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Amifostine (Ethyol®): Dosing, Administration and Patient Management Guidelines

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Cytoprotection utilising amifostine (Ethyol®, WR-2721) is an evolving strategy to protect normal cells from the toxicity of chemotherapy. The dosing and administration guidelines are reviewed. The recommended dose of amifostine is 910 mg/m^2 as a 15-min infusion prior to chemotherapy. Toxicity of this agent is moderate with hypotension and nausea/vomiting being observed in variable numbers of patients. Administration of amifostine with chemotherapy is simple and is associated with acceptable toxicity. Copyright © 1996 Elsevier Science Ltd

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INTRODUCTION

THE CONCEPT of selective cytoprotection of normal cells and tissues from the cytotoxic effects of chemotherapeutic agents and radiation therapy has provided an interesting avenue for research. Various agents and strategies have been examined, including regional approaches such as cryotherapy [1] and sodium thiosulphate [2], as well as diethyldithiocarbamate to decrease the systemic toxicity of cisplatin [3]. The most extensively evaluated agent and the one having the most clinical potential is amifostine (WR-2721, Ethyol®). This agent is now approved in the United States and in selected European and South American countries as a cytoprotectant to decrease the myelosuppressive and nephrotoxic effects of therapy with cyclophosphamide and cisplatin.

Amifostine was developed by the Walter Reed Army Research Institute [4]. More than 4000 compounds were screened as radioprotectants; amifostine was selected for further investigation because of its activity. This agent is an organic thiophosphate compound that is dephosphorylated by alkaline phosphatase to the active metabolite WR-1065. Preclinical studies in various rodent models demonstrated that amifostine increases resistance to treatment with alkylating agents [5,6], radiotherapy [4] and cisplatin [6]. Based on these preclinical observations, a series of clinical trials was performed to assess the toxicity and effectiveness of this agent. Many of these studies are reviewed in this publication and have demonstrated the potential utility and side effects of this drug.

The principal side effects of amifostine that have been observed include nausea, vomiting, transient hypotension, flushing and sneezing. The frequency of these toxicities has been variable in phase I and II trials (Table 1). These data demonstrate the side-effect profile of amifostine when administered with either carboplatin [7] or the combination of cisplatin and R-24 [8], a murine monoclonal antibody against the ganglioside GD_3. These two trials were phase I studies conducted at The Cleveland Clinic Foundation, Cleveland, Ohio. The contribution of the various agents or combinations to the toxicities is not entirely clear. The randomised controlled study of cisplatin and cyclophosphamide with or without amifostine in patients with ovarian cancer [9] clearly demonstrated the

Table 1. Toxicity of amifostine and chemotherapy in phase I trials: Cleveland Clinic Foundation regimens

	Regimen	
	I	II
Amifostine*	740 and 185–740 mg/m^2 before and following carboplatin	740 mg/m^2 before cisplatin
Carboplatin	400–625 mg/m^2 d 1	–
R-24	–	8–40 mg/m^2 d 1–5†
Cisplatin	–	120 mg/m^2 d 1‡
No. of patients	35	19
Nausea/vomiting		
Grade I–II	86%	100%
≥ Grade III	3%	–
Hypotension		
Grade I–II	63%	21%
≥ Grade III	–	5%
Hypocalcaemia		
Grade I–II	34%	–
≥ Grade III	–	–

* Administered as a 15-min infusion.
† Administered as a 6-h infusion.
‡ Administered in 250 cc of 3% NaCl preceded by hydration with 125 cc of 0.9% NaCl for 12 h.
Data from Budd and coworkers [7] and Bukowski and coworkers [8].

Table 2. Toxicity of cisplatin (P) and cyclophosphamide (C) with and without amifostine

Toxicity	Overall incidence of selected toxicity (%)	
	Amifostine plus CP (n = 122)	CP (n = 120)
Nausea/vomiting	96%	88%
Hypotension	57%	-
Flushing/warm feeling	39%	2%
Sneezing	25%	2%
Dizziness/lightheadedness	11%	2%

* No blood pressure values in control arm.
Data from Glick and coworkers [9] and Ethyol monograph [10].

incidence of these effects (Table 2). Based on these observations and on experiences with the use of this agent, administration guidelines and suggestions for toxicity management have been developed by the Schering–Plough International [10]. These are detailed below.

AMIFOSTINE PREPARATION AND DOSE CALCULATION

The recommended adult dose of amifostine is 910 mg/m^2, administered as a 15-min infusion approximately 30 min before initiation of chemotherapy. Experience with longer infusion times has suggested a higher incidence of side effects. More frequent or shorter infusion times have also been utilised, but data on these schedules are preliminary.

