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Exploration of Platinum-based Dose-intensive Chemotherapy Strategies with Amifostine (Ethyol®)

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The preclinical evaluation of amifostine confirms selective protection of normal tissues against toxicity due to cisplatin therapy while maintaining the antitumour effects. The mechanism of protection relates to the selective uptake of the free thiol, amifostine, into normal tissue compared with tumour tissue, intracellular binding and therefore detoxification of anticancer drugs, as well as through the scavenging of oxygen free radicals. Although vigorous hydration schedules have helped to alleviate nephrotoxicity, ototoxicity and cumulative dose-related peripheral neuropathy, these side effects remain important dose-limiting toxicities related to cisplatin therapy.The preclinical and clinical results to date demonstrate that amifostine can protect against cisplatin toxicities, in particular nephrotoxicity. Recent studies have demonstrated that higher single and cumulative cisplatin doses have an important impact on survival outcome; however, the improvement in survival comes at the cost of increased acute and cumulative haematological, renal and neurological toxicities that can result in serious morbidity. The role of amifostine as a unique supportive measure to reduce these toxicities offers the possibility of improving the quality of life of patients receiving chemotherapy. Copyright © 1996 Elsevier Science Ltd

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INTRODUCTION

CURRENTLY available modalities for the treatment of malignancies have significant limitations because chemotherapy and radiation therapy cannot discriminate between normal and malignant cells. As a result, therapy is associated with significant toxicity, which may affect quality of life and can be life threatening. In addition, adverse reactions associated with treatment may limit the intensity of the treatment delivered, thereby affecting its efficacy.

Approaches for improving the therapeutic index of treatment have included measures of enhancing sensitivity of the tumour relative to normal tissue or, alternatively, reducing toxicity to normal tissues while leaving tumour resistance unchanged. The latter involves the use of agents that interact with cytotoxic agents to ameliorate toxicity. Amifostine (Ethyol®) represents a prototype of this class of agents and has recently been approved in both the United States and Europe for the prevention of certain toxicities associated with cancer therapy.

AMIFOSTINE

In 1949, Pratt and associates [1] reported that the sulphydryl amino acid cysteine administered before radiation could protect rates against lethal irradiation by protecting the bone marrow. Since then, numerous investigators have confirmed the importance of sulphydryl-containing compounds, including thiols and glutathione, in reducing toxicity of both radiation therapy and alkylating agent chemotherapy [2]. However, early drugs showed limited selective advantage for normal tissues and were associated with considerable toxicity. From more than 4000 sulphydryl compounds screened, the aminothiol S-2(3-aminopropylamino) ethylphosphorothioic acid, designated amifostine (Walter Reed [WR]-2721), was selected for further clinical evaluation because it was found to be one of the least toxic and most effective compounds [3]. Amifostine is the prodrug that is dephosphorylated to the active metabolite, designated WR-1065. The protection of normal tissues correlates with activation of the prodrug within tissues and selective entry of the active metabolite into normal cells. Protection of cell damage by WR-1065 is thought to occur through binding to the active species of platinum and alkylating agents, by scavenging oxygen free radicals and through hydrogen donation to repair damaged target molecules [3].

Preclinial data

Preclinical studies of amifostine from multiple laboratories have demonstrated that amifostine provides protection against cisplatin-induced toxicities, particularly neurotoxicity and nephrotoxicity. In animal studies, amifostine protects against cisplatin-induced nephrotoxicity by factors of 1.3–1.7. Yuhas and Culo [4] have demonstrated that pretreatment of tumour-bearing animals with amifostine (200 mg/kg) 30 min before weekly doses of cisplatin (2 mg/kg) allowed for the administra-

tion of this agent three times longer before nephrotoxic injury occurred. In addition, amifostine pretreatment increased the cisplatin dose required to produce a blood urea nitrogen elevation from 2.1 to 3.1 mg/kg/d. This amounts to a 1.5-fold increase in resistance. Nephrotoxicity has been assessed histologically in the treated animals. One month after treatment, tubular degenerative changes and tubular epithelial nuclei were quantitated. The amifostine-pretreated animals showed far less renal tubular injury than did the control animals given the same dose of cisplatin [5]. Recent *in vitro* studies have suggested that the mechanism of protection mediated by WR-1065 is through the prevention of cisplatin-induced cellular damage rather than through reversal of damage [6]. Additional studies have demonstrated that there is a time dependence for protection of cisplatin-induced nephrotoxicity [7]. Amifostine administered 30 and 5 min prior to cisplatin allowed a 2.2-fold increase in cisplatin dose before the occurrence of nephrotoxicity. However, protection from cisplatin-induced nephrotoxicity was absent when amifostine was administered 30 min after cisplatin.

Mollman [8] demonstrated protection of neurons by amifostine from cisplatin using a cultured chick dorsal root ganglion. This has also been studied by Mueller [9] using the central nervous system of a snail. The results showed that the addition of amifostine to cisplatin prevented induction of lysosomes (a measure of neurotoxicity) compared with cisplatin alone.

