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Review Paper

Alternate delivery route for amifostine as a radio-/chemo-protecting agent

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Abstract

Amifostine (ethiofos, WR-2721) is an organic thiophosphate prodrug that serves as an antineoplastic adjunct and cytoprotective agent useful in cancer chemotherapy and radiotherapy. The selective protection of certain tissues of the body is believed to be due to higher alkaline phosphatase activity, higher pH and vascular permeation of normal tissues. Amifostine is conventionally administered intravenously before chemotherapy or radiotherapy. It is approved by the Food and Drug Administration (FDA) to reduce cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer. It was originally indicated to reduce the cumulative renal toxicity from cisplatin in non-small cell lung cancer although this indication was withdrawn in 2005. Amifostine is also FDA approved for patients with head and neck cancer to reduce the incidence of moderate to severe xerostomia in patients who are undergoing postoperative radiation treatment where the radiation port includes a substantial portion of the parotid glands. The potential of amifostine as a cytoprotective agent is unlikely to be fully realized if the method of administration is restricted to intravenous administration. Attempts have been made to develop non-invasive methods of delivery such as transdermal patches, pulmonary inhalers, and oral sustained-release microspheres. It is the goal of this article to explore non-intravenous routes of administration associated with better efficacy of the drug. This review will primarily focus on the variety of more recently studied (2002 and later) alternative modes for amifostine administration, including subcutaneous, intrarectal and oral routes.

Introduction

Amifostine, also known in the literature as ethiofos, WR-2721 and the trade name Ethyol, is an organic thiophosphate prodrug that serves as an antineoplastic adjunct and cytoprotective agent useful in cancer chemotherapy and radiotherapy. Amifostine is dephosphorylated in-vivo by alkaline phosphatase to the active cytoprotective thiol metabolite, WR-1065, the form of the drug that is taken up into cells and is the major cytoprotective metabolite. The selective protection of certain tissues of the body is believed to be due to higher alkaline phosphatase activity, higher pH and vascular permeation of normal tissues. Protective properties of amifostine include free-radical scavenging, auto-oxidation leading to intracellular hypoxia, chemical repair by hydrogen atom donation and an ability to modulate the complex transcriptional regulation of genes involved in apoptosis, cell cycle and DNA repair (Bensadoun et al 2006; Brizel 2007). Oncologists administering amifostine must balance drug dosage with the severity of side effects. A common and potentially dangerous side effect in patients receiving intravenous amifostine is hypotension, which has been reported to occur in approximately 62% of patients treated at a dose of $910\,mg\,m^{-2}$. To combat potentially severe side effects during intravenous amifostine administration, blood pressure is closely monitored during infusion in addition to maintaining proper patient hydration and administration of the treatment with the patient in the supine position. Nausea or vomiting occurs frequently after intravenous infusion with amifostine and may be severe. Administration of antiemetics are recommended before, or in conjunction with, amifostine infusion. If the above-described side effects associated with intravenous amifostine administration are too severe, amifostine treatment must be halted and may be resumed upon acceptable reduction of side effects. The potential of amifostine as a cytoprotective agent is unlikely to be fully realized if the method of administration is restricted to intravenous administration. Several novel routes of administration are currently under investigation and may further

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simplify the use of the drug by reducing the incidences of severe side effects (Kouvaris et al 2007). Attempts have been made to develop non-invasive methods of delivery such as transdermal patches, pulmonary inhalers and oral sustained-release microspheres. It is the goal of this article to explore non-intravenous routes of administration associated with better efficacy of the drug. This review will primarily focus on the variety of more recently studied (2002 and later) alternative modes for amifostine administration including subcutaneous, intrarectal and oral routes.

Subcutaneous route

Although intravenous administration is the approved route, the use of the subcutaneous route of administration has become more prevalent (Bachy et al 2004) than intravenous administration (Table 1). Several studies have been performed to investigate the use of subcutaneous injection as an alternative drug delivery route and have produced promising results with respect to efficacy, occurrence of side effects and ease of administration. Preclinical and clinical data suggest that subcutaneous administration of amifostine may be better tolerated with similar efficacy to intravenous administration of amifostine. The subcutaneous route, due to its simplicity, presents multiple advantages over the intravenous route when amifostine is used during fractionated radiotherapy (Koukourakis et al 2000). The costs associated with subcutaneous amifostine administration have been shown to be offset over time due to fewer complications.

