treatment (p<0.005) Days in hospital (p=0.019)	Kidney (p=0.003) Peripheral nerve (p=0.02) Cranial nerve VIII (p=0.108) No tumor protection	21 (1996)
Phase II, Uncontrolled trial	Metastatic non-small-cell lung cancer	Cisplatin 120 mg/m^2 Vinblastine 5 mg/m^2 amifostine 740 or 910 mg/m^2	-	Renal protection (compared with historical control)	47 (1996)
Randomized controlled trial	Advanced solid tumor	Carboplatin 500 mg/m^2 amifostine 910/ mg/m^2	Platelet protection (p=0.023)	No tumor protection	48 (1997)
Phase II, Randomized controlled trial	Non-small-cell lung cancer	Carboplatin 600 mg/m^2 amifostine 910/ mg/m^2 x 3 doses per day	↓ median time to platelet recovery (p=0.04) ↓ antibiotic treatment (p=0.06) NS in RBC, WBC protection	-	49 (1995)
Controlled trial	Locally advanced head and neck tumor	amifostine 910 mg/m^2 prior to each radiation Radiotherapy 5 x 2 Gy for 6 weeks	-	↓ Xerotomia (p=0.0001) ↓ Dermatitis (p=0.0014) ↓ Dysphagia (p<0.0001) ↓ Mucositis (p<0.0001)	50 (1998)
Randomized controlled trial	Stage III/IV carcinoma of head and neck	Radiotherapy 2 Gy/day x 5 days/week for 6 weeks Carboplatin 70 mg/m^2 amifostine 500/ mg/m^2 prior to Carboplatin (single dose)	↓ Thrombocytopenia (p=0.012) ↓ Leucopenia (p=0.001) ↓ Anemia (p=0.014) ↓ antibiotic treatment(p=0.017) ↓ G-CSF treatment (p=0.019) ↓ GM-CSF treatment (p=0.001)	↓ Mucositis (p<0.0001) ↓ Xerotomia (p=0.0001) ↓ Dermatitis (p=0.002) ↓ Loss of taste (p=0.001) ↓ Dysphagia (p=0.0001)	51 (1995)
Multicenter randomized controlled trial	Advanced colorectal cancer	Mitomycin-C20 mg/ m^2 amifostine 910 mg/m^2	↓ Thrombocytopenia (p=0.026) NS in RBC, WBC protection	Pulmonary toxicity (No difference)	52 (1994)
Pilot study	Stage IV malignant melanoma	Fotemustine 100 mg/m^2 Amifostine 740 mg/m^2	No severe myelosupression (historial control group 40% major thrombocytopenia 45% severe leucopenia)	-	53 (1998)
Phase I Trial	Refractory cancer in children	Melphalan 35-45 mg/m^2 Amifostine 1,000 mg/m^2	No hematologic protection	-	54 (1995)

NS = non significant

in an 88 per cent reduction (p=0.169) in the number of platelet units transfused and a 29 per cent reduction in the RBC units transfused (p=0.230). In addition to the hematologic protection, this trial showed protective effects of amifostine from cisplatin induced nephrotoxicity, neurotoxicity and ototoxicity (p=0.003, 0.029, 0.108, respectively). Moreover, the pretreatment of amifostine before CP regimen did not show tumor cell protection.

There have been many clinical trials investigating the efficacy of the cytoprotective ability of amifostine to various cytotoxic agents in patients with various neoplasms; these are summarized in Table 1[21,23,43,47-54]. Table 1 shows that amifostine has broad spectrum cytoprotective properties as follows : 1, hematologic protection from cyclophosphamide, carboplatin, mitomycin C, fotemustine and radiotherapy; 2, renal and peripheral nerve protection from cisplatin; 3, mucosa, skin, and salivary gland from radiotherpy; 4, no tumor protection. However, amifostine cannot protect against hematologic toxicity induced by melphalan[54].

Chemotherapy - or radiotherapy-induced secondary malignancy is an important late complication of cancer therapy. Preclinical studies demonstrated that amifostine is anticarcinogenic, antimutagenic, anticlastogenic and antitransforming[29, 55-59]. In addition to the cytoprotective ability, amifostine has been shown to enhance the tumor effect of carboplatin, nitrogen mustard, melphalan, and cisplatin combined with 5-FU or vinblastine in preclinical studies[10,29,33,60-63].

Recently, List et al provided data that amifostine could stimulate hematopoiesis from both preclinical and clinical studies[8,64,65]. They evaluated the hematological stimulation of amifostine (phase I/II trial) in 18 patients with myelodysplastic syndrome (MDS)[64]. The data showed that there were single- and multi-lineage hematologic responses in 15 patients (83%). Fourteen patients (78%) had a rise in absolute neutrophil count (ANC) exceeding 50 of baseline (range ANC increased 426 to 11,348/mm^3), and platelet count increased in 6 of 14 patients (43%) (range 16,000-110,000/mm^3). Five of 15 red cell transfusion-dependent patients (33%) had a $\geq$ 50 per cent reduction in transfusions. Three patients (2 RAEB-t, 1 RAEB) had an increase in BM blast percentage and two of them progressed to acute myeloid leukemia.

