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Cytoprotection by Amifostine during Autologous Stem Cell Transplantation for Advanced Refractory Hematologic Malignancies

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ABSTRACT

This study evaluated whether amifostine protects against mucositis and other toxicities in patients with advanced, refractory, or recurrent hematologic malignancies undergoing high-dose chemotherapy and total body irradiation. Thirty-five patients (20 with non-Hodgkin lymphoma, 12 with Hodgkin disease, and 3 with acute myelogenous leukemia) who underwent autologous stem cell transplantation were conditioned with total body irradiation 2 Gy twice daily on days −8 through −6; cyclophosphamide 6 g/m^2, etoposide 1.8 g/m^2, and carboplatin 1 g/m^2 on days −5 through −3; and amifostine 500 mg/m^2 on days −8 through −2. Prior institutional experience in patients treated without amifostine was used as a historical comparison (no-amifostine group). Severe mucositis occurred in 14 (40%) of 35 patients in the amifostine group, compared with 33 (94%) of 35 in the no-amifostine group ($P < .0001$). Total parenteral nutrition was used by 4 (11%) of 35 amifostine-treated patients and 34 (97%) of 35 no-amifostine patients ($P < .0001$). The median duration of narcotic use decreased from 15.5 days with no amifostine to 11 days with amifostine ($P = .002$). Granulocyte and platelet engraftment times were similar. Prospective trials with innovative designs and clearly defined stopping rules are warranted to confirm whether amifostine reduces the toxicities of a myelosuppressive conditioning regimen before autologous stem cell transplantation without compromising therapeutic response.
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KEY WORDS

Amifostine • Mucositis • Total parenteral nutrition

INTRODUCTION

Mucositis is a significant dose-limiting complication in cancer treatment. The global incidence of mucositis related to cancer therapy is estimated at 500 000 annually [1]. Mucositis occurs with an overall incidence of approximately 30% to 40% during chemotherapy, and severe, debilitating mucositis is more common with conditioning regimens for hematopoietic stem cell transplant [2]. For high-dose chemotherapy, the incidence is much higher and exceeds 90% in some studies [3-7].

Identification of reliable risk factors to predict the severity and sequelae of mucositis is limited, in part because of the lack of uniform mucositis evaluation criteria [8-14]. Despite these drawbacks, the development of mucositis models to investigate the effects of inflammatory cytokines and new therapeutic interventions to counter these effects shows promise for reduction of both the incidence and the severity of mucositis [2].

Significant improvement in the prevention of mucositis may evolve from exploitation of differences between healthy and tumor tissue. The delivery of therapy in doses sufficient to completely eradicate the tumor typically exceeds the tolerance of healthy tissue, thereby limiting dose escalation to a level that is sufficient for cure [5,15]. Damage to healthy tissue has the consequence of increased patient morbidity, a longer hospital stay, and a negative economic effect

Table 1. *Conditioning Regimen*

Day	Dose mg/m^2/d	−8	−7	−6	−5	−4	−3	−2	−1	0
Total body irradiation	2 Gy bid	X	X	X						
Cyclophosphamide	2000 IV				X	X	X			
Etoposide	600 IV				X	X	X			
Carboplatin	333 CI				X	X	X			
PBSC infusion										X
Amifostine*	500 IV	X	X	X	X	X	X			

*The no-amifostine group received the same conditioning regimen but without amifostine. IV indicates intravenous; CI, continuous IV infusion; PBSC, peripheral blood stem cells; bid, twice daily.

[5,15,16]. Thus, selective targeting of healthy tissue for cytoprotection, exploiting differences in apoptosis between healthy and tumor cells, and minimizing infections are all important issues for investigation.

Amifostine (Ethyol; MedImmune Oncology, Inc., Gaithersburg, MD) is an aminothiol that selectively protects healthy tissues against the cumulative renal toxicity associated with platinum therapy [17] and the moderate to severe xerostomia associated with irradiation of the parotid glands [18]. This study was undertaken in patients with advanced refractory hematologic malignancies to determine whether amifostine could protect against mucositis and other toxicities without compromising the therapeutic response in patients undergoing a conditioning regimen that included high-dose chemotherapy and total body irradiation (TBI) before autologous stem cell transplantation.

PATIENTS AND METHODS

Patients

Patients with non-Hodgkin lymphoma (NHL) or Hodgkin disease (HD) were eligible for this study if their disease progressed or recurred after at least 1 course of combination chemotherapy. Patients with acute myelogenous leukemia (AML) were eligible if they had a high-risk first remission or a subsequent complete remission (CR). High risk was defined as disease that necessitated a second induction therapy to achieve a CR, unfavorable cytogenetics, or extramedullary disease. Eligibility criteria also included age >16 and <65 years, an Eastern Cooperative Oncology Group performance status of 0 to 2, a white blood cell (WBC) count $>1.5 \times 10^9$/L, an absolute neutrophil count (ANC) $>0.5 \times 10^9$/L, a platelet count $>50 \times 10^9$/L, aspartate aminotransferase and bilirubin <2 times normal, serum creatinine <177 μmol/L or creatinine clearance >1.0 mL/s, pulmonary diffusion capacity >50% of predicted, and negative testing for human immunodeficiency virus and hepatitis B surface antigens. Exclusion criteria included serious medical or psychiatric illnesses that would prevent informed consent or preclude general anesthesia; uncontrolled or

severe cardiovascular disease, such as recent myocardial infarction or congestive heart failure within 6 months of transplantation; active uncontrolled bacterial, viral, or fungal infection; or an active duodenal ulcer. All patients signed informed consent documents reviewed and approved by the University of North Carolina Committee for the Protection of the Rights of Human Subjects.

