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The Cytoprotective Effect of Amifostine Against Radiation Induced Toxicity

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1. Introduction

Radiation treatment is an important therapeutic option for a number of malignancies (American Cancer Society), but its use is frequently limited by adverse effects on normal tissues (Stone et al., 2003). Thus, the goal of most oncology treatments is to maximize the antineoplastic effect while minimizing deleterious outcomes for the patient. WR-2721 was developed by the U.S. Army Anti-Radiation Drug Development Program for its potential to protect against damage caused by ionizing radiation (Yuhas & Stoner, 1969). Today, WR-2721 is known as amifostine (Ethyol®; MedImmune Oncology, Inc., Gaithersburg, MD). Initial preclinical studies demonstrated that amifostine could protect treated mice from lethal doses of radiation, and this protection did not extend to transplanted mammary tumor cells (Yuhas & Stoner, 1969).

Amifostine, a thiol that protects cells from damage by scavenging oxygen-derived free radicals, was later evaluated for a potential role in reducing the toxicities from radiation and chemotherapeutic agents, such as alkylating agents and platinum agents. In contrast to organ-specific protectants, amifostine is considered a broad-spectrum cytoprotective agent (Hensley et al., 1999). Preclinical studies demonstrated that amifostine can selectively protect almost all normal tissues from the cytotoxic effects of some chemotherapeutic agents and radiation therapy. Neoplastic tissues do not benefit from amifostine’s protection (Koukourakis, 2003; Sasse et al., 2006; Yuhas et al., 1980). Amifostine is an inactive prodrug that cannot protect until dephosphorylated to the active metabolite, WR-1065, by alkaline phosphatase in the plasma membrane (Calabro-Jones et al., 1985). The selective protection of normal tissue is the result of a greater accumulation of WR-1065 in normal tissues than in tumor cells. Tumors are relatively hypovascular, thus resulting in comparative hypoxia and a low interstitial pH. Furthermore, alkaline phosphatase expression is reduced in malignant tissues. Taken together, the combination of hypovascularity, low pH, and reduced enzyme levels results in low accumulation of active drug in tumor tissues. Thus, normal tissues may be able to maintain as much as a 100-fold greater concentration of the free thiol than tumor tissue (Yuhas, 1980).

Once inside the cell, WR-1065 scavenges free radicals, protecting cellular membranes and DNA from damage. However, other studies have suggested that additional mechanisms may also play important roles in the action of amifostine. In vitro studies have shown that
oxidation of WR-1065 to its polyamine-like disulfide metabolite (WR-33278) is followed by a rapid consumption of oxygen in culture medium, suggesting that induction of cellular anoxia may be a mechanism for radioprotection (Purdie et al., 1983). This was supported by a study by Glover et al. that showed a rapid increase in the oxygen saturation of the venous blood after i.v. administration of amifostine without affecting the oxygen dissociation curves of hemoglobin, again suggesting that a decrease in oxygen consumption by normal tissues may be involved in amifostine-related radioprotection (Glover et al., 1984). In another study, high concentrations of WR-33278 condensed DNA, thereby limiting potential target sites for free-radical attack (Savoye et al., 1997). This activity would clearly account for a decrease in the number of double-strand breaks after radiotherapy, in turn leading to a reduction of the transient block at the G2 phase of cell division induced by radiation (Rubin et al., 1996). The enhanced cellular proliferation that results from a reduction in damage to DNA may be an important pathway to accelerated recovery of endothelial tissues that are affected soon after radiation exposure (Rubin et al., 1996) and seems to be important for the recovery of irradiated mucosa (Koukourakis et al., 1999). In addition, amifostine, indirectly through hypoxia, may upregulate the expression of a variety of proteins involved with DNA repair and inhibition of apoptosis, such as Bcl-2 and hypoxia-inducible factor-1 (Carmeliet et al., 1998; Kajstura et al., 1996; Shimizu et al., 1996).

Early phase I trials with amifostine were not able to demonstrate a maximum-tolerated dose but did establish a tolerable dose range of 740–910 mg/m² for use in phase II studies (Blumberg et al., 1982). Amifostine is generally well tolerated, although transient adverse events may be dose related and include hypotension, nausea, vomiting, sneezing, somnolence, a metallic taste during infusion, and occasional allergic reactions that may include rash, fever, and anaphylactic shock (Blumberg et al., 1982). Although hypotension is the most clinically significant adverse event, treatment interruptions caused by a significant decline in blood pressure are rare, occurring in <5% of patients receiving amifostine. Emesis can be reduced with judicious use of an antiemetic regimen before amifostine administration. Transient hypocalcemia caused by inhibition of parathyroid hormone secretion has also been reported (Glover et al., 1983). The incidence and severity of amifostine-related adverse events have been shown to vary based on the route of administration. A recent meta-analysis of randomized studies using amifostine reported a significantly greater risk for grade 3 or 4 hypotension when amifostine was administered as a slow i.v. infusion (Sasse et al., 2006). Studies examining the s.c. administration of amifostine have demonstrated a lower incidence of hypotension and nausea/vomiting than with i.v. administration (Koukourakis et al., 2000; Anne & Curran, 2002; Anne et al., 2007). However, s.c. administration of amifostine has been reported to be associated with a higher incidence of fever and cutaneous reactions than with i.v. administration in these studies (Sasse et al., 2006; Koukourakis et al., 2000; Anne & Curran, 2002; Anne et al., 2007).