Amifostine is supplied as a lyophilised powder in 10-ml vials containing 500 mg of amifostine and 500 mg of mannitol. When reconstituted with 9.5 ml of sterile 0.9% sodium chloride, the solution may be kept for 6 h at room temperature (15–25°C) or 24 h refrigerated (2–8°C). There are no known incompatibilities, but mixing with other agents is not recommended. Care must be taken to ensure the stability of the prepared solution. Drug products that are to be administered parenterally should be inspected visually for particulate matter and discolouration prior to administration. In addition, aseptic technique and proper environmental precautions must be observed during the preparation of amifostine.

Each vial of amifostine should be reconstituted with 9.5 ml of sterile 0.9% sodium chloride solution to bring the total volume of the solution to 10.0 ml. The lyophilised powder should dissolve fully within 1 min. Each milliliter of the resulting solution will contain 50 mg of amifostine and 50 mg of mannitol. The final volume of solution to be added to the empty infusion container should equal 50 ml. Reconstituted solutions may be further diluted with sterile 0.9% sodium chloride solution for dosage adjustment. Common dosages and total volume of solution for amifostine administration are summarised in Table 3.

*Table 4. Guidelines for interruption of amifostine due to hypotension**

Baseline systolic blood pressure (mm Hg)	Decrease in systolic blood pressure (mm Hg)
< 100	≥ 20
100 – 119	≥ 25
120 – 139	≥ 30
140 – 179	≥ 40
≥ 180	≥ 50

* Administered as a 15-min infusion at a dose of 910 mg/m^2.

AMIFOSTINE DOSAGE AND ADMINISTRATION GUIDELINES

Because of the observed incidence of hypotension, patients receiving amifostine should be adequately hydrated and treated while in a supine position. A baseline blood pressure should be obtained and then rechecked every 3–5 min. Guidelines for interrupting amifostine, based on a decrease in systolic blood pressure, have been developed (Table 4). Generally, the hypotension observed is transient, occurs at a median of 13 min after initiation of amifostine and returns to baseline within minutes (median 5 min). Management of the hypotension includes interruption of amifostine, placement of patients in the Trendelburg position and administration of an infusion of 0.9%

Table 3. Amifostine dosage summary

Body surface area (m^2)	Amifostine dosage		Amifostine dosage	
	910 mg/m^2	Total volume reconstituted*	740 mg/m^2	Total volume reconstituted*
1.2	1092 mg	21.84 ml	888 mg	17.76 ml
1.3	1183 mg	23.66 ml	962 mg	19.24 ml
1.4	1274 mg	25.48 ml	1036 mg	20.72 ml
1.5	1365 mg	27.30 ml	1110 mg	22.20 ml
1.6	1456 mg	29.12 ml	1184 mg	23.68 ml
1.7	1547 mg	30.94 ml	1258 mg	25.16 ml
1.8	1638 mg	32.76 ml	1332 mg	26.64 ml
1.9	1729 mg	34.58 ml	1406 mg	28.12 ml
2.0	1820 mg	36.40 ml	1480 mg	29.60 ml
2.1	1911 mg	38.22 ml	1554 mg	31.08 ml
2.2	2002 mg	40.04 ml	1628 mg	32.56 ml
2.3	2093 mg	41.86 ml	1702 mg	34.04 ml
2.4	2184 mg	43.68 ml	1776 mg	35.52 ml
2.5	2275 mg	45.50 ml	1850 mg	37.00 ml

* Amifostine: 50 mg/1 ml.

normal saline. Rarely, more prolonged hypotension occurs (5–15 min), and production of symptoms is very uncommon. It is also recommended that antihypertensive agents be withheld for 24 h before administration of amifostine and that they be carefully monitored during therapy.

If hypotension is observed but returns to baseline within 5 min, the infusion of amifostine may be restarted and completed. If the full dose cannot be administered, the dose level should be reduced by 20% from 910 to 740 mg/m^2 in subsequent cycles. These recommendations are summarised in Figure 1.

The availability of effective antiemetic regimens for patients receiving an emetogenic chemotherapy, and the slight increased frequency of nausea and vomiting when amifostine is administered, indicate that antiemetics should be administered prior to infusion of this agent. Suggested guidelines for pretreatment therapy relative to the time of amifostine administration are outlined in Table 5.

Additionally, hypocalcaemia has been reported during amifostine therapy [11], primarily when doses of 740–910 mg/m^2 are administered on a daily basis, and therefore serum calcium levels should be monitored in patients at risk for this complication. This would include individuals receiving hypocalcaemic agents or those with the nephrotic syndrome.

Drug interactions with amifostine have not been observed.