Human patient data indicate a higher plasma bioavailability of the active metabolite (WR-1065) following intravenous administration than after subcutaneous administration, although currently there are no corresponding data showing human tissue levels of the active metabolite of amifostine (WR-1605) following either subcutaneous or intravenous administration due to the difficulty in obtaining human specimens. A study performed by Bachy et al (2004) compared plasma and tissue pharmacokinetics of WR-1065 in primates utilizing both routes of administration. Following intravenous administration, plasma WR-1065 levels peaked rapidly and showed a bi-exponential decline, whereas WR-1065 levels rose slowly and declined exponentially following subcutaneous administration. Subcutaneous administration resulted in a lower relative plasma bioavailability of WR-1065 at 30 and 60 min than intravenous administration. WR-1065 tissue concentration was equal to, or slightly greater, at 30 min following subcutaneous administration and comparable at 60 min. This primate plasma bioavailability study confirms human plasma data. Despite the lower plasma bioavailability following subcutaneous administration, equal to or greater tissue concentration levels of the active metabolite in animals that received the drug subcutaneously strengthens the argument for subcutaneous administration of amifostine in radiation oncology (Bachy et al 2004).

An additional animal model was utilized to investigate the use of amifostine for oral mucosal protection and pharmacokinetics via subcutaneous administration and intravenous administration by Cassat et al (2003) utilizing a rat model. The investigators found that amifostine administered intravenously or subcutaneously 1 h before radiation protected rats from mucositis, but the protective effect was more prolonged when amifostine was administered subcutaneously, suggesting that subcutaneous administration of amifostine was at least as effective as administration by the intravenous route.

Preliminary data of a phase III trial by Bardet et al (2002) compared intravenous and subcutaneous administration of amifostine for head and neck tumours treated by external radiotherapy indicated that drug tolerance was better with subcutaneous than with intravenous administration, particularly because of the absence of hypotension, which facilitates patient monitoring and management in radiotherapy departments. In a more extensive study of subcutaneous amifostine on thoracic, head and neck cancer patients, Anné (2002) assessed the availability of subcutaneously administered amifostine in a phase II trial comparing subcutaneous amifostine versus no amifostine in a patient population similar to that studied in a phase III trial of intravenous amifostine to allow comparisons of outcomes. Subcutaneous amifostine was well tolerated, with nausea, vomiting and hypotension being less severe after subcutaneous amifostine than after intravenous amifostine, although cutaneous toxicity was found to occur more frequently. In addition, the reduction in radiation therapy-induced acute xerostomia with subcutaneous amifostine was similar to that with intravenous amifostine. Anné concluded that if cutaneous toxicity is judged an acceptable risk, then subcutaneous amifostine may represent a second, more convenient, option for treating physicians. Ozsahin et al (2006) assessed the feasibility and efficacy of subcutaneous amifostine therapy in patients with head and neck cancer treated with curative accelerated radiotherapy. The major adverse effect of subcutaneous administration found was nausea, despite prophylactic anti-emetic medication, resulting in discontinuance of amifostine therapy in 33% of patients. The authors concluded that subcutaneous amifostine administration in combination with accelerated concomitant-boost radiotherapy with or without chemotherapy is practicable.

Although nausea is more frequent with amifostine administration, an additional major adverse effect that may compromise amifostine therapy is acute hypotension. Nichols et al (2004) performed a study to assess the degree and severity of changes in systolic blood pressure (SBP) after the daily subcutaneous administration of amifostine before the delivery of fractionated external beam radiotherapy in patients suffering from primary head and neck or non-small cell lung cancer. They demonstrated the safety and feasibility of subcutaneous amifostine administration in the setting of daily fractionated radiotherapy and suggested that the data presented may be used to roughly predict the expected post-injection SBP in patients receiving subcutaneous amifostine in the dose range of the study. In a later study, Nichols & Fullmer (2005) investigated the safety of subcutaneous amifostine in a prospective safety study. In this study on patients suffering from non-small cell lung cancer, five targeted adverse events were evaluated as to their occurrence and possible relationship with amifostine. The following reported adverse events are listed most common to least common: nausea/vomiting, radiation dermatitis, local skin reaction, hypotension and skin rashes.

Table 1 Summary of literature describing model, route and key findings

Reference	Model	Route	Findings
Bachy et al (2004)	Primate plasma and tissue pharmacokinetics	IV vs SC	IV plasma WR-1065 levels peaked rapidly and showed a bi-exponential decline. SC plasma WR-1065 levels rose slowly and declined exponentially. Relative SC plasma bioavailability was lower at 30 and 60 min. SC tissue WR-1065 concentrations were equal or slightly greater at 30 min and comparable at to IV at 60 min.
Koukourakis et al (2000)	Thoracic, head and neck and pelvic cancer	SC	Patients received 500 mg dose or no dose prior to radiation. Treatment was well tolerated in 85% of patients. Approx. 5% of patients interrupted treatment due to cumulative asthenia and 10% due to a fever/rash reaction. Hypotension was not noted; however, nausea was frequent. A significant reduction of pharyngeal esophageal and rectal mucositis was noted in the amifostine arm. Delays in radiotherapy due to grade 3 mucositis was significantly longer in the radiotherapy alone arm. Amifostine significantly reduced the incidence of acute perineal skin and bladder toxicity.
Cassat et al (2003)	Rat plasma and tissue pharmacokinetics	IV vs SC	Rats received 50, 100, or 200 mg/kg doses via IV or SC administration prior to radiation. Tissue levels of WR-1065 were equivalent. Correlation between tissue levels and protection was strong. Correlation between blood levels and protection was weak. The protective effect against mucositis was more prolonged following SC administration.
Bardet et al (2002)	Head and neck cancer	IV vs SC	Patients received 200 mg IV or two 500 mg SC doses before radiation. Preliminary data: acute toxicity included nausea/vomiting (12% vs 13%), hypotension (6% vs 0%), skin rash (15% vs. 16%), and asthenia (4% vs. 0%). Acute xerostomia ≥ grade 2 (23% vs 19%).
Anné (2002)	Thoracic, head and neck and pelvic cancer	IV vs SC	Results were compared with separate IV study. Acute xerostomia grade 2 occurred in 56% with SC amifostine and 51% with IV amifostine (78% in the no-amifostine group in phase III trial), with median time to onset being 40 days and 45 days, respectively (30 days with no amifostine). Amifostine SC was well tolerated, with three quarters of patients receiving > 75% of the planned dose. Nausea, vomiting, and hypotension were less severe with SC amifostine, but cutaneous toxicity was more frequent.
Ozsahin et al (2006)	Head and neck cancer	SC	Patients received 500 mg dose prior to radiation. 45% of patients showed no intolerance, 33% of patients discontinued treatment due to nausea, 18% due to hypotension. No grade 3 cutaneous toxic effects were observed. Grade 3 acute toxic effects included mucositis 42%, erythema 42%, and dysphagia 39%. Late toxic effects included grade > 2 xerostomia 51% and fibrosis 9%. Grade > 2 xerostomia was observed in 42% of patients receiving > 20 injections vs. 64% of 14 patients receiving fewer than 20 injections.
Nichols et al (2004)	Head and neck and non-small cell lung cancer	SC	Patients received 500 mg amifostine prior to radiation. No patient suffered a significant hypotensive episode requiring intervention. Mean and median SBP declines were 12.4 mmHg and 12 mmHg respectively for all injections delivered. 90% of all declines in SBP were less than 25 mmHg. The greatest single decline in SBP seen was 42 mmHg.
Nichols & Fullmer (2005)	Non-small cell lung cancer	SC	Patients received 500 mg dose prior to radiation. Patients experienced adverse effects (AEs) nausea/vomiting (56%), radiation dermatitis (37%), local skin reaction (35%), hypotension (23%), and skin rashes (20%). 20% of AEs required discontinuation of amifostine. 91% of patients did not require changes in dosage.
Leung et al (2005)	Nasopharynx cancer	SC vs no amifostine	Patients received 500 mg dose prior to radiation over a 6.6–8.6 week course of treatment. Significantly less grade 2 chronic xerostomia was observed in patients receiving amifostine while acute xerostomia grades were similar. Xerostomia questionnaire scores and total saliva flow rates were similar both at early post-radiation and one year post-radiation time points.
Law et al (2005)	Head and neck cancer	SC	Patients received two 250 mg doses prior to radiation. Locoregional tumour control rates were 958% and 88% at 12 and 18 months, respectively. Distant disease free rates were 95% and 82%. The incidence of grade > 2 xerostomia was 42% at 12 months and 29% at 18 months. The one year and two year survival estimate was 95% and 83%.
Koukourakis et al (2003)	Chemotherapy patients	IV vs SC	Patients received 1000 mg amifostine prior to chemotherapy cycles by IV, IV followed by SC if patients developed protracted vomiting and malaise and/or clinical hypotension for two consecutive IV administrations, and SC. In the IV/SC study, 13.5% of patients showed protracted emesis/malaise and/or clinical hypotension during the first two cycles with an additional 6.6% developing similar side effects during subsequent cycles. In the SC study, vomiting or clinical hypotension was absent with no other systemic side effects.
Buchsmann et al (2004)	Various cancers	SC	27% of patients receiving 500 mg dose before radiation suffered Grade 3 or greater side effects. The following side effects had been documented in patient sample n = 37: Nausea 8x, vomiting 8x, hypotonus 5x, allergic reaction 1x, severe dyspnoea 2x, upper abdominal pain 6x, erythema 2x, generalized urticaria 1x, vertigo 1x, loss of consciousness 1x. The time when the side effects appeared was completely different. In four patients it appeared between the 10^{th} and 28^{th} application; in six patients between the first and 6^{th} application.