Another mechanism of protection by amifostine is through direct binding to the active species of the alkylating agents and platinums. A study by Treskes and Nijtmans [10] demonstrated that WR-1065 can prevent the formation of cisplatin–DNA adducts that, as well as being mediators of toxicity, are thought to be responsible for the antitumour effects of cisplatin. WR-1065 has been shown to prevent cisplatin–DNA adduct formation in a dose-related manner and, to a lesser extent, to reverse cisplatin-DNA adduct formation. Thompson and coworkers [11] proposed alternative mechanisms for the protective effects of amifostine. In a Fischer rat model, these investigators demonstrated that the protetive effects observed are most likely due to a direct reaction between the platinum complex and amifostine. More recently, Wittenkeller and coworkers [12] demonstrated that amifostine enhances cisplatin–vinblastine antitumour activity against nonsmall-cell lung cancer in a nude mouse model.

Clinical studies

Based upon encouraging preclinical studies, the protective effect of amifostine against cisplatin-induced toxicity has been evaluated in a series of clinical trials initiated in the 1980s. Four phase I clinical studies of amifostine and escalating doses of cisplatin have been conducted with and without mannitol diuresis by Glover and coworkers [13]. Doses of cisplatin were escalated from 50 to 150 mg/m^2. Escalating doses of amifostine were administered over 15 min, at 15 min prior to cisplatin. Transient nephrotoxicity was observed in 27% of patients treated with cisplatin at 150 mg/m^2 and in 7% of patients given 120 mg/m^2. Grade 1–2 peripheral neuropathies occurred in 26% of patients after a median cumulative cisplatin dose of 725 mg/m^2. Compared with historical cohorts treated with high-dose single-agent cisplatin with vigorous hydration schedules, the data from these studies suggest that amifostine protects against cisplatin-induced nephrotoxicity, neurological toxicity, haematological toxicity and ototoxicity. To further address the role of amifostine as a cytoprotective agent in patients receiving cisplatin, Mollman and coworkers [14] conducted a prospective study of patients receiving cisplatin as a single agent or in combination with other chemotherapeutic agents to determine risk factors that contributed to platinum-related toxicities. Patients receiving cisplatin in combination with amifostine were reported to have a significantly lower incidence of neuropathy, 25%, compared with an overall incidence of 49% ($P < 0.05$). In addition, there was a near doubling of the mean dose of cisplatin prior to the onset of neuropathy, which was 635 mg/m^2 with amifostine compared with 383 mg/m^2 for patients treated without the protective agent ($P < 0.005$).

Several studies have been completed utilising high-dose cisplatin and amifostine in patients with metastatic melanoma and non-small-cell lung cancer. Glover and coworkers [13] examined the role of amifostine (740–1100 mg/m^2 infused over 15 min) administered 30 min prior to high-dose cisplatin (60–150 mg/m^2, administered over 30 min) for the treatment of metastatic melanoma in a phase II trial. These patients also received a bolus injection of mannitol prior to cisplatin and a 6-h continuous infusion of mannitol following the cisplatin infusion. Haematologic toxicity was mild and infrequent: 9 patients developed peripheral neuropathy following a median cisplatin dose of 670 mg/m^2 and 5% of patients exhibited some evidence of nephropathy, defined as any serum creatinine > 2 mg/dL. These results are favourable relative to the nephrotoxicity reported with other trials of high-dose (> 100 mg/m^2) single-agent cisplatin, including studies that utilised vigorous hydration schedules, but used less rigorous monitoring schedules. Importantly, antitumour activity was fully preserved, with 53% of patients with metastatic melanoma achieving an objective response. The effective dose range of cisplatin was identified as 120–150 mg/m^2, whereas no responses were observed at doses of 100 mg/m^2 or lower. This compares favourably to those reported with single-agent chemotherapy studies of dacarbazine or combination chemotherapy studies with cisplatin. The results of this study provided the basis for an expanded phase II study of amifostine (910 mg/m^2) plus cisplatin (120 mg/m^2) in patients with metastatic melanoma conducted by Avril and coworkers [16] at the Institute Gustave-Roussy, France. Of 18 assessable patients, 3 attained a complete response and 4 a partial response. Most of the responses occurred in patients with cutaneous and nodal metastases, and the time to tumour progression was short. However, these preliminary results provide further evidence that amifostine does not negatively impact the antitumour activity of cisplatin in patients with metastatic melanoma.

Less activity and greater toxicity were reported by Buzaid and coworkers [17] in a phase II study of high-dose cisplatin and amifostine in patients with metastatic melanoma. Patients received a lower dose of cisplatin, 100 mg/m^2, with hypertonic saline on days 1 and 8 every four weeks. Cisplatin was preceded by amifostine at a dose of 740 mg/m^2. The few assessable patients developed some degree of ototoxicity as measured by serial audiograms and the creatinine increased to 1.5 times the baseline values in 2 patients. Significant nausea and vomiting were reported despite the use of antiemetics. In addition, fatigue, as measured by a decline in performance status, developed in 6 of 8 patients. No responses were seen with this regimen in 6 assessable patients, and the study was closed.

Investigators at the University of Wisconsin have reported preliminary results of patients with locally advanced nonsmall-cell lung cancer treated with amifostine, cisplatin (120 mg/m^2), and vinblastine (5 mg/m^2) [18]. Response rates of 73% have

been reported. Similarly, a phase II trial of amifostine, cisplatin and vinblastine has been initiated by the same investigators in patients with metastatic nonsmall-lung cancer; 25 patients have been treated. Toxicities have included transient grade 3 renal dysfunction in 14% of patients, grade 3 neuropathy in 5 patients and ototoxicity in 3 patients. 4 patients were hospitalised for neutