AMIFOSTINE REDUCES SIDE EFFECTS AND IMPROVES COMPLETE RESPONSE RATE DURING RADIOTHERAPY: RESULTS OF A META-ANALYSIS

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Purpose: To evaluate the efficacy of amifostine in diminishing radiotherapy side effects and whether or not it protects the tumor.

Methods and Materials: We performed a systematic review and meta-analysis of 14 included randomized controlled trials, comprising 1451 patients, comparing the use of radiotherapy vs. radiotherapy plus amifostine for cancer treatment.

Results: The use of amifostine significantly reduced the risk of developing mucositis (odds ratio [OR], 0.37; 95% confidence interval [CI], 0.29–0.48; p < 0.00001), esophagitis (OR, 0.58; CI, 0.36–0.92; p < 0.0001), acute xerostomia (OR, 0.24; CI, 0.15–0.36; p = 0.0001), late xerostomia (OR, 0.33; CI, 0.21–0.51; p = 0.00001), dysphagia (OR, 0.26; CI, 0.07–0.92; p = 0.04), acute pneumonia (OR, 0.15; CI, 0.07–0.31; p < 0.00001) and cystitis (OR, 0.17; CI, 0.09–0.32; p < 0.0001). There was no difference in overall response rate between the groups. However, complete response rate was superior for patients using amifostine (OR, 1.83; CI, 1.10–2.96; p = 0.02).

Conclusions: This systematic review shows that amifostine significantly reduces the side effects of radiotherapy. The efficacy of radiotherapy was not itself affected by the use of this drug and patients receiving amifostine were able to achieve higher rates of complete response. © 2006 Elsevier Inc.

Radiotherapy, Amifostine, Side effects, Toxicity, Radiation-protective agents.

INTRODUCTION

One of the cornerstones of cancer treatment is the continuity of chemotherapy cycles and radiation therapy treatment regimens. Interruptions during a planned course of treatment, due primarily to treatment breaks as a result of side effects, may diminish a patient’s likelihood of tumor response and jeopardize the treatment outcome (1).

During the past decade, control of cancer treatment side effects has greatly improved. One of the reasons for this was the use of new cytoprotective drugs, such as amifostine.

Amifostine, developed as part of the nuclear warfare program, is an inorganic thiophosphate that has been demonstrated to protect normal tissues against the toxic effects of some chemotherapy drugs and radiotherapy. This drug was approved by the Food and Drug Administration to reduce nephrotoxicity from chemotherapy containing cisplatin and to diminish xerostomia secondary to radiation therapy (2).

Many phase III randomized studies have been published in the last few years. Unfortunately, the results are some-times conflicting. For instance, Leong et al. (3) found no reduction in esophagitis in patients treated with concurrent chemoradiation for non-small-cell lung cancer by adding amifostine to the treatment regimen. However, Antonadou et al. (4) reported significantly lower rates of esophagitis for patients with the same disease who received amifostine and were treated with concurrent chemoradiation (38.9% vs. 84.4%; p < 0.001).

The American Society of Clinical Oncology’s panel of experts reviewed, in 2002, the published data and determined that there were insufficient data to recommend the use of amifostine in the prevention of mucositis associated with radiation therapy (5). Xerostomia is the most common toxicity associated with radiotherapy to the head-and-neck region. Whereas acute xerostomia from radiation is due to an inflammatory reaction, late xerostomia, which includes xerostomia occurring 1 year after radiation, reflects fibrosis of the salivary gland and, as such, is usually permanent. The American Society of Clinical Oncology panel also recommends that amifostine may be considered to decrease the
incidence of acute and late xerostomia in patients who undergo fractionated radiation therapy in the head-and-neck region therapy (5). Conflicting opinions on the efficacy and safety of amifostine led to an interesting debate between well-known authors, demonstrating that even after 20 years of its clinical development and use, there is still great controversy about its clinical application (2). Although no publications to date have demonstrated an adverse clinical cancer outcome in patients treated with concurrent amifostine in conjunction with chemotherapy or radiation therapy, the fundamental question that has yet to be definitively answered is whether or not amifostine protects tumor cells as well as normal cells. Although some narrative reviews state that there is a lack of strong evidence confirming tumor protection, the published data suggest that patients receiving amifostine have an equal or even superior tumor control when compared with patients in those studies treated without concurrent amifostine (6, 7). However, the statistical confirmation of these facts has yet to be published. To answer this question and also to quantify the degree of the reduction of side effects achieved by the use of amifostine, this systematic review and meta-analysis was performed.