(Continued)

Table 1 *(Continued)*

Reference	Model	Route	Findings
Srinivasan et al (2002)	Murine	SC pellet vs placebo pellet and conventional SC	Mice were subcutaneously implanted with biodegradable amifostine drug pellet or placebo pellet without amifostine before radiation. Significant radioprotection (85–95% survival) was observed in the three amifostine pellet group 3–5 h post implantation at 10 Gy. The three amifostine pellet group had sustained blood WR-1065 levels 2 h after implantation. Conventional SC reported a sharp peak at 30 min. Locomotor activity was significantly reduced in the amifostine pellet group and delayed as compared with groups receiving 400 and 750 mg kg^{-1} conventional SC and placebo implant.
Kouloulias et al (2005)	Prostate and gynaecologic cancer	IR vs SC	Patients received a dose of 1500 mg as an aqueous solution in 40 mL of enema or a SC administration of a 500 mg dose. IR amifostine reduced grades I–II rectal radiation morbidity (11% vs 42%). Subjective rectosigmoid scores were significantly lower in the IR group (0.44 vs 2.45 and 3.9 vs 6.0). SC administration reduced urinary toxicity (48% vs 15%).
Ben-Josef et al (1995)	Rat model	IR	Rats received 2% WR-2721 gel. Concentrations of total WR-1065 in the rectal wall increased with time but not substantially in the prostate. Concentration in the rectal wall was found to be significantly higher at all times.
Ben-Josef et al (2002)	Prostate cancer	IR	Cohorts received 500 to 2500 mg doses before radiation. At a median follow-up of 26 months 33% of patients developed grade 1/2 rectal bleeding. At 9 months, 66% of patients developed grade 1/2 telangiectasia. This was mostly confined to the anterior rectal wall. No visible mucosaloedema, ulcerations, or strictures were noted. No significant differences were found between the proctoscopy findings at 9 and 18 months. Late rectal bleeding developed significantly more often in patients receiving 0.5–1 g than in patients receiving 1.5–2.5 g amifostine (50% vs 15%).
Kouvaris et al (2003)	Prostate and gynaecologic cancer	IR	AUC analysis indicated a homogeneous dose–volume effect. Grade 2 or higher acute toxicity did not occur in the IR group. Grade 1 or higher acute rectal toxicity occurred in 11% of the IR group and 89% in the no amifostine group. The onset and duration of acute rectal toxicity was improved in the IR group as was overall mucositis.
Kouloulias et al (2004)	Prostate cancer	IR	Patients received 1.5 g dose as an aqueous solution in 40 mL of enema or no amifostine. 15% of IR patients showed grade 1 mucositis while 44% of no amifostine patients exhibited grade 1/2 mucositis. The incidence of urinary toxicity was the same for both groups.
Simone et al (2006)	Prostate cancer	IR	Patients received 1 g and 2 g doses prior to radiation. There was a clear trend towards protection from rectal toxicity using 2 g as compared with a 1 g amifostine dose.
Singh et al (2006)	Prostate cancer	IR	Patients received 1 g and 2 g doses prior to radiation. Incidence of acute grade 2 rectal toxicity was 33% in 2 g group vs 0% in 1 g group. No grade 3 or higher occurred.
Elas et al (2003)	Measured EPR signal decay	Oral vs IP	Mice received a coadministration of carbamoyl-proxyl spin probe and 400 mg/kg IP dose or 400 mg/kg oral dose before radiation. Treatment with amifostine decreased the first order rate of decay of the CP EPR signal (23% (IP) vs 18% (oral)).
Bonner & Shaw (2002)	Healthy subjects	IV vs oral and SC	Subjects received IV 200 mg doses compared with oral and SC 500 mg doses. SC and not oral administration provided a more effective dosing regimen in terms of both a reasonable AUC for the bound form of WR-1065 and decreased toxicity compared to IV.
Pamujula et al (2004)	Murine	Oral	Mice received PLGA nanoparticles orally (dose equivalent to 250 mg kg^{-1}). WR-1065 was detected in significant amounts in all tissues, including bone marrow, jejunum and the kidneys, and there was some degree of selectivity in its distribution in various tissues.
Pamujula et al (2005)	Murine	Oral	Mice were administered orally active nanoparticles (dose equivalent to 500 mg kg^{-1}) before radiation. At 30-day survival, haemopoietic progenitor cell and jejunal crypt cell survival was significantly enhanced.

CP, carbamoyl proxyl; IP, intraperitoneal; IR, intrarectal; IV, intravenous; SC, subcutaneous.

They found that subcutaneous amifostine was well tolerated by patients with a low incidence of severe grade 3 or 4 adverse events.

Longer-term studies focusing on subcutaneous administration of amifostine in comparison with intravenous administration have also supported the effectiveness of the subcutaneous route for the reduction of amifostine-associated side effects in radiotherapy. Leung et al (2005) addressed the use of subcutaneous amifostine for the reduction of radiation xerostomia, the most common long-term toxicity for nasopharynx cancer after radiation therapy. They concluded that subcutaneous amifostine reduced the occurrence of severe xerostomia at one year after radiation therapy for nasopharynx cancer. An additional long-term study was performed by Law et al (2005) on follow-up data from a phase II trial evaluating the radioprotective effects of subcutaneous amifostine in patients with head and neck cancer. They concluded that subcutaneous amifostine provides long-term (at least 18 months) radioprotection from xerostomia without evidence of loss of tumour control.

The focus of the majority of studies on the subcutaneous route of administration and the comparison of the subcutaneous and intravenous routes of administration of amifostine is in radiotherapy. Comparisons between these routes were investigated for both radiotherapy and chemotherapy in separate studies by Koukourakis et al (2000, 2003). The earlier study (Koukourakis et al 2000) involved patients with thoracic, head and neck and pelvic tumours undergoing radical radiotherapy in a phase II trial to assess the feasibility, tolerance and cytoprotective efficacy of amifostine administered subcutaneously. Subcutaneous administration of amifostine was well tolerated in 85% of patients and there were no occurrences of hypotension, although nausea was frequent. The authors concluded that subcutaneous administration effectively reduced radiotherapy's early toxicity and prevented delays in radiotherapy. In the later study, Koukourakis et al (2003) investigated whether the subcutaneous administration of amifostine was better tolerated than intravenous administration in patients receiving chemotherapy. They found that amifostine, at a dose of 1000 mg, is better tolerated when administered subcutaneously rather than intravenously. Moreover they discovered that switching to subcutaneous administration in patients exhibiting poor tolerance to intravenous administration allowed for the continuation of cytoprotection with minor side effects.