Pharmacokinetic studies in patients have demonstrated that amifostine is rapidly cleared from the plasma compartment, with a half-life of <1 minute, and >90% cleared within 6 minutes (Shaw et al., 1986). However, very little amifostine, or the metabolites WR-1065 and WR-33278, is excreted in urine 1 hour after injection. These data show that once amifostine enters the plasma, it is rapidly metabolized and distributed in the tissues, whereas the excretion of the metabolic products is very slow. Timely administration of amifostine relative to radiation or chemotherapeutic treatment is necessary. One study by Buentzel et al., in which amifostine was administered 30 minutes before chemoradiotherapy, demonstrated no significant difference in the incidence of grade 2 acute or chronic
xerostomia or grade 3 oral mucositis between patients receiving i.v. amifostine and those receiving placebo (Buentzel et al., 2006). On days when combined radiochemotherapy was administered, timing between amifostine and radiotherapy may have exceeded 60 minutes. The authors suggest that timing of the amifostine doses relative to the beginning of radiotherapy may have influenced efficacy because of inadequate exposure to amifostine. In addition, the observed rates of grade 2 acute xerostomia and grade 3 oral mucositis in the placebo group were unexpectedly low, reducing the ability of the study to show significant benefit with amifostine. In contrast, studies in which amifostine was administered within 30 minutes of radiotherapy have shown promise with regard to protection from acute and chronic xerostomia (Andonadou et al., 2002; Brizel et al., 2000; Vacha et al., 2003). Taken together, it appears that administration of amifostine within 30 minutes of radiotherapy or chemoradiotherapy may provide optimal benefit for cytoprotection of normal tissues.

Of primary concern with the use of any substance or technique that is intended to spare normal tissues from treatment-related toxicities is the unintended and undesirable protection of tumor cells. Clearly, procedures that protect tumors are not clinically useful. A recent meta-analysis of the available clinical data concluded that, in addition to reducing the toxicities associated with radiation therapy, amifostine does not affect the efficacy of radiotherapy (Sasse et al., 2006). To the contrary, patients receiving amifostine with radiotherapy achieved higher rates of complete response, presumably the result of fewer treatment interruptions because of reduced acute toxicity of the treatment.

1.1 Xerostomia and oral mucositis

Xerostomia and mucositis are significant and potentially debilitating toxicities associated with radiation therapy. The risk for these complications depends on the area receiving radiation, the dose and schedule of therapy, whether radiation therapy is combined with chemotherapy, and other factors (Sonis & Fey, 2002). Although rarely life threatening, the acute and long-term consequences can be significant, causing discomfort, reduced nutrition, and a diminished quality of life. Xerostomia is the most common toxicity associated with standard fractionated radiation therapy to the head and neck. Whereas acute xerostomia from radiation is the result of an inflammatory reaction, late xerostomia, observed 1 year after radiation, is usually a permanent result of fibrosis of the salivary gland. The dry mouth of xerostomia affects the patient's ability to eat and speak. The decreased salivary output in patients with xerostomia can be responsible for an increased risk for dental caries, oral infections, and osteonecrosis.