Data extraction

The outcomes of interest were: mortality, response rate (complete, partial, and overall), relapse, incidence of side effects of radiotherapy (acute and late xerostomia, mucositis, dysphagia, pneumonitis, dermatitis, and cystitis), and side effects secondary to the administration of amifostine (nausea, vomiting, transient hypotension, and allergic reactions).

Data from all studies were extracted independently by at least two of the authors. When disagreements occurred, a third reviewer was consulted. The name of the first author and the year of publication of the article were used for identification purposes, and data were extracted directly from the text or, when feasible, were independently calculated according to the available information.

Statistical methods

We used the RevMan 4.2 software (Cochrane Collaboration's Information Management System) to perform this meta-analysis. The results were calculated as odds ratio or risk difference (RD) and are presented with the corresponding 95% confidence interval (CI). Statistical heterogeneity of the results of the trials was assessed by the test of chi-square (ch2) (9) and is expressed as an index I² as described by Higgins et al. (10). When heterogeneity was detected, a possible explanation for it was intensively pursued. If a reasonable cause was found, a separate analysis was then performed. If the cause was not apparent and heterogeneity was caused by divergent data in terms of direction of results (i.e., data favoring one or other treatment), we chose not to pool the data.

RESULTS

Thirty-three potentially eligible trials, published between 1973 and 2005, were retrieved. Of these, 18 were excluded: 4 were not really randomized trials (11–14), 1 had amifostine in both arms (15), 3 dealt with chemotherapy and not radiotherapy (3, 16, 17), and 10 were duplicated publications (4, 18–26). Fourteen studies, comprising 1451 patients, met the inclusion criteria and were included in this meta-analysis (27–40). The primary sites targeted were head and neck in six articles (28, 31, 34, 36, 39, 40), pelvic tumors in four articles (30, 36–38), and thoracic tumors in six articles (27, 29, 35, 36, 39, 40). Six studies evaluated patients receiving radiotherapy plus chemotherapy (28, 29, 32, 34, 35, 40) and eight focused on radiotherapy alone (27, 30, 31, 33, 36–39). Amifostine was administered intravenously in 12 trials (27–31, 33–35, 37–40), subcutaneously in 2 (32, 36), before daily radiotherapy in 12 (27–33, 36–40), and twice weekly before chemoradiation in 2 (34, 35). The dose of amifostine used ranged from 150 mg/m² to 340 mg/m².

From the 14 included studies, 2 were funded by a pharmaceutical company exclusively and 5 had a mixed sponsorship, meaning that they were funded by the manufacturer and by an academic institution. In seven studies, there was no mention of sponsorship (Table 1).

Mucositis/Esophagitis/Proctitis

Data from 12 trials comparing amifostine to placebo or observation were pooled (27–29, 31, 33–40). Five studies evaluated mucositis in patients with head-and-neck cancer.
(28, 31, 33, 34, 36), six evaluated esophagitis in patients with thoracic tumors (27, 29, 35, 36, 39, 40), and three evaluated proctitis in patients with pelvic tumors (36–38). Koukorakis et al. evaluated mucositis for all these sites (36). Meta-analysis showed that amifostine reduced the odds of developing Grade 3–4 mucositis by 63%, when compared with placebo or observation (OR, 0.37; 95% CI, 0.29–0.48; p < 0.00001) (Fig. 1). The results were statistically significant for head-and-neck radiotherapy, with odds reduction of Grade 3–4 mucositis of 56% (OR, 0.44; 95% CI, 0.30–0.65; p < 0.0001). In the thoracic radiotherapy set there was a reduction of esophagitis of 62% (OR, 0.38; 95% CI, 0.26–0.54; p < 0.00001). For pelvic tumors, the meta-analysis revealed a reduction of proctitis of 83% (OR, 0.17; 95% CI, 0.07–0.43; p = 0.0002). We found extreme statistical heterogeneity among the studies in this subset (chi-square = 54.06, df = 13, p < 0.00001; I² = 76.09%). As planned, the possible causes of heterogeneity were explored to determine if it was appropriate to pool the trials. Separated analyses were performed according to the doses of amifostine used. For the endpoint of mucositis, when we excluded studies that used amifostine in less than 50% of radiotherapy courses (34, 35, 40) and studies that used a lower dose of amifostine (150–200 mg/m²) (31, 33, 39), the analysis resulted in absence of statistical heterogeneity (chi-square = 10.08, df = 7, p = 0.18; I² = 30.5%), and the significance of the effect was still maintained (OR, 0.11; 95% CI, 0.06–0.18; p < 0.00001). Our interpretation is that amifostine, when given in previously all courses of radiotherapy and in higher doses (i.e., >300 mg/m²), consistently reduces mucositis caused by radiotherapy.