Hematopoietic Stem Cells

For patients with NHL or HD, stem cell collection was accomplished after salvage chemotherapy and before initiation of the conditioning regimen. In patients with AML, stem cells were collected after the patient achieved CR and underwent at least 1 cycle of consolidation chemotherapy. No patient with AML had stem cells collected during initial remission for use after a subsequent relapse. Peripheral blood stem cells (PBSCs) were used when possible for rescue therapy. However, if fewer than 2×10^6 CD34$^+$ cells per kilogram were collected, patients received a combination of marrow and PBSCs or marrow alone as previously described [19].

Patients with NHL received pretransplantation salvage therapy whenever possible to reduce their tumor burden before high-dose chemotherapy. Salvage therapies included ifosfamide, carboplatin, and etoposide [20]; etoposide, methylprednisolone, cytarabine, and cisplatin [21]; and dexamethasone, cisplatin, and cytarabine [22]. High-risk patients with AML received stem cell transplantation while in CR after initial induction and consolidation or, for relapsed patients, after reinduction of remission.

Treatment Plan

An indwelling central venous catheter was placed in all patients before stem cell collection. The conditioning regimen (Table 1). consisted of TBI 2 Gy twice daily on days −8 through −6 followed by cyclophosphamide (total dose, 6 g/m^2) and etoposide (total dose, 1.8 g/m^2) on days −5 through −3 and a continuous infusion of carboplatin (total dose, 1 g/m^2) for 3 days starting on day −5. Amifostine 500 mg/m^2

was administered once daily on days -8 through -2 as a 3-minute intravenous (IV) push 15 to 30 minutes before the morning dose of TBI or first daily dose of chemotherapy. Standard antiemetic therapy was given before chemotherapy. Patients received hydration at 250 mL/m^2/h during chemotherapy and for a minimum of 24 hours after the completion of chemotherapy (ie, throughout days -5 through -1). All patients received granulocyte colony-stimulating factor (G-CSF; 5 μg/kg/d) beginning on day $+5$ and continuing until the ANC was $>0.5 \times 10^9$/L on 2 consecutive days.

Standard supportive care included ciprofloxacin 500 mg orally (PO) twice daily beginning on day -1 and continuing until body temperature was $>38.3°C$, after which ciprofloxacin treatment was discontinued and patients received vancomycin 15 mg/kg IV every 12 hours and cefepime 2 g IV every 8 hours. Doses were adjusted in the event of renal impairment. Patients did not routinely receive bladder irrigation or mesna therapy. Fluconazole 400 mg PO once daily was initiated on day -4, and acyclovir 200 mg PO 3 times daily was started on day 0 if the patient was serologically positive for herpes simplex virus. Total parenteral nutrition (TPN) was used when oral caloric intake was inadequate (ie, after a 10% loss in baseline body weight or inability to eat solid food for >7 days).

Study End Points

The primary end point was the occurrence and severity of toxicities, particularly mucositis. Mucositis was graded with the oral mucositis assessment scale [23]. Additional toxicities were assessed according to the National Cancer Institute Cancer Therapy Evaluation Program Common Toxicity Criteria [24]. Other end points included the number of days that patients required TPN; the number of days with fever; the number of days on which antibiotics, narcotics, or G-CSF were administered; and the total number of days of hospitalization.

Clinical Response Criteria

A CR was defined as the disappearance of all measurable disease signs, symptoms, and biochemical changes related to the tumor for >4 weeks. No new lesions could have appeared during this time. A partial response was defined as a reduction of $>50\%$ in the sum of the products of the perpendicular diameters of all measurable lesions that lasted >4 weeks and during which time no new lesions appeared and no existing lesions enlarged. Stable disease was characterized as $<50\%$ reduction and $<25\%$ increase in the sum of the products of 2 perpendicular diameters of all measured lesions and the appearance of no new lesions for >8 weeks. Progressive disease was defined as an increase in the product of 2 perpendicular diameters of any measured lesion by $>25\%$ or the appearance of new areas of disease. Increasing symptoms alone did not

constitute progressive disease, although their appearance generated a new evaluation of the extent of disease. A CR for patients with AML consisted of elimination of all cytogenetic and morphologic evidence of leukemia with recovery of platelet counts to $>50 \times 10^9$/L without transfusion for a minimum of 30 days after transplantation.

Statistical Methods

Descriptive statistics were computed for key outcome measures. Where appropriate and available, data were compared with those of a historical control group—a subset of a previous study in which patients received an identical treatment regimen for their malignancies but did not receive amifostine for cytoprotection [5]. Of the 67 patients in that study, 35 were included in the historical control group because they received the same TBI dose of 12 Gy that was used in this study.