The results of numerous randomized controlled studies suggest that amifostine may protect against radiation- and chemoradiation-induced toxicity in patients with head and neck cancer (Table 1) (Sasse et al., 2006). In one study by Buentzel et al., 28 patients received radiation therapy in conjunction with carboplatin (Buentzel et al., 1998). Amifostine was administered to 14 patients on the day of carboplatin at a fixed dose of 500 mg (equivalent to 250–340 mg/m²). Acute grade 3 or 4 mucositis was experienced by 12 of 14 patients (86%) treated with radiochemotherapy alone compared with none of the amifostine-treated patients (p < .001). Additionally, at a 12-month follow-up, 17% of patients who received amifostine experienced late grade 2 xerostomia, compared with 55% of the patients treated without amifostine (p = .05). An international phase III trial of radiation therapy with and without amifostine was conducted in 315 patients with squamous cell carcinoma of the head
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Treatment</th>
<th>Main conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>RT</strong></td>
<td></td>
</tr>
<tr>
<td>McDonald et al., 1994</td>
<td>9</td>
<td>RT + i.v. amifostine, 100 mg/m²</td>
<td>Flow rates of unstimulated whole saliva recovered to 20% of baseline at 12 months post-treatment</td>
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<td>Wagner et al., 1998</td>
<td>14</td>
<td>RT 4 · i.v. amifostine, 200 mg/m²</td>
<td>i.v. amifostine treatment led to significant reduction in oral symptoms and duration of mucositis</td>
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<tr>
<td>Bourhis et al., 2000</td>
<td>26</td>
<td>RT + i.v. amifostine, 150 mg/m², versus RT alone</td>
<td>i.v. amifostine treatment led to significant reduction in duration of acute mucositis and duration of feeding tube use compared with RT treatment alone</td>
</tr>
<tr>
<td>Koukourakis et al., 2000</td>
<td>40</td>
<td>RT + s.c. amifostine, 500 mg, versus RT alone</td>
<td>s.c. amifostine led to significant reduction in severity of oral mucositis compared with RT treatment alone</td>
</tr>
<tr>
<td>Brizel et al., 2000</td>
<td>315</td>
<td>RT + i.v. amifostine, 200 mg/m², versus RT alone</td>
<td>i.v. amifostine led to significant reduction in acute and chronic xerostomia versus RT alone and increased saliva production versus RT alone; no significant reduction in grade ≥3 mucositis versus RT treatment alone</td>
</tr>
<tr>
<td>Wasserman et al., 2005</td>
<td>315</td>
<td>2-yr follow-up of Brizel et al. (2000) [26]</td>
<td>i.v. amifostine led to significant decrease in severity and duration of xerostomia at 2 yrs post-treatment without compromising tumor control</td>
</tr>
<tr>
<td>Anne el al., 2002, 2007</td>
<td>54</td>
<td>RT + s.c. amifostine, 500 mg</td>
<td>Incidence of acute grade ≥2 xerostomia, 56%; 1-yr rates of locoregional tumor control, progression-free survival, and overall survival, 78%, 75%, and 85%, respectively</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>RCT</strong></td>
<td></td>
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<tr>
<td>Buntzel et al., 1998</td>
<td>39</td>
<td>RT + carboplatin + i.v. amifostine, 500 mg, versus RT + carboplatin (control)</td>
<td>i.v. amifostine treatment led to significant reductions in acute xerostomia, grade ≥3 mucositis, and grade ≥3 thrombocytopenia compared with control treatment</td>
</tr>
<tr>
<td>Peters et al., 1999</td>
<td>28</td>
<td>RT + carboplatin + i.v. amifostine, 500 mg, versus RT + carboplatin (control)</td>
<td>i.v. amifostine treatment had no significant effect on xerostomia or mucositis compared with control treatment</td>
</tr>
<tr>
<td>Atttonadou et al., 2002</td>
<td>50</td>
<td>RT + carboplatin + i.v. amifostine, 300 mg/m², versus RT + carboplatin (control)</td>
<td>i.v. amifostine treatment led to significant reduction in acute and late grade ≥2 xerostomia and grade ≥3 mucositis compared with control treatment</td>
</tr>
</tbody>
</table>
Table 1. Clinical trials of amifostine therapy during radiation therapy or radiochemotherapy for head and neck cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Treatment</th>
<th>Main conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vacha et al., 2003</td>
<td>52</td>
<td>RT + carboplatin + i.v. amifostine, 250 mg, versus RT + carboplatin (control)</td>
<td>i.v. amifostine treatment led to significant reduction in xerostomia compared with control treatment: reduction in mucositis was not significant between treatment groups</td>
</tr>
<tr>
<td>Bucntzel et al., 2006</td>
<td>132</td>
<td>RT + carboplatin + i.v. amifostine, 200-300 mg/ m², versus RT + carboplatin (control)</td>
<td>No difference between i.v. amifostine treatment and control treatment with regard to incidence of grade ≥2 xerostomia or grade ≥3 mucositis: low incidence of grade ≥2 xerostomia and grade ≥3 mucositis in control patients; no evidence of tumor protection was observed with either treatment</td>
</tr>
</tbody>
</table>

Abbreviations: CRT, radiochemotherapy; RT, radiotherapy.

and neck in which at least 75% of each parotid gland was present in the radiation fields (Brizel et al., 2000). The amifostine dose was 200 mg/m² daily, 15–30 minutes before each fraction of radiation therapy (1.8–2.0 Gy/day, 5 days per week for 5–7 weeks, to a total dose of 50–70 Gy). Amifostine significantly reduced acute and late xerostomia and associated symptoms. Using Radiation Therapy Oncology Group (RTOG) grading criteria, patients receiving amifostine had a lower incidence of grade 2 or higher acute xerostomia (51% versus 78%; p < .001) and a lower incidence of grade 2 or higher late xerostomia (34% versus 57%; p = .002). The proportion of patients with meaningful saliva production after 1 year was significantly higher with amifostine (72% versus 49%; p = .003). Despite a trend toward lower severity of mucositis with amifostine (p = .14), the difference in the incidence of grade 3 or higher mucositis was not statistically significant (p = .48). Importantly, at 1 year, with a median follow-up of 20 months, the locoregional tumor control rates did not differ, and disease-free and overall survival times were comparable. Two-year follow-up data from this study demonstrate the continued benefits of amifostine treatment on the incidence of grade 2 xerostomia (p = .002 versus patients who did not receive amifostine) (Wasserman et al., 2005). Furthermore, no significant differences in locoregional tumor control rate, progression-free survival time, or overall survival rates were observed 2 years post-treatment between the amifostine group and the control group (Wasserman et al., 2005).

In another study, 50 patients with head and neck cancer were randomized to receive radiotherapy plus carboplatin with or without amifostine (Antonadou et al., 2002). Treatment interruptions were more frequent in the control group. Consequently, patients receiving amifostine experienced significantly shorter treatment durations (p = .013). Patients treated with amifostine experienced less severe acute mucositis and dysphagia; all patients who did not receive amifostine in the control group experienced grade 2 mucositis by week 3. In contrast, only 9% of patients treated with amifostine experienced grade 2 mucositis (p < .001). By the fifth week, grade 4 mucositis was experienced by 52% and 4.5%
of the patients in the respective groups (p < .001). Dysphagia was similarly reduced among patients given amifostine. After 3 months of follow-up, grade 2 xerostomia was reported in 27% and 74% of patients treated with and without amifostine, respectively (p < .001).

Another consideration in the treatment of head and neck cancer is the tolerance dose of the parotid glands and the potential for raising this threshold with amifostine. Eisbruch et al. [31] reported a threshold of 26 Gy, using conformal or intensity-modulated radiotherapy, as a mean dose to spare parotid gland function (Eisbruch et al., 1999). With the use of amifostine, the threshold radiation dose for chronic xerostomia may be increased, allowing for greater dose coverage (Munter et al., 2007).

1.2 Esophagitis and pneumonitis

Damage from radiation treatment is also a major complication in the treatment of thoracic cancers, with higher rates of acute and late toxicity associated with concurrent chemoradiotherapy. Several studies have investigated the cytoprotective efficacy of amifostine against radiation-induced esophagitis and pneumonitis. Antonadou et al., in a multicenter trial of patients with advanced lung cancer, investigated whether daily pretreatment with amifostine could reduce the incidence of acute and late lung toxicity and esophagitis without affecting antitumor efficacy of radiation treatment (Antonadou et al., 2001). One hundred forty-six patients received radiotherapy in daily fractions of 2 Gy, 5 days per week, to a total of 55–60 Gy with or without daily amifostine, 340 mg/m² 15 minutes before irradiation. There was a significantly lower incidence of grade 2 or higher pneumonitis among patients receiving amifostine (9% versus 43%; p < .001). At 6 months post-treatment, fibrosis was present in 53% of patients not receiving amifostine compared with 28% of patients receiving amifostine (p < .05). The incidence of grade 2 or higher esophagitis during the fourth week of treatment was 4% among patients receiving amifostine, compared with 42% of patients receiving radiotherapy alone (p < .001). No evidence of tumor protection by amifostine was noted: complete or partial responses were observed in 75% and 76% of patients receiving amifostine or radiotherapy alone, respectively.

Komaki et al. evaluated the cytoprotective role of amifostine for esophagitis and hematologic and pulmonary toxicities in a randomized study of patients with stage II or III non-small cell lung cancer receiving concurrent chemoradiotherapy. Patients in the study group received amifostine, 500 mg i.v., twice weekly before chemoradiation, and patients in the control group received chemoradiation without Amifostine (Komaki et al., 2004). The median survival time was longer, but not significantly so, for patients receiving amifostine (26 months versus 15 months). Significantly fewer patients who received amifostine also received morphine to relieve severe esophagitis (7.4%) than patients who received chemoradiotherapy alone (31%; p = .03). Amifostine treatment was also associated with a significantly lower incidence of acute pneumonitis (3.7% versus 23%; p = .037). Although not statistically significant, 26% of patients receiving amifostine had a complete response, compared with 8% of patients who did not receive amifostine (p = .07).

Despite a limited number of studies, a recent meta-analysis reported that amifostine treatment was observed to reduce the incidence of pneumonitis and esophagitis for patients
undergoing radiotherapy for lung cancer [6]. However, results from the largest multicenter study conducted to date were unable to show a reduction in the incidence of esophagitis with amifostine treatment (Movsas et al., 2005). A phase III study conducted by the RTOG (trial 9801) treated 243 patients with favorable-prognosis inoperable stage II–IIIA/B non-small cell lung cancer with concurrent hyperfractionated radiotherapy plus paclitaxel (50 mg/m2) and carboplatin (dosed to achieve area under the concentration–time curve of 2) (Movsas et al., 2005). Half of the patients also received i.v. amifostine (500 mg) before the afternoon radiation treatment. During the course of the study, esophagitis was measured via National Cancer Institute Common Toxicity Criteria maximum esophagitis grade, physician dysphagia log, and patient daily self-assessment of swallowing ability. No significant differences in esophagitis were observed for patients receiving amifostine compared with those who did not receive amifostine, with the exception of the patient-reported lower rate of swallowing dysfunction observed in amifostine-treated patients (z test, p = .025). The authors attributed the lack of significant reduction in esophagitis with amifostine to several factors, including the timing of amifostine administration (Movsas et al., 2005), given that preclinical studies suggest that a single morning dose of amifostine provides superior radioprotection than with a single afternoon dose (Bachy et al., 2003; Fanzenbaker et al., 2003). The randomized trials involved in cytoprotection for lung irradiation are shown in table 2.

1.3 Lower gastrointestinal mucositis

Lower gastrointestinal mucositis frequently results from pelvic irradiation. Several clinical trials have demonstrated that amifostine pretreatment before radiotherapy or chemoradiotherapy can reduce the incidence and severity of gastrointestinal toxicities that commonly occur following these treatments (Table 2) (Koukourakis et al., 2000; Antoniadou et al., 2004; Athanasiou et al., 2003; Ben-Josef et al., 2002; Dunst et al., 2000; Kouloulias et al., 2004; Kouloulias et al., 2005; Kouvaris et al., 2003; Liu et al., 1992; Simone et al., 2005; Singh et al., 2006). Guidelines published by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology recommend the use of amifostine (340 mg/m²) to prevent proctitis in patients receiving standard-dose radiotherapy (Bensadoun et al., 2006). Furthermore, these studies demonstrate that various routes of administration of amifostine (i.v., s.c., and intrarectal) are effective at reducing radiation- and chemoradiation-induced gastrointestinal toxicities in patients with pelvic malignancies. One study, conducted in 53 patients with prostate or gynecologic cancer, directly compared intrarectal amifostine administration with s.c. administration and found that intrarectal administration was more effective at reducing radiotherapy-induced rectal toxicities, whereas s.c. administration was more effective at reducing radiotherapy-induced urinary toxicities (Table 3) (Kouloulias et al., 2005). These results suggest that optimal cytoprotection may be achieved by combining routes of amifostine administration during treatment.

1.4 Dermatitis

Protection by amifostine against radiation-induced dermatitis was assessed in a retrospective analysis in which 100 patients with pelvic tumors treated with radiotherapy and amifostine were compared with 120 historical controls who was not administered
<table>
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<tr>
<th>Reference</th>
<th>Radiation dose</th>
<th>Chemotherapy</th>
<th>Amifostine dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Movsas et al., 2005</td>
<td>69.6 Gy at 1.2 Gy (hyperfractionation)</td>
<td>Induction PC</td>
<td>500 mg i.v.</td>
<td>No difference by NCI-CTC esophagitis, Swallowing diaries ((p &lt; 0.03)) and weight loss ((p &lt; 0.05)) favour amifostine (median survival, 15.6 and 15.8 mo)</td>
</tr>
<tr>
<td>Leong et al., 2003</td>
<td>60–66 Gy at 2.0 Gy</td>
<td>Induction PC</td>
<td>740 mg/m² with each chemo (Days 1, 22, 43, 50, 57, 64, 71, 78)</td>
<td>Esophagitis Grade 2–3: 43% in amifostine, 70% in control (not significant) (median survival, 12.5 and 14.5 mo)</td>
</tr>
<tr>
<td>Senzer et al., 2002</td>
<td>64.8 Gy at 1.8 Gy</td>
<td>Concurrent PC, gemcitabine and cisplatin X 3 after chemoradiation</td>
<td>500 mg i.v. before weekly chemo; 200 mg i.v. daily before RT</td>
<td>No difference in toxicity, no survival data (ongoing trial)</td>
</tr>
<tr>
<td>Antonadou et al., 2001</td>
<td>55–60 Gy at 2.0 Gy</td>
<td>None</td>
<td>340 mg/m²/d before RT</td>
<td>↓Pneumonitis ↓Esophagitis (no survival data)</td>
</tr>
<tr>
<td>Antonadou et al., 2003</td>
<td>55–60 Gy at 2.0 Gy</td>
<td>Concurrent weekly Por C</td>
<td>300 mg/m²/d before chemoradiation and RT</td>
<td>↓esophagitis ((p &lt; 0.001)) ↓pneumonitis ((p = 0.009)) (no survival data)</td>
</tr>
<tr>
<td>Komaki et al., 2004</td>
<td>69.6 Gy at 1.2 Gy (hyperfractionation)</td>
<td>Concurrent i.v. cisplatin Days 1, 8, 29, 36; Oral etoposide Days 1–5 8–12, 29–33, 36–40</td>
<td>500 mg i.v. 1st, 2nd day each wk before chemo and 1st RT fraction</td>
<td>↓Degree of esophagitis, ↓Pneumonitis, ↓Neutropenic fever (median survival, 19 and 20 mo)</td>
</tr>
</tbody>
</table>

**Abbreviations:** P = paclitaxel; C = carboplatin; RT = radiotherapy; NCI-CTC = National Cancer Institute-Common Toxicity Criteria.