**Acute xerostomia**

The rates for acute xerostomia were reported in four (28, 33, 34, 36) of the six studies included in the meta-analysis. Compared with placebo or observation, amifostine significantly reduced the odds of Grade 2–3 acute xerostomia by 76% (OR, 0.24; 95% CI, 0.15–0.36; p < 0.00001) in patients receiving radiotherapy alone. We found some statistical heterogeneity across the trials (chi-square = 7.46, df = 3, p = 0.05; I² = 61.8%), but again all four trials had an estimate point that favored amifostine, and three of the studies reached statistical significance. We concluded that amifostine is effective in preventing acute xerostomia in patients with head-and-neck cancer receiving radiotherapy alone.

**Late xerostomia**

For the head-and-neck cancer set of patients, late xerostomia rates were reported in only two studies (28, 33). The analysis showed that when compared with placebo or observation, amifostine significantly reduced the chance of developing Grade 2–3 late xerostomia by 67% (OR, 0.33; 95% CI, 0.21–0.51; p < 0.00001) in patients receiving radiotherapy. We found evidence of statistical heterogeneity across the trials (chi-square = 4.06, df = 1, p = 0.04; I² = 75.4%), but because both studies analyzed had estimate points that statistically significantly favored the use of ami-
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Fig. 1. Meta-analysis of studies evaluating the effect of amifostine in Grade III-IV radiation-related mucositis. n = number of events. N = total number of patients; OR = odds ratio; CI = confidence interval; df = degrees of freedom; I² = index of heterogeneity.

Amifostine, our interpretation is that amifostine is effective in preventing late xerostomia in patients receiving radiotherapy alone for head-and-neck cancer.

**Dysphagia**

Data on dysphagia were extracted from three (28, 31, 34) of the six included studies. Compared with placebo or observation, amifostine significantly reduced Grade 3–4 dysphagia by 74% (OR, 0.26; 95% CI, 0.07–0.92; p = 0.04). (Fig. 2). Because there was statistic homogeneity among the trials (chi-square = 0.78, df = 2, p = 0.68; I² = 0%), we concluded that amifostine is effective in preventing dysphagia in patients receiving radiotherapy.

**Pneumonitis**

For those patients receiving thoracic radiotherapy, data for pneumonitis were available in three (27, 29, 35) of the six studies evaluated. Compared with placebo or observation, amifostine significantly reduced the odds of acute pneumonitis by 85% (OR, 0.15; 95% CI, 0.07–0.31; p < 0.00001). Once again, because there was statistic homogeneity among the trials evaluated (chi-square = 0.43, df = 3, p = 0.81; I² = 0%), we concluded that amifostine is effective in preventing pneumonitis in patients receiving radiotherapy.

Fig. 2. Meta-analysis of studies measuring the effect of amifostine in dysphagia secondary to radiation therapy in head-and-neck neoplasms. N = the total number of patients; OR = odds ratio; CI = confidence interval; df = degrees of freedom.
We concluded that amifostine is effective in preventing pneumonitis in patients receiving radiotherapy (Fig. 3).

**Cystitis**

Data extracted from four trials (30, 36–38), including patients receiving pelvic radiotherapy, demonstrated that amifostine significantly reduced the chance of developing cystitis by 83% (OR, 0.17; 95% CI, 0.09–0.32; p < 0.00001) (Fig. 4). The trials also revealed statistical homogeneity (chi-square = 3.94, df = 3, p = 0.27; I² = 23.8%), leading to the conclusion that amifostine is effective in preventing cystitis in patients receiving radiotherapy.