The Fisher exact test was used for data categorized into contingency tables to test general associations. The nonparametric Jonckheere-Terpstra method was used to test for ordered differences among categories (for example, the 2×5 renal toxicity table). With this test, the null hypothesis is that the distribution of the response does not differ across ordered categories. For continuous variables such as days on narcotics, the Wilcoxon rank-sum test (using Van der Waerden normal scores) was used for group comparisons. The Kaplan-Meier (or product-limit) method was used to estimate the overall survivorship, disease-free survivorship, and disease progression functions. Statistical analyses were performed with SAS statistical software, versions 8.2 and 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Patients

Thirty-five patients with advanced hematologic malignancies participated in this study between March 1999 and December 2002, including 20 with NHL, 12 with HD, and 3 with AML. There were no significant differences in age or sex between the amifostine group and the historical control group (no-amifostine group), but there were more black patients ($P = .045$), more patients with HD or AML ($P = .01$), more patients with CR with induction ($P = .03$), and greater use of PBSCs alone ($P = .01$) in the amifostine group than in the no-amifostine group (Table 2).

Hematologic Recovery

In the amifostine group, the median time to WBC engraftment (ANC $>0.5 \times 10^9$/L on 2 consecutive days) was 10 days (range, 8-41 days), and the median time to platelet engraftment ($>20 \times 10^9$/L on 2 consecutive days) was 11 days (range, 8-40 days). Two patients remained transfusion dependent. In the no-amifostine group, the median times to WBC and platelet engraft-

Table 2. *Patient Characteristics*

Variable	Amifostine	No Amifostine	P Value
No. of patients	35	35	
Age, y, median (range)	46 (21-61)	47 (19-66)	.25
Sex, n			
Male	22 (63%)	24 (69%)	.80
Female	13 (37%)	11 (31%)	
Race, n			
Black	9 (26%)	2 (6%)	.045
White	26 (74%)	33 (94%)	
Pretreatment diagnosis, n			
Non-Hodgkin lymphoma	20 (57%)	30 (86%)	.01
Hodgkin disease	12 (34%)	5 (14%)	
Acute myelogenous leukemia	3 (9%)	0 (0%)	
Pretreatment status, n			
Complete remission	16 (46%)	10 (0%)	.03
Partial response	10 (26%)	20 (57%)	
Relapse	3 (9%)	0 (0%)	
Primary induction failure—sensitive	2 (6%)	0 (0%)	
Refractory	4 (11%)	3 (9%)	
Stem cell source, n			
Peripheral blood stem cell	27 (77%)	20 (57%)	.01
Bone marrow	5 (14%)	2 (6%)	
Both	3 (9%)	13 (37%)	

ment were 11 and 17 days, respectively. These differences were not statistically significant.

Mucositis

All 35 patients (100%) in the amifostine group experienced at least grade 1 mucositis. The incidence of grade 3 or 4 mucositis in the amifostine group was 14 (40%) of 35, including only 2 occurrences (6%) of grade 4 mucositis (Table 3). The incidence of grade 3 or 4 mucositis in the no-amifostine group was 33 (94%) of 35 ($P < .0001$).

On the basis of criteria set for the study, only 4 patients (11%) in the amifostine group required TPN for 1, 12, 16, and 17 days (Table 4). In contrast, 34 patients (97%) in the no-amifostine group required TPN ($P < .0001$) for a median duration of 16 days. The median duration of narcotic use in patients who received amifostine was 11 days, compared with 15.5 days in the no-amifostine group ($P = .002$; Table 4).

Renal Toxicity

Normal renal function was preserved in most patients. Patients who received amifostine had sig-

nificantly less renal toxicity of any severity (26%) than those in the no-amifostine group (54%; $P = .03$; Table 5). Of the patients in the amifostine group who were admitted with a normal creatinine level, only 9 (26%) developed a creatinine ≥ 133 μmol/L. One patient was admitted with a creatinine level of 159 μmol/L and had a peak creatinine level of 221 μmol/L but was discharged with a normal creatinine level. Another patient was admitted with a creatinine level of 88 μmol/L and developed a peak creatinine level of 345 μmol/L. This patient's creatinine level remained abnormal during the remainder of the admission, and the patient was discharged with a creatinine level of 292 μmol/L. Grade 2 oral mucositis was documented in this patient, who also received 31 days of antibiotics for fever without an identified source.

Gastrointestinal Toxicity

Gastrointestinal toxicity was recorded only in the amifostine group. Twenty-two patients (63%) had grade 1 diarrhea, 12 (34%) had grade 2 diarrhea, and 1 (3%) had grade 3 diarrhea. The median duration of

Table 3. *Incidence and Duration of Mucositis by Severity in the Amifostine Group (n = 35)*

	Mucositis Grade			
Variable	1	2	3	4
Most severe grade, n	2 (6%)	19 (54%)	12 (34%)	2 (6%)
Any report of mucositis				
No. of patients	33 (94%)*	33 (94%)	14 (40%)	2 (6%)
Median duration, d (range)†	6 (2-12)	5 (1-12)	4 (1-9)	5 (4-6)

*Two patients had grade 2 mucositis without experiencing grade 1 mucositis.

†Among patients reporting that grade of mucositis; does not include 0 days.