Table 2. Randomized trials with amifostine in lung cancer

Amifostine (Kouvaris et al., 2002). There was a 77% lower risk for radiation-induced dermatitis with amifostine use. The severity of dermatitis was also significantly lower among patients receiving amifostine compared with historical controls: the mean gross dermatitis scores were 0.18 ± 0.09 versus 1.0 ± 0.11 (\(p < .001\)). In another study of 40 patients receiving radiation treatment for pelvic tumors, grade 2 or 3 dermatitis of the perineal/vulvar area was observed in all patients with gynecologic and rectal cancer who did not receive amifostine (500 mg s.c.) (Koukourakis et al., 20000). Among patients who received amifostine, only grade 1 dermatitis was noted.
<table>
<thead>
<tr>
<th>Author et al., 1992</th>
<th>N</th>
<th>Rectal Toxicity (Control vs Amifostine)</th>
<th>P Value</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al., 1992</td>
<td>100</td>
<td>14% vs 0%; moderate or severe late toxicities</td>
<td>0.03</td>
<td>Randomized (intravenous)</td>
</tr>
<tr>
<td>Dunst et al., 2000</td>
<td>30</td>
<td>1.07±1.03 vs 0.40±0.63; maximum diarrhea score</td>
<td>0.044</td>
<td>Nonrandomized (intravenous)</td>
</tr>
<tr>
<td>Antonadou et al., 2004</td>
<td>124</td>
<td>5.6% for amifostine vs 22.2% for control</td>
<td>&lt;0.011</td>
<td>Randomized</td>
</tr>
<tr>
<td>Kligerman et al., 1992</td>
<td>100</td>
<td>5% vs 0% moderate or severe late toxicity</td>
<td>&lt;0.01</td>
<td>Randomized (intravenous)</td>
</tr>
<tr>
<td>Kligerman et al., 1992</td>
<td>220</td>
<td>Grade I/II toxicity, 70% vs 42%</td>
<td>&lt;0.001</td>
<td>Nonrandomized (retrospective, intravenous)</td>
</tr>
<tr>
<td>Antonadou et al., 2004</td>
<td>29</td>
<td>Grade I/II toxicity, 50% (500–1000 mg amifostine) vs 15% (1500–2500 mg amifostine)</td>
<td>0.0325</td>
<td>Nonrandomized (intrarectal)</td>
</tr>
<tr>
<td>Kouvaris et al., 2002</td>
<td>40</td>
<td>Grade III/IV observed in 15% for control vs 0% for amifostine group</td>
<td>&lt;0.05</td>
<td>Randomized</td>
</tr>
<tr>
<td>Kouvaris et al., 2003</td>
<td>36</td>
<td>Grade I/II toxicity, 88% vs 11%</td>
<td>&lt;0.001</td>
<td>Randomized (intravenous)</td>
</tr>
<tr>
<td>Muller et al., 2004</td>
<td>6</td>
<td>Leukocytes and lymphocytes irradiated were radioprotected (comet assay measurements)</td>
<td>&lt;0.05</td>
<td>Nonrandomized</td>
</tr>
<tr>
<td>Athanasiou et al., 2003</td>
<td>205</td>
<td>Grade II/III acute toxicity, 22.1% vs 5.5% (3rd wk of radiation)</td>
<td>0.001</td>
<td>Randomized (intravenous)</td>
</tr>
<tr>
<td>Kououlia et al., 2004</td>
<td>67</td>
<td>Grade I/II acute toxicity, 44% vs 15% for IR</td>
<td>0.026</td>
<td>Randomized (intrarectal)</td>
</tr>
<tr>
<td>Singh et al., 2006; Simone et al., 2005</td>
<td>30</td>
<td>33% in 1gr IR vs 0% in 2gr IR</td>
<td>0.06</td>
<td>Randomized</td>
</tr>
<tr>
<td>Kououlia et al., 2005</td>
<td>53</td>
<td>Grade I/II acute toxicity, 42% for s.c. Vs 11% for IR</td>
<td>0.04</td>
<td>Randomized (subcutaneous vs intrarectal)</td>
</tr>
</tbody>
</table>

IR=intrarectal; s.c.=subcutaneous

Table 3. Clinical Trials of Amifostine With Radiotherapy in Pelvic Tumors

2. Different ways of administration

2.1 i.v. Amifostine

The American Society of Clinical Oncology guidelines for cytoprotective agents recommend amifostine at a dose of 200 mg/m² daily, given as a slow i.v. push over 3 minutes, 15–30 minutes before each fraction of radiation therapy (Hensley et al., 1999). Adverse events are reduced at this lower dose. Nonetheless, administration of amifostine requires close patient monitoring. Many patients require antiemetics. Hypotension associated with amifostine at this dose is less frequent but still requires close monitoring. Blood pressure should be measured before and immediately after the 3-minute amifostine infusion.
2.2 s.c. Amifostine

The s.c. administration of amifostine has been proposed to reduce treatment-related and dose-limiting adverse events (Koukourakis et al., 2000). In a pharmacokinetic study, the plasma concentration of WR-1605 after s.c. injection of 500 mg of amifostine was 67% of that after a 200 mg/m² i.v. dose (Shaw et al., 1997). Lower plasma levels of amifostine after s.c. injection do not necessarily translate to lower tissue concentrations. Because the amount of amifostine that is absorbed and converted to the active metabolites is not dependent on plasma pharmacokinetics, i.v. or s.c. administration may not have a significant impact on whether therapeutic levels are achieved in the tissues. Precise determination of the protective efficacy of different routes of administration will require more comprehensive studies that measure intracellular levels of the metabolites or assess radiation-induced DNA double-strand breaks in tissues after i.v. or s.c. administration of amifostine. Nonetheless, the efficacy of s.c. amifostine administration is best addressed in the context of a clinical trial.