**Dermatitis**

Only one of the studies found a significant difference in dermatitis between patients with pelvic tumors treated with amifostine before radiotherapy and controls (36). Four trials found no difference between the groups: one in pelvic (38), one in thoracic (40), and two (31, 34) in head-and-neck radiotherapy. Meta-analysis could not be performed because there was excessive heterogeneity between the studies.

**Treatment response**

Data for treatment response were reported in 9 (27–29, 35–38) of the 14 studies evaluated. Partial response rates were similar among the groups (OR, 0.93; 95% CI, 0.65–1.33; p = 0.69). However, the complete response rates were superior for patients using amifostine (OR, 1.81; 95% CI, 1.10–2.96; p = 0.02), with no evidence of statistical heterogeneity among the trials (chi-square = 4.28, df = 7, p = 0.75; I² = 0%) (Fig. 5). Overall response rates did not show statistical difference between the groups (OR, 1.31; 95% CI, 0.90–1.89; p = 0.16). Five trials (28, 29, 33, 34, 37) presented data on relapse rates, and we found no relation between the use of amifostine and this endpoint (RD, 95% CI, −0.08 to 0.07; p = 0.92), with no evidence of statistical heterogeneity across the trials (chi-square = 1.74, df = 6, p = 0.78; I² = 0%). Thus we conclude that there is sufficient evidence to state that amifostine does not protect the tumor.

**Side effects**

We were able to retrieve data on toxicity from amifostine in 10 of 14 trials. Nausea and vomiting are described as common side effects of amifostine administration, but only

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**Fig. 3.** Meta-analysis of studies evaluating the effect of amifostine in pneumonitis secondary to radiation therapy on thoracic neoplasms. Abbreviations as in Figs. 1 and 2.

**Fig. 4.** Meta-analysis of the studies measuring the effect of amifostine in cystitis from radiation therapy in pelvic neoplasms. Abbreviations as in Figs. 1 and 2.
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<table>
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<td>Test for overall effect: $Z = 2.36 (P = 0.01)$</td>
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Fig. 5. Meta-analysis of studies evaluating the impact of amifostine in complete response rates with radiation therapy for head-and-neck, thoracic, and pelvic neoplasms. Abbreviations as in Figs. 1 and 2.

one (32) of the studies found a significant increase in Grade 3–4 nausea, and another (33) in Grade 3–4 emesis. However, the incidence of Grade 3–4 nausea was higher for patients using amifostine (OR = 2.47; 95% CI, 1.38–4.40; p = 0.002), with no evidence of statistical heterogeneity across the trials (chi-square = 5.69, df = 6, p = 0.46, $I^2 = 0\%$). The incidence of Grade 3–4 emesis was also higher for patients using amifostine (OR = 2.23; 95% CI, 1.09–4.75; p = 0.03), with no evidence of statistical heterogeneity across the trials (chi-square = 3.78, df = 4, p = 0.44, $I^2 = 0\%$). These side effects were effectively controlled with standard antiemetic medications in seven trials (38–41, 54, 55, 57). The use of amifostine significantly increased the risk of transient Grade 3–4 hypotension in trials using slow intravenous infusion (RD, 0.03; 95% CI, 0.01–0.05; p = 0.0001), although this side effect was satisfactorily controlled with usual precautions as recommended by the manufacturer.

In trials using subcutaneous administration, there was not an increase in Grade 3–4 hypotension (32, 36). Allergic reaction was a minor effect, and was found in less than 3% of all patients receiving amifostine.

**DISCUSSION**

This meta-analysis demonstrates both the efficacy and tolerability of amifostine. Amifostine (previously WR-2731), a spinoff of the nuclear warfare program, is a cytoprotector capable of protecting normal but theoretically nonmalignant tissue against the toxic effects of chemotherapy or radiation.

Amifostine is dephosphorylated to the active principal (free thiol) by a cell-bound alkaline phosphatase either not present in tumors or not active in the low pH found in tumors. It may be used in the treatment of different types of tumors (e.g., head-and-neck, lung, pelvic tumors), concomitantly with chemotherapy or radiotherapy alone. However, the exact mechanism of how this drug can exhibit radioprotective effects on so many normal tissues is still uncertain.