Buchsmann et al (2004) investigated the use of subcutaneous amifostine as a result of several radiotherapists' attempts to reproduce the above mentioned results while experiencing deleterious effects of subcutaneous amifostine on their patients. They examined a sample of patients irradiated because of different kinds of cancers who received amifostine subcutaneously before radiation and found that 27% of all patients had suffered side effects of grade 3 or greater. In addition, they found that the time when the side effects appeared was completely different. Contrary to previous studies and based on their findings, the authors concluded that amifostine serving as a radioprotector in radiotherapy should not be given subcutaneously. To avoid side effects associated with conventional subcutaneous administration of amifostine, Srinivasan et al (2002) proposed an alternative route. The use of a subcutaneously implantable, biodegradable pellet was examined to serve as a drug delivery system in a murine model. The biodegradable amifostine pellet was found to be effective with radioprotection comparable between amifostine pellet implantation and conventional subcutaneous administration.

Rectal route

Several studies have been performed to investigate the use of intrarectal amifostine administration as an alternative drug delivery route to intravenous and subcutaneous amifostine administration and have found promising results with respect to efficacy and occurrence of side effects. Preclinical and pilot clinical data have suggested that intrarectal administration of amifostine may be better tolerated with similar efficacy to subcutaneous administration of amifostine (Kouloulias et al 2005). In addition, intrarectal administration is simple, painless and does not require the same level of training needed for administration by the intravenous, subcutaneous or intraperitoneal routes. However, a major drawback of the intrarectal route is the method by which it inherently is delivered with respect to patient acceptance. Additionally, intrarectal amifostine delivery for protection is limited by the location of the cancer and would not be efficacious for the protection of xerostomia or oral mucositis.

Ben-Josef et al (1995) utilized a rat model to investigate the merits of a 2% WR-2721 gel for intrarectal application. The concentration of WR-1065 was found to increase within the rectum but not the prostate after intrarectal administration. Additionally, the concentration in the rectal wall was found to be significantly higher at all times. They concluded that intrarectal topical application resulted in preferential accumulation of WR-2721 in the rectal wall. In a later study, the same investigators (Ben-Josef et al 2002) performed a phase I dose-escalation clinical trial on patients with localized prostate cancer utilizing amifostine administered intrarectally as an aqueous solution. All of the patients completed the therapy with no amifostine-related toxicity at any dose level. The team concluded that intrarectal application of amifostine was feasible and well tolerated. In addition, they found that systemic absorption of amifostine and its metabolites were negligible and close monitoring of patients was not required with intrarectal administration.

The cytoprotective effect of intrarectal amifostine against radiation-induced acute toxicity to the rectal mucosa in patients with either prostate or gynaecological cancer was evaluated by Kouvaris et al (2003). The investigators found that amifostine was well tolerated and showed a significant cytoprotective efficacy in acute radiation-induced rectal mucositis in terms of symptomatic and objective end-points. Kouloulias et al (2004) utilized the intrarectal route for amifostine administration in patients suffering from prostate cancer to investigate effects on acute radiation-induced rectal toxicity. Following the phase II study, they suggested that intrarectal administration of amifostine exhibits a cytoprotective efficacy in acute radiation-induced rectal mucositis. In a later study investigating and comparing the cytoprotective effect of subcutaneous and intrarectal administration of

amifostine against acute radiation toxicity, the same authors (Kouloulias et al 2005) concluded that intrarectal administration of amifostine expressed a superior cytoprotective efficacy in acute radiation rectal mucositis but was inferior to subcutaneous administration in terms of urinary toxicity.