A phase II randomized trial with 140 patients assessed the feasibility, tolerance, and activity of the s.c. route (Koukourakis et al., 2000). A dose of amifostine of 500 mg s.c. was administered 20 minutes before each fraction of radiotherapy. The s.c. administration of amifostine was well tolerated by 85% of patients. In approximately 15% of patients, amifostine therapy was interrupted because of cumulative asthenia or a fever/rash reaction. Mild nausea was frequent (29%), and the incidence of hypotension was negligible (3%). Significantly less pharyngeal, esophageal, and rectal mucositis was observed among patients receiving amifostine (p < .04). Treatment delays because of grade 3 mucositis were significantly longer in patients treated with radiotherapy alone (p < .04).

2.3 Endorectal

Initial attempts with rectal administration of amifostine admixed in a foam did not demonstrate protection in patients receiving large pelvic fields of radiation (Montana et al., 1992). However, after successful topical application of amifostine in the rectum of male rats (Ben-Josef et al., 1995), subsequent significant clinical benefit of endorectal administration of amifostine was demonstrated in a phase I study (Ben-Josef et al., 2002).

A randomized trial of 67 patients undergoing radiotherapy for prostate cancer further assessed intrarectal administration of amifostine (Kouloulias et al., 2002). Patients were treated with or without amifostine at a dose of 1,500 mg intrarectally 20–30 minutes before each radiotherapy session. All patients receiving amifostine completed therapy without amifostine-related toxicities, suggesting that intrarectal amifostine was feasible and well tolerated. According to RTOG grading criteria, amifostine was superior to no treatment, with a significantly lower incidence of rectal mucositis (15% versus 44%; p < .04). The mean rectal mucositis index of patients who received amifostine was 0.3 ± 0.1 compared with 2.2 ± 0.4 in patients without cytoprotection (p < .001). The severity of rectal mucositis was significantly lower in patients who received amifostine (p < .001). Urinary toxicity was comparable between the two groups (p = .76). A more recent study suggests that the efficacy of intrarectal amifostine may be dose dependent. Although not statistically significant, the incidence of acute grade 2 rectal mucositis was lower in patients receiving a 2-g suspension of amifostine (n = 12) than in those receiving 1 g (n = 18; p = .06) (Sigh et al., 2006). No breaks
in treatment for radiation-induced toxicities were required in that study. A combination of intrarectal and s.c. amifostine administration might be optimal for cytoprotection with pelvic irradiation.

3. New grading scale for acute pelvic radiation induced toxicity

The past years all the trials with amifostine and pelvic radiotherapy used as endpoints the WHO and RTOG/EORTC scales as shown in table 4.

<table>
<thead>
<tr>
<th>WHO Toxicity Grade</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Increase of 2–3 stools per d over pretreatment</td>
<td>Increase of 4–6 stools per d, or nocturnal stools, or moderate cramping</td>
<td>Increase of 7–9 stools per d, or incontinence, or severe cramping</td>
<td>Increase of &gt;10 stools per d or grossly bloody diarrhea, or need for parenteral support</td>
<td></td>
</tr>
</tbody>
</table>

| EORTC-RTOG scale for lower gastrointestinal | None | Increased frequency or change in quality of bowel habits not requiring medication, rectal discomfort not requiring analgesics | Diarrhea requiring parasympatholytic drugs, mucous discharge not necessitating sanitary pads, rectal or abdominal pain requiring analgesics | Diarrhea requiring parenteral support, severe mucous or blood discharge necessitating sanitary pads/abdominal distension (flat plate radiograph demonstrates distended bowel loops) | Acute or subacute obstruction, fistula or perforation; gastrointestinal bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion |


Table 4. WHO Toxicity Criteria and RTOG Acute Radiation Morbidity Scoring Criteria

A specific analytical for subjective and objective measurements was introduced. Endoscopy offers accurate endpoints for the evaluation of tissue damage, whereas the criteria of rectosigmoidoscopy findings are still not well defined in the literature. The literature deals mainly with symptomatic patients presenting with rectal bleeding, pain, increased stool frequency, urgency and incontinence, whereas systematic endoscopic analysis including asymptomatic patients rarely exists. A valid scoring system is essential for adequate description of acute rectal toxicity. For the benefit of sharing and comparing data collected from endoscopy after RT, we have introduced a graduation system based on
rectosigmoidoscopic criteria focused on acute effects and standardized terminology published by the European Society for Gastrointestinal Endoscopy. The scale is shown in table 5.

<table>
<thead>
<tr>
<th>Subjective</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenesmus</td>
<td>Occasional</td>
<td>Intermittent</td>
<td>Persistent</td>
<td>Refractory</td>
</tr>
<tr>
<td>Mucosal loss</td>
<td>Occasional</td>
<td>Intermittent</td>
<td>Persistent</td>
<td>Refractory</td>
</tr>
<tr>
<td>Sphincter control</td>
<td>Occasional</td>
<td>Intermittent</td>
<td>Persistent</td>
<td>Refractory</td>
</tr>
<tr>
<td>Stool frequency</td>
<td>2–4 per d</td>
<td>4–8 per d</td>
<td>&gt;8 per d</td>
<td>Uncontrolled diarroha</td>
</tr>
<tr>
<td>Pain</td>
<td>Occasional &amp; minimal</td>
<td>Intermittent &amp; tolerable</td>
<td>Persistent &amp; intense</td>
<td>Refractory &amp; excruciating</td>
</tr>
<tr>
<td>Objective</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>Occult</td>
<td>Occasionally &gt;2 per wk</td>
<td>Persistent, daily</td>
<td>Gross hemorrhage</td>
</tr>
<tr>
<td>Mucosa surface</td>
<td>Localized spotted, congested mucosa</td>
<td>Punctate, congested mucosa</td>
<td>Diffused, congested mucosa</td>
<td>Bleeding mucosa</td>
</tr>
<tr>
<td>Ulceration</td>
<td>Superficial ≤1 cm²</td>
<td>Superficial &gt;1 cm²</td>
<td>Deep ulcer</td>
<td>Surgical intervention</td>
</tr>
</tbody>
</table>

*Modification to Subjective Objective Management Analytic scale to fit radiation-induced acute toxicity to the rectum. Subjective and objective items were used for evaluation of acute radiation-induced rectal mucositis. The second and third items of the objective scale were based on findings from flexible rectosigmoidoscopy and were in accordance with the endoscopic terminology of the World Organization for Digestive Endoscopy. The final score was the sum of scores of the 8 items (score=0 in the absence of toxicity).

Table 5. Rectal Toxicity Grade*

Our experience has shown that the terminology is practicable and provides a definition of terms usable by radiation oncologist and endoscopists. The S-RS scale showed a satisfied clinical validity and reliability (Kouvaris et al., 2003). In a previous publication (Kouloulias et al., 2004) the rectosigmoidoscopic findings for amifostine versus no amifostine showed significant differences, as shown in figure 1.

4. Conclusion

Normal tissues vary in the extent that they are protected from radiation damage by amifostine. Because amifostine does not cross the blood–brain barrier, the central nervous system, often the dose-limiting organ in radiotherapy, is not protected (Millar et al., 1982; Washburn et al., 1976). Protection factors for other tissues range from three in the hematopoietic system and salivary glands to approximately one in the lung, kidney, and bladder (Rojas et al., 1984; Rojas et al., 1986; Travis 1984). Within the same tissues, a range of protection factors has been reported (Rojas et al., 1984; Mori et al., 1984). Discrepancies in WR-1065 concentrations in tissues within 15–30 minutes of administration (Utley et al., 1984)
and the normal interval between administration of amifostine and radiotherapy may explain these differences. Nonhomogenous distribution of amifostine and its metabolites within a tissue, even at the level of the DNA (savoye et al., 1997), may also contribute to this heterogeneity.

Fig. 1. Rectosigmoidoscopic findings. Panels A and B illustrate a regular rectal mucosa in patients after intrarectal administration of amifostine. Panels C and D are from patients who did not receive amifostine and illustrate congested mucosa with superficial ulceration >1 cm² (indicated by the arrows).

The U.S. Food and Drug Administration has approved the i.v. use of amifostine to reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer and to reduce the incidence of moderate to severe xerostomia in patients undergoing postoperative radiation treatment for head and neck cancer, where the radiation port includes a substantial portion of the parotid glands. Amifostine has been
proven to be a useful addition to the arsenal of the radiation oncologist, helping improve patients' quality of life and in some cases allowing more aggressive radio- and chemotherapeutic regimens. Currently, s.c. administration of amifostine is a standard practice for patients with head and neck cancer as well as for patients with recurrent ovarian carcinoma (Hensley et al., 2009), while there is evidence now that the s.c is not superior to i.v. administration of amifostine (Bardet et al., 2011). Refinements in doses and administration of amifostine lead to constant improvement in the adverse event profile, resulting in fewer interruptions in treatment and ultimately improving patient outcomes (Jellena et al., 2006; Bourhis et al., 2011). At last but not least, recent meta-analysis from 16 randomized trials (1,554 patients) confirmed the lack of any tumor protection in routine radiotherapy practice when amifostine is administered (Bourhis et al., 2011).

It has to be mentioned that the graduation system designed by our group is user-friendly and more than this, it is an interface between radiation-oncologists and gastroenterologists by means of common terminology between specializations for radiation induced rectal toxicity.

5. References


Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries. It is an enormous global health encumbrance, growing at an alarming pace. Global statistics show that in 2030 alone, about 21.4 million new cancer cases and 13.2 million cancer deaths are expected to occur, simply due to the growth, aging of the population, adoption of new lifestyles and behaviors. Amongst the several modes of treatment for cancer available, Radiation treatment has a major impact due to technological advancement in recent times. This book discusses the pros and cons of this treatment modality. This book "Modern Practices in Radiation Therapy" has collaged topics contributed by top notch professionals and researchers all around the world.

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