Because there has been some controversy with respect to its full potential to ameliorate treatment side effects, we sought to resolve this controversy by performing a meta-analysis on the available published data. Despite recent technical radiotherapeutic advances, such as the use of three-dimensional conformal radiation therapy and intensity-modulated radiation therapy, designed to deliver optimal doses of radiation with high precision while sparing normal tissue, patients still suffer from acute and late toxic side effects of therapy. Acute side effects, such as mucositis and esophagitis, although not directly life-threatening, are very debilitating because of pain, which is sometimes hard to control and often results in weight loss. Those symptoms may be severe enough for the physician to delay the treatment, which is often a drawback to a good outcome, or for the patient to abandon therapy completely.

Some side effects, such as xerostomia, appear late in the course of treatment or even after its completion, and have a negative impact on quality of life.

Oral health plays an important role in the quality of life.
for patients during a course of radiation therapy (41) and xerostomia interferes with daily activities, such as eating and speaking.

The aim of this systematic review was to compile the pieces of evidence, provided exclusively by randomized clinical trials about amifostine as radioprotectant, to establish its true clinical efficacy.

Several technical issues have to be mentioned in relation to this meta-analysis. All our analyses were based on published data and not on individual patient data. The results must therefore be interpreted cautiously. Publication bias is a significant threat to the validity of the results of this meta-analysis. Although we found no evidence of publication bias in relation to the graphical or statistical methods, it is difficult to completely rule out this possibility from all aspects of the trials.

Heterogeneity among trials may be another limitation of our meta-analysis. We identified the use of amifostine in less than 50% of radiotherapy courses and the low doses of amifostine used as sources of heterogeneity in some endpoints (mucositis and xerostomia). As planned, separated analyses were performed according to different situations. When we excluded trials with low-dose amifostine or that used amifostine in less than 50% of radiotherapy courses, the analyses resulted in resolution (in mucositis) or substantial reduction (in xerostomia) of the statistical heterogeneity, and the significance of the effect was maintained. Considering that all trials had an estimated point that favored the use of amifostine, and some of these studies reached statistical significance, our interpretation is that amifostine consistently reduces mucositis and xerostomia caused by radiotherapy.

Another possible source of bias in this review is the sponsorship of the included studies (42). We have restricted our analysis to the published literature. Because there is no good method to detect a particular review has suffered this bias, we have to be cautious about literature-based meta-analysis (43, 44). Most of the studies included in this review were sponsored by the manufacturer of amifostine. We did not find any study funded solely by an independent sponsor.

Therefore, this systematic review confirms that amifostine significantly reduces the risks for mucositis, both acute and late xerostomia, dysphagia, pneumonitis, and cystitis, in patients undergoing radiotherapy.

Side effects associated with amifostine are frequent but generally mild and transient. The major concerns are nausea, emesis, and transient hypotension, although these side effects were satisfactorily controlled with regular use of antiemetic medications and usual precautions, as recommended by the manufacturer.

One major point of concern among radiotherapists and oncologists was the possibility of tumor protection with the use of amifostine, even though this was never confirmed in the published randomized trials. However, as is often the case, a given individual randomized clinical trial would not have had statistical power to definitively answer the question.

Despite the lack of evidence suggesting tumor protection, many physicians have refused to use amifostine for fear of a reduction in treatment effectiveness. Worldwide discussions on this topic have occurred. The opposing opinions shown in one article in particular (2), although very interesting and well put, could not solve the question. We do indeed agree with one of the debaters that "absence of evidence is not evidence of absence." The efficacy of radiotherapy itself was not affected by amifostine. This meta-analysis not only confirms the lack of tumor protection with the use of amifostine, but also proved that patients receiving this drug were able to achieve higher levels of complete response. This has been speculated to be due to fewer interruptions of the planned treatment course and diminished acute side effects. The use of amifostine does sometimes cause side effects such as hypotension and nausea, but these were less intense with the subcutaneous route of administration and were rarely severe enough to interrupt the treatment, provided that the recommended precautions are followed.

REFERENCES

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