Table 4. *Mucositis Associated with Combined-Modality Chemoradiotherapy before Autologous Stem Cell Transplantation, with or without Amifostine Pretreatment*

Variable	Amifostine (n = 35)	No Amifostine (n = 35)	P Value
Mucositis grade 3 or 4, n	14 (40%)	33 (94%)	<.0001
Median (range) duration of narcotic use for mucositis, d	11 (1-23)	15.5 (5-48)	.002
Required TPN, n	4 (11%)	34 (97%)	<.0001

grade 1 or 2 diarrhea was 3 days (range, 1-7 days). Nausea and vomiting occurred in most patients, but these were usually transient and were not dose limiting. Delayed nausea or vomiting occurred in 3 patients (9%): 2 (6%) had grade 2 and 1 (3%) had grade 3. No patient had grade 4 gastrointestinal toxicities.

Amifostine Side Effects

No case of nausea, hypotension, or hypocalcemia more severe than grade 1 was observed in the amifostine group. Nearly all patients had significant nausea, but none required intervention with more than antiemetics. Intravenous calcium replacement was provided as needed after corrections for hypoalbuminemia were made.

Other Outcomes and Events

Infections documented by microbiological culture occurred in 13 patients (37%) in the amifostine group and included 6 (17%) with bacteremia, 1 (3%) with genitourinary infection, 1 (3%) with pleural fluid, and 2 (6%) with vancomycin-resistant enterococcal infections. In addition, 1 patient with AML had a pulmonary aspergillus infection documented before transplantation; he was treated prophylactically with antifungal agents, and his fungal infection was not reactivated. Finally, 1 patient developed reactivation of varicella-zoster virus, and 1 had herpes simplex virus 2.

Comparison of the pretreatment and posttreatment left ventricular ejection fraction within each group and between groups almost reached statistical significance when the absolute changes from baseline values were compared (P = .06) and when the percentage changes from baseline were compared (P =

Table 5. *Renal Toxicity Associated with Combined-Modality Chemoradiotherapy before Autologous Stem Cell Transplantation, with or without Amifostine Pretreatment*

Variable	Amifostine (n = 35)	No Amifostine (n = 35)	P Value
No toxicity, n	26 (74%)	16 (46%)	
Any grade, n	9 (26%)	19 (54%)	.03
Grade 1	5 (14%)	11 (31%)	
Grade 2	4 (11%)	4 (11%)	
Grade 3	0 (0%)	1 (3%)	
Grade 4	0 (0%)	3 (9%)	.02

.06) between patients who received amifostine and the no-amifostine group.

The values for hematocrit and volume-corrected diffusion capacity (carbon monoxide diffusion in the lung) were similar from baseline to the final visit in both groups and were not significantly different between the amifostine and no-amifostine groups. Only 2 serious adverse events were reported in the amifostine group, and both were cardiac in origin. One patient had a grade 3 cardiac arrhythmia that was related to the conditioning regimen, and the patient recovered uneventfully. The other patient had a moderately large pericardial effusion that also resolved uneventfully.

In the amifostine group, there were 12 deaths, and the median follow-up time in survivors was 26 months (Figure 1). Disease progression occurred in 15 patients.

DISCUSSION

In this study, amifostine administered at a dose of 500 mg/m²/d for 7 days during a conditioning regimen that included high-dose chemotherapy and TBI before hematopoietic stem cell transplantation substantially reduced the incidence and severity of mucositis compared with results obtained previously in patients treated with an identical regimen minus ami-
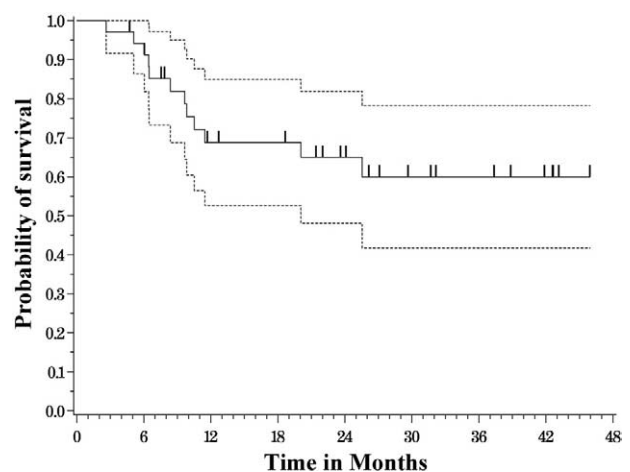

Figure 1. Probability (and 95% confidence interval) of overall survival among patients who received amifostine during conditioning therapy.

fostine [5]. The incidence of severe (grade 3 or 4) mucositis in the earlier study was more than 2-fold higher than when amifostine was included. Because the oral manifestations of mucositis are very painful and interfere with nutrition, the observed difference in mucositis rates with or without amifostine treatment accounted for significant reductions in the number of patients who required TPN (11% versus 97%) and the median duration of narcotic use (11 versus 15.5 days).

Amifostine administration was associated with mild and transient side effects (nausea, vomiting, hypotension, and hypocalcemia) in most, but not all, patients, but these effects did not cause interruption of therapy in any patient. Similar response rates and engraftment times were observed when comparing patients who were treated with the conditioning regimen with and without amifostine. The risk for tumor protection when cytoprotective agents are administered during chemotherapy has been a theoretical argument against the use of drugs to protect healthy tissue. In the case of amifostine, previous study results have shown no evidence of tumor protection [17,18]. The results presented here suggest that amifostine is associated with selective protection from mucositis without significant tumor protection. However, differences in disease characteristics and treatment regimens were observed between the amifostine and no-amifostine groups at baseline. Therefore, confirmation of these results with a prospective, randomized, controlled trial is warranted. In light of the striking differences observed between the amifostine group and the historical control group in this retrospective analysis, prospective trials in this setting should include clearly defined rules for stopping the trial early if interim analyses demonstrate evidence of cytoprotection with amifostine compared with the control group. Innovative study designs, such as the identification and use of surrogate markers for treatment toxicities, might also be useful for identifying the response to amifostine more clearly and more rapidly.