Table 5. Guidelines for pretreatment therapy relative to the time of amifostine administration

Relative time of amifostine	Pre-treatment 1
− 4 h	5% Dextrose solution or 0.9% normal saline 1–2 l, 250 ml/h
− 1 h	Thiethylperazine maleate 10 mg, orally
− 30 min	Dexamethasone mg IV 20 mg, IV $5HT_3$ antagonist

The rapid clearance of amifostine may minimise this possibility, but because of the side effect profile, caution should be exercised when treating patients receiving concomitant antihypertensive agents or drugs for therapy of hypercalcaemia. The use of amifostine during pregnancy or in lactating women has not been studied, and its use in these situations, therefore, should be avoided.

Absolute contraindications for the use of amifostine include dehydration or known sensitivity to aminothiol compounds or mannitol. In certain situations or some patient populations (Table 6) caution should be exercised.

In summary, the administration of amifostine in combination

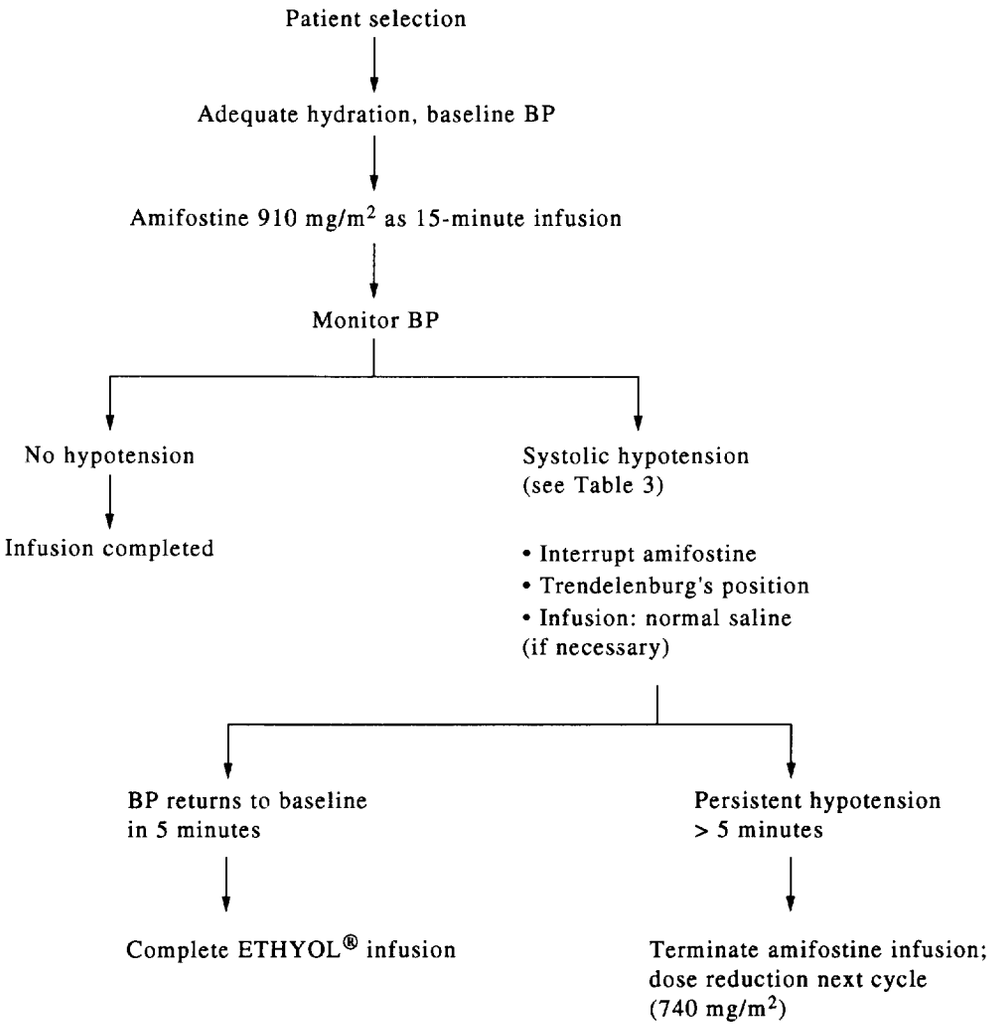

Figure 1. Patient guidelines: therapy of hypotension during amifostine administration

Table 6. Precautions during amifostine administration

Contradindications:
- Known sensitivity to aminothiol compounds or mannitol
- Dehydration
- Pregnancy, lactating females

Caution should be exercised:
- Concomitant antihypertensive agents
- Concomitant administration hypocalcaemic agents
- Severe hepatic and/or renal impairment
- Patients ≥ 70 years
- Children ≤ 18 years
- Patients at risk for hypocalcaemia

with chemotherapy is simple and is associated with an acceptable toxicity profile. Careful attention to patient selection, monitoring and pretreatment can minimise some of the associated toxicity. Further investigation of the cytoprotective effects of amifostine with other forms of chemotherapy, dose-intensive regimens, in combination with haematopoietic growth factors, and in alternate schedules will provide additional information on the utility of this drug and its toxicity.

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