Side effect

The two major side effects of amifostine that causes treatment discontinuation are vomiting and hypotension[3,5,6,21,46]. The minor side effects include flushing, sneezing, sleepiness, dizziness, hiccups, chills, metallic taste, allergic reaction, and hypocalcemia[3,4,5,21,39,46,66,67].

Transient hypotension occurs in about 60 per cent of patients but serious hypotension (decrease in systolic blood pressure > 20 mmHg for over 5 per cent minutes or symptomatic hypotension) is rare, occurring in about 5 of patients[5,21, 36,66]. Hypotension usually occurs at the end of the infusion and lasts less than 10 minutes[5,21].

Vomiting is dose related and often occurs within 30 minutes of amifostine administration[5, 36]. However, this incidence is reduced by pretreatment with dexamethasone and serotonin antagonists[5,21,66].

Transient hypocalcemia is common but symptomatic hypocalcemia is rare[66]. The sympto-matic hypocalcemia is usually reported in patients given multiple doses of amifostine[66].

Guidelines for amifostine therapy

Results of preclinical and clinical studies led to the USFDA approval in 1995 for use of amifostine as a cytoprotectant in patients treated with cyclophosphamide and cisplatin for advanced ovarian cancer[6]. The recommended dose for adults is 910 mg/m^2 administered as a 15-minute intravenous infusion 30 minutes before the initiation of chemotherapy[6,21,66,68]. The drug has to be given daily for fractionated chemotherapy or radiotherapy[5]. Repeated doses may be required when combined with long half-life chemotherapy such as carboplatin[1,6]. Dose should be reduced to 740 mg/m^2, if patients experience significant hypotension. The dose used for radioprotection ranges from 200 to 910 mg/m^2[5,7,50,51].

Other guidelines are recommended to reduce or treat hypotension events as follows[1,5, 6,21,66,68] : 1, all hypertensive drugs should be withheld for 24 hours prior to amifostine infusion; 2, the patients should be hydrated before the amifostine infusion; 3, the patients should be in supine position during treatment period; 4, monitor patient blood pressure every 5 minutes during amifostine infusion; 5, if there is significant drop in blood pressure or hypotensive symptoms, the drug has to be stopped and the patients should receive normal saline and be placed in the Trendelenburg position.

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อมิฟอสทีนกับผลต่อระบบทางโลหิตวิทยา

จันทราภา ศรีสวัสดิ์, พ.บ., แสงสุรีย์ จูฑา, พ.บ.**, ฟรังซีส เจ, จายส์, พ.บ.****

อมิฟอสทีนจัดเป็นยาออกฤทธิ์ป้องกันผลข้างเคียงจากการรักษาด้วยยาเคมีบำบัด หรือรังสีรักษาตัวหนึ่ง หลังจากเข้าสู่ร่างกาย ยานี้จะถูกเปลี่ยนเป็นตัวยาที่ออกฤทธิ์คือ ดับเบิลยู-อาร์-1065 โดย แอลคาไลน์ ฟอสฟาเทส เอนไซ ยานี้ถูกขับจากร่างกายอย่างรวดเร็ว พบว่ามากกว่า 90% ของยาที่ถูกขับออกจากร่างกายภายใน 6 นาที และระดับความเข้มข้นของยาสูงสุดในเนื้อเยื่อคือ 10 ถึง 30 นาที หลังฉีดเข้าทางหลอดเลือดดำ อมิฟอสทีน มีคุณสมบัติเฉพาะในการป้องกันเนื้อเยื่อปกติจากผลข้างเคียงของยาเคมีบำบัด หรือรังสีรักษาโดยไม่มีผลต่อการรักษามะเร็ง จากการศึกษามากมาย พบว่ายานี้สามารถป้องกันเซลล์ทางระบบเลือดจากยาเคมีบำบัดหลายชนิด ยิ่งกว่านั้นยานี้ยังสามารถป้องกันอวัยวะอื่นๆ ได้อีก เช่น ไต หัวใจ ปอด ตับ ต่อมน้ำลาย และลำไส้เล็ก อมีฟอสทีน จัดเป็นยาที่ค่อนข้างปลอดภัย จากการศึกษาพบผลข้างเคียงที่สำคัญคือ อาการคลื่นไส้ อาเจียน และความดันโลหิตต่ำ ปัจจุบันนี้ยานี้ได้รับการรับรองให้ใช้ในสหรัฐอเมริกา ในการป้องกันผลข้างเคียงจากการรักษาด้วยยาไซโคลฟอสฟาไมล์และซีสพลาดิน ในผู้ป่วยที่เป็นมะเร็งรังไข่และมะเร็งปอด

คำสำคัญ : อมิฟอสทีน, สารป้องกันเนื้อเยื่อจากเคมีบำบัด

จันทราภา ศรีสวัสดิ์ และคณะ
จดหมายเหตุทางแพทย์ ฯ 2543; 83: 374-382

* ภาควิชาอายุรศาสตร์, โรงพยาบาลพระมงกุฎเกล้า, กรุงเทพมหานคร 10400
** ภาควิชาอายุรศาสตร์, คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี, กรุงเทพมหานคร 10400
*** ภาควิชาลิวคีเมีย, สถาบันโรคมะเร็ง เอ็มดี แอนดอร์สัน, ฮุสตัน, เท็กซัส, สหรัฐอเมริกา