The results of this study are consistent with those of other published studies demonstrating that amifostine can provide selective cytoprotection for healthy tissues in patients undergoing myeloablative conditioning regimens before stem cell transplantation. In a randomized trial, 40 patients with solid tumors undergoing autologous PBSC transplantation received high-dose carboplatin-based chemotherapy (carboplatin, ifosfamide, and etoposide) with or without amifostine (910 mg/m^2) [25]. All patients received G-CSF. Nephrotoxicity and gastrointestinal toxicity were substantially diminished in patients who received amifostine. For example, amifostine significantly reduced the incidence of mucositis ($P = .01$) and diarrhea ($P = .01$). Amifostine-treated patients also had fewer days with fever, more rapid hematologic recov-

ery, and earlier discharge from the hospital; this resulted in a cost savings of approximately 30% for supportive care [25]. However, Chauncey et al. [26] did not find a benefit to the use of amifostine. They evaluated 21 patients conditioned with busulfan, melphalan, and thiotepa who were also treated with amifostine only during melphalan and thiotepa treatment after completion of the busulfan portion of conditioning. The lack of benefit observed for the reduction of nonhematologic toxicities in that study may have resulted because amifostine was not also included during busulfan administration. Mucositis associated with the combination of radiation and carboplatin in a randomized trial for the treatment of head and neck cancer was significantly reduced by the infusion of amifostine 300 mg/m^2 before radiation administration [27]. Because of fewer treatment interruptions, the treatment duration was significantly shorter in the amifostine group ($P = .01$). At week 5, grade 4 mucositis was present in 52.2% of patients in the control group but in only 4.5% of patients treated with amifostine ($P = .0006$) [27]. It should also be pointed out that the theoretical risks of tumor protection by the administration of amifostine were not observed in any of the trials listed previously nor in the study reported here.

A reduction in the severity of mucositis may permit more intensive chemoradiotherapy. Phillips [15] used amifostine to minimize mucositis in a dose-escalation trial in which melphalan was increased from 200 to 280 mg/m^2. Thieblemont et al. [28] reported a reduction in mucositis from 65% without amifostine to 33% with amifostine 740 mg/m^2. Capelli et al. [29] also reported a reduction in grade 3 or 4 mucositis from 53% in the control group to 21% in the treatment group when amifostine was given with melphalan; reductions in the duration of narcotic use and diarrhea were also reported. In another randomized study of 46 patients with stage II and III multiple myeloma treated with amifostine before a conditioning regimen that included high-dose melphalan and busulfan, patients were randomized to receive amifostine 740 mg/m^2 or no amifostine before melphalan. The treatment group had a 13% incidence of World Health Organization grade 3 and 4 mucositis, compared with 35% in patients who did not receive amifostine [30].

Severe mucositis can have a profound adverse effect during blood or marrow transplantation, and in many cases, mucositis limits treatment intensity [5]. Oral mucositis presents particular problems in pain management, reduces nutrition, limits patient communication, and increases infection risk [31-37]. The duration of oral mucositis in transplantation is typically 3 to 9 days [4], and 50% of patients develop grade 3 to 4 mucositis [6]. The variability in the severity of mucositis is thought to be related to the intensity of the conditioning regimen, cytokine production during
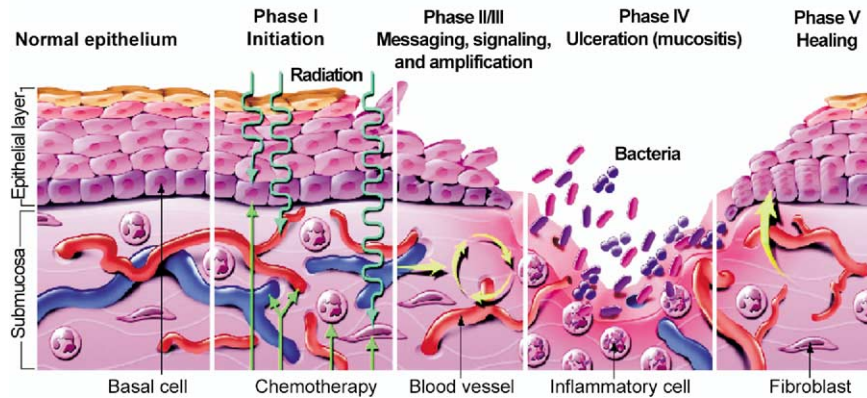
Figure 2. Pathobiology of mucositis. Mucositis is thought to occur in the following 5 phases: initiation, upregulation and message generation, signaling and amplification, ulceration, and healing. Possible actions of amifostine to reduce mucositis include scavenging of reactive intermediates generated by radiotherapy and chemotherapy in the initiation phase, as well as activity of the symmetric, disulfide, dimeric form of amifostine at other phases in this model [47,49]. Reprinted with permission of McNeil-PPC, Inc. [2].

conditioning, alteration of microbial flora, antimicrobial drugs, direct effects of chemotherapy, and stem cell source [6,38-41]. Other contributing factors include reductions in the volume of saliva and reductions in the salivary immunoglobulin concentration [42].