The protective benefits of increased concentrations of intrarectal amifostine have recently been explored in two separate studies. Protection of the rectal mucosa utilizing daily intrarectal amifostine was assessed in a pilot study of patients with localized prostate cancer by Simone et al (2006). A clear trend towards protection from rectal toxicity was demonstrated using 2 g versus 1 g of amifostine. Singh et al (2006) tested the ability of an intrarectal amifostine suspension to reduce symptoms of radiation proctitis using varying concentrations of amifostine. Their findings suggested a greater rectal radioprotection from acute effects with 2 g vs 1 g amifostine intrarectal suspension.

Oral route

Although there are advantages to using subcutaneous and intrarectal amifostine instead of intravenous amifostine, an oral form of amifostine delivery represents the most convenient form of delivery discussed thus far. Advantages include convenience with respect to portability and ease of administration unlike the trained personnel requirements for intravenous, subcutaneous and intraperitoneal routes of treatment. Costs can be reduced in various areas such as drug production and administration. From the patient perspective, ease of use is greatly increased with oral delivery in addition to a lack of pain with administration, unlike the intravenous and subcutaneous routes. Amifostine is not orally active (Bonner & Shaw 2002) and is therefore best utilized when modified in a sophisticated drug-delivery system. For example, active drug can be delivered to the body utilizing nanoparticles. Additionally, such a system can be manipulated to control drug concentration and release times.

Rapid measurement of amifostine bioavailability was investigated by Elas et al (2003) in a study designed to determine the systemic incorporation of amifostine and effectiveness of oral and intraperitoneal administration by calculating a reduction of nitroxides in a murine model. Consistent changes in measurements of nitroxide signal decay were monitored using in-vivo electron paramagnetic resonance (EPR) and were used to evaluate the interaction between radiation and amifostine. They found that oral administration and intraperitoneal injection of amifostine were both effective in affecting the carbamoyl proxyl spin probe EPR signal decay rate, serving as a strong indicator of similar bioavailability in mice from both routes of administration.

Bonner & Shaw (2002) conducted a phase I clinical trial to evaluate the relative bioavailability of amifostine and its pharmacologically active metabolite, WR-1065, following oral, subcutaneous and intravenous administration. Results showed that subcutaneous administration of amifostine and not oral administration could provide a more effective dosing regimen, in terms of both a reasonable AUC for the bound form of WR-1065 and decreased toxicity, compared with intravenous delivery, suggesting that the protein-bound form of WR-1065 plays an important role in contributing to the bioavailability amifostine.

To harness the convenience of the oral delivery of amifostine while retaining drug efficacy, Pamujula et al (2004) developed an orally active biodegradable sustained-release formulation of amifostine using poly (lactide-co-glycolide) (PLGA) as carrier particles using a spray drying technique. A murine model was utilized to demonstrate that the amifostine nanoparticles given orally delivered the drug in significant concentrations to a variety of tissues, including key target tissues, with some degree of selectivity. In a later study, the same investigators (Pamujula et al 2005) evaluated this slow-release formulation of orally active amifostine nanoparticles for radioprotection efficacy in mice. The results demonstrated that the oral administration of amifostine nanoparticles provided significant protection from acute whole-body gamma irradiation injury.

Conclusion

Recent work on alternatives to intravenous administration of amifostine has been evaluated, including subcutaneous, intrarectal and oral delivery. Several studies focused on subcutaneous administration have shown promising results with respect to efficacy, occurrence of side effects and ease of administration in comparison with intravenous administration, although one study suggested that subcutaneous administration was not feasible. Studies performed to investigate the use of intrarectal administration have also shown promising results with respect to efficacy and occurrences of side effects when compared with either subcutaneous or intravenous administration. Intrarectal administration may reduce the need for required training of administrators of the drug but patient compliance is likely to be hindered due to complications inherent with this form of delivery. Additionally, intrarectal amifostine delivery for protection is limited by the location of the cancer and is not able to be utilized for protection against xerostomia or oral mucositis. Although there are advantages to using subcutaneous and intrarectal amifostine as an alternative to intravenous amifostine, oral delivery of amifostine represents the most desirable form of delivery. Recent work on orally active biodegradable sustained-release amifostine nanoparticles has provided a feasible method for the delivery of orally active amifostine and further work on this oral formulation holds great clinical promise.

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