The mechanism of action of amifostine to diminish the severity and occurrence of mucositis is currently not clear. Sonis [2,43] proposed a 5-step model for the evolution of mucositis (Figure 2). The first phase of this model is the initiation phase, in which healthy tissue sustains damage to both nuclear and cytoplasmic elements. The second phase, referred to as the message-generation phase, begins with interference of cellular control mechanisms. It is postulated that the institution of chemotherapy or radiotherapy leads to activation of transcription factors, including nuclear factor κB, that in turn activate many genes [44]. During this phase, ceramide-induced apoptosis in mucosal endothelial cells occurs [45]. The message-generation phase is followed by the signaling and amplification phase, in which inflammatory cytokines are produced [44]. The appearance of the ulceration phase marks the most clinically significant period of mucositis. During this time, pseudomembranes and bacteria overgrowth appear. Pain during this phase may inhibit phonation and food ingestion. Bacteria may penetrate into the submucosa and result in bacteremia [46]. The healing phase is heralded by the migration of epithelial cells into the ulcer to restore normal mucosal contours that then decrease pain.

The mechanism of action for amifostine may target several points in this model. Its initial effect is likely to occur during the tissue damage phase, when it scavenges reactive intermediates generated by therapy [47]. The symmetric disulfide dimeric form of amifostine, which is in equilibrium with the parent compound in the plasma and is structurally similar to the polyamine, spermidine, may also be important at other points in this model [47]. The ability of amifostine to modulate the intracellular oxidative state seems to be related to its activation of nuclear factor κB, superoxide dismutase, and p53 [47-49]. These factors may be important for cytoprotection and antitumor effects [48].

Severe mucositis adds substantial costs to patient treatment [50,51]. In general, mucositis is associated with longer hospitalization, longer need for TPN, longer use of narcotics, and increased 100-day mortality [51]. In an economic analysis by Bennett and colleagues [50] of a small randomized trial that used amifostine to reduce mucositis, a highly significant reduction in the severity of thrombocytopenia and xerostomia was observed that was calculated to yield an overall reduction in the cost of the transplantation. A similar analysis by Sonis and colleagues [51] also indicated a significant increase in costs when mucositis occurred.

Careful mouth care is an essential element in the management of oral mucositis [52]. The use of topical antibiotics [46], phototherapy [53,54], and oral rinses containing interleukin 11 and granulocyte-macrophage colony-stimulating factor [55,56] have been disappointing. However, subcutaneously injected keratinocyte growth factor does seem to reduce the incidence of mucositis [57,58].

In summary, a considerable amount of data on the use of amifostine in patients undergoing myeloablative regimens before stem cell transplantation, including the results from this study, demonstrates that amifostine treatment can reduce the toxicities associated with conditioning therapy during autologous stem cell transplantation. Randomized, comparative clinical trials with innovative study designs and clear stopping rules are warranted to establish the cytopro-

tective benefits of amifostine when it is used with a conditioning regimen before autologous stem cell transplantation.

ACKNOWLEDGMENTS

REFERENCES

1. Duncan M, Grant G. Oral and intestinal mucositis—causes and possible treatments. *Aliment Pharmacol Ther*. 2003;18:853-874.

2. Sonis ST. A biological approach to mucositis. *J Support Oncol*. 2004;2:21-36.

3. Eisen D, Essell J, Broun ER. Oral cavity complications of bone marrow transplantation. *Semin Cutan Med Surg*. 1997;16:265-272.

4. McGuire DB, Altomonte V, Peterson DE, Wingard JR, Jones RJ, Grochow LB. Patterns of mucositis and pain in patients receiving preparative chemotherapy and bone marrow transplantation. *Oncol Nurs Forum*. 1993;20:1493-1502.

5. Shea TC, Bruner R, Wiley JM, et al. An expanded phase I/II trial of cyclophosphamide, etoposide, and carboplatin plus total body irradiation with autologous marrow or stem cell support for patients with hematologic malignancies. *Biol Blood Marrow Transplant*. 2003;9:443-452.

6. Wardley AM, Jayson GC, Swindell R, et al. Prospective evaluation of oral mucositis in patients receiving myeloablative conditioning regimens and haemopoietic progenitor rescue. *Br J Haematol*. 2000;110:292-299.

7. Woo SB, Sonis ST, Monopoli MM, Sonis AL. A longitudinal study of oral ulcerative mucositis in bone marrow transplant recipients. *Cancer*. 1993;72:1612-1617.

8. Bellm LA, Cunningham G, Durnell L, et al. Defining clinically meaningful outcomes in the evaluation of new treatments for oral mucositis: oral mucositis patient provider advisory board. *Cancer Invest*. 2002;20:793-800.

9. Donaldson GW. The factorial structure and stability of the McGill Pain Questionnaire in patients experiencing oral mucositis following bone marrow transplantation. *Pain*. 1995;62:101-109.

10. McGuire DB, Yeager KA, Dudley WN, et al. Acute oral pain and mucositis in bone marrow transplant and leukemia patients: data from a pilot study. *Cancer Nurs*. 1998;21:385-393.

11. McGuire DB, Peterson DE, Muller S, Owen DC, Slemmons MF, Schubert MM. The 20 item oral mucositis index: reliability and validity in bone marrow and stem cell transplant patients. *Cancer Invest*. 2002;20:893-903.

12. Schubert MM, Williams BE, Lloid ME, Donaldson G, Chapko MK. Clinical assessment scale for the rating of oral mucosal changes associated with bone marrow transplantation. Development of an oral mucositis index. *Cancer*. 1992;69:2469-2477.

13. Tardieu C, Cowen D, Thirion X, Franquin JC. Quantitative scale of oral mucositis associated with autologous bone marrow transplantation. *Eur J Cancer B Oral Oncol*. 1996;32B:381-387.

14. Walsh LJ, Hill G, Seymour G, Roberts A. A scoring system for the quantitative evaluation of oral mucositis during bone marrow transplantation. *Spec Care Dentist*. 1990;10:190-195.

15. Phillips GL II. The potential of amifostine in high-dose chemotherapy and autologous hematopoietic stem cell transplantation. *Semin Oncol*. 2002;29:53-56.

16. Gabriel DA, Shea T, Olajida O, Serody JS, Comeau T. The effect of oral mucositis on morbidity and mortality in bone marrow transplant. *Semin Oncol*. 2003;30:76-83.

17. Kemp G, Rose P, Lurain J, et al. Amifostine pretreatment for protection against cyclophosphamide-induced and cisplatin-induced toxicities: results of a randomized control trial in patients with advanced ovarian cancer. *J Clin Oncol*. 1996;14:2101-2112.

18. Brizel DM, Wasserman TH, Henke M, et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. *J Clin Oncol*. 2000;18:3339-3345.

19. Bentley SA, Brecher ME, Powell E, Serody JS, Wiley JM, Shea TC. Long-term engraftment failure after marrow ablation and autologous hematopoietic reconstitution: differences between peripheral blood stem cell and bone marrow recipients. *Bone Marrow Transplant*. 1997;19:557-563.

20. Moskowitz CH, Bertino JR, Glassman JR, et al. Ifosfamide, carboplatin, and etoposide: a highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma. *J Clin Oncol*. 1999;17:3776-3785.

21. Velasquez WS, McLaughlin P, Tucker S, et al. ESHAP—an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. *J Clin Oncol*. 1994;12:1169-1176.

22. Velasquez WS, Cabanillas F, Salvador P, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). *Blood*. 1988;71:117-122.

23. Sonis ST, Eilers JP, Epstein JB, et al. Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Mucositis Study Group. *Cancer*. 1999;85:2103-2113.

24. Cancer Therapy Evaluation Program: Common Toxicity Criteria, Version 2.0, DCTD, NCI, NIH, DHHS. March 1998. Available at: http://ctep.cancer.gov/reporting/ctc.html. Accessed Sep 6, 2005.

25. Hartmann JT, von Vangerow A, Fels LM, et al. A randomized trial of amifostine in patients with high-dose VIC chemotherapy plus autologous blood stem cell transplantation. *Br J Cancer*. 2001;84:313-320.

26. Chauncey TR, Gooley TA, Lloid ME, et al. Pilot trial of cytoprotection with amifostine given with high-dose chemotherapy and autologous peripheral blood stem cell transplantation. *Am J Clin Oncol*. 2000;23:406-411.

27. Antonadou D, Pepelassi M, Synodinou M, Puglisi M, Throuvalas N. Prophylactic use of amifostine to prevent radiochemotherapy-induced mucositis and xerostomia in head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2002;52:739-747.

28. Thieblemont C, Dumontet C, Saad H, et al. Amifostine reduces mucosal damage after high-dose melphalan conditioning and autologous peripheral blood progenitor cell transplantation for patients with multiple myeloma. *Bone Marrow Transplant*. 2002;30:769-775.

29. Capelli D, Santini G, De Souza C, et al. Amifostine can reduce mucosal damage after high-dose melphalan conditioning for

peripheral blood progenitor cell autotransplant: a retrospective study. *Br J Haematol.* 2000;110:300-307.

30. Patriarca F. Amifostine pretreatment for protection against melphalan plus busulfan-induced toxicity in high-dose therapy for multiple myeloma patients [abstract]. *Blood* 1999;94(suppl 1):404b.

31. Donnelly JP, Muus P, Horrevorts AM, Sauerwein RW, De Pauw BE. Failure of clindamycin to influence the course of severe oromucositis associated with streptococcal bacteraemia in allogeneic bone marrow transplant recipients. *Scand J Infect Dis.* 1993;25:43-50.

32. Elting LS, Cooksley C, Chambers M, Cantor SB, Manzullo E, Rubenstein EB. The burdens of cancer therapy. Clinical and economic outcomes of chemotherapy-induced mucositis. *Cancer.* 2003;98:1531-1539.

33. Garfunkel AA, Tager N, Chausu S, Chausu G, Haze C, Galili D. Oral complications in bone marrow transplantation patients: recent advances. *Isr J Med Sci.* 1994;30:120-124.

34. Kostler WJ, Hejna M, Wenzel C, Zielinski CC. Oral mucositis complicating chemotherapy and/or radiotherapy: options for prevention and treatment. *CA Cancer J Clin.* 2001;51:290-315.

35. Lark RL, McNeil SA, VanderHyde K, Noorani Z, Uberti J, Chenoweth C. Risk factors for anaerobic bloodstream infections in bone marrow transplant recipients. *Clin Infect Dis.* 2001;33:338-343.

36. Lucas VS, Beighton D, Roberts GJ, Challacombe SJ. Changes in the oral streptococcal flora of children undergoing allogeneic bone marrow transplantation. *J Infect.* 1997;35:135-141.

37. Ruescher TJ, Sodeifi A, Scrivani SJ, Kaban LB, Sonis ST. The impact of mucositis on alpha-hemolytic streptococcal infection in patients undergoing autologous bone marrow transplantation for hematologic malignancies. *Cancer.* 1998;82:2275-2281.

38. Alvarado Y, Bellm LA, Giles FJ. Oral mucositis: time for more studies. *Hematology.* 2002;7:281-289.

39. Blijlevens NM, Donnelly JP, De Pauw BE. Mucosal barrier injury: biology, pathology, clinical counterparts and consequences of intensive treatment for haematological malignancy: an overview. *Bone Marrow Transplant.* 2000;25:1269-1278.

40. Stiff P. Mucositis associated with stem cell transplantation: current status and innovative approaches to management. *Bone Marrow Transplant* 2001;27(suppl 2):S3-S11.

41. Verdi CJ. Cancer therapy and oral mucositis. An appraisal of drug prophylaxis. *Drug Saf.* 1993;9:185-195.

42. Epstein JB, Tsang AH, Warkentin D, Ship JA. The role of salivary function in modulating chemotherapy-induced oropharyngeal mucositis: a review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2002;94:39-44.

43. Sonis ST. Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. *Oral Oncol.* 1998;34:39-43.

44. Sonis ST. The biologic role for nuclear factor-kappaB in disease and its potential involvement in mucosal injury associated with anti-neoplastic therapy. *Crit Rev Oral Biol Med.* 2002;13:380-389.

45. Paris F, Fuks Z, Kang A, et al. Endothelial apoptosis as the primary lesion initiating intestinal radiation damage in mice. *Science.* 2001;293:293-297.

46. Donnelly JP, Bellm LA, Epstein JB, Sonis ST, Symonds RP. Antimicrobial therapy to prevent or treat oral mucositis. *Lancet Infect Dis.* 2003;3:405-412.

47. North S, El-Ghissassi F, Pluquet O, Verhaegh G, Hainaut P. The cytoprotective aminothiol WR1065 activates p21waf-1 and down regulates cell cycle progression through a p53-dependent pathway. *Oncogene.* 2000;19:1206-1214.

48. Kataoka Y, Murley JS, Khodarev NN, Weichselbaum RR, Grdina DJ. Activation of the nuclear transcription factor kappaB (NFkappaB) and differential gene expression in U87 glioma cells after exposure to the cytoprotector amifostine. *Int J Radiat Oncol Biol Phys.* 2002;53:180-189.

49. Murley JS, Kataoka Y, Hallahan DE, Roberts JC, Grdina DJ. Activation of NFkappaB and MnSOD gene expression by free radical scavengers in human microvascular endothelial cells. *Free Radic Biol Med.* 2001;30:1426-1439.

50. Bennett CL, Lane D, Stinson T, Glatzel M, Büntzel J. Economic analysis of amifostine as adjunctive support for patients with advanced head and neck cancer: preliminary results from a randomized phase II clinical trial from Germany. *Cancer Invest.* 2001;19:107-113.

51. Sonis ST, Oster G, Fuchs H, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. *J Clin Oncol.* 2001;19:2201-2205.

52. Borowski B, Benhamou E, Pico JL, Laplanche A, Margainaud JP, Hayat M. Prevention of oral mucositis in patients treated with high-dose chemotherapy and bone marrow transplantation: a randomised controlled trial comparing two protocols of dental care. *Eur J Cancer B Oral Oncol.* 1994;30B:93-97.

53. Cowen D, Tardieu C, Schubert M, et al. Low energy helium-neon laser in the prevention of oral mucositis in patients undergoing bone marrow transplant: results of a double blind randomized trial. *Int J Radiat Oncol Biol Phys.* 1997;38:697-703.

54. Whelan HT, Connelly JF, Hodgson BD, et al. NASA light-emitting diodes for the prevention of oral mucositis in pediatric bone marrow transplant patients. *J Clin Laser Med Surg.* 2002;20:319-324.

55. Antin JH, Lee SJ, Neuberg D, et al. A phase I/II double-blind, placebo-controlled study of recombinant human interleukin-11 for mucositis and acute GVHD prevention in allogeneic stem cell transplantation. *Bone Marrow Transplant.* 2002;29:373-377.

56. Bez C, Demarosi F, Sardella A, et al. GM-CSF mouthrinses in the treatment of severe oral mucositis: a pilot study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1999;88:311-315.

57. Meropol NJ, Somer RA, Gutheil J, et al. Randomized phase I trial of recombinant human keratinocyte growth factor plus chemotherapy: potential role as mucosal protectant. *J Clin Oncol.* 2003;21:1452-1458.

58. Spielberger R, Stiff P, Bensinger W, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *N Engl J Med.* 2004;351:2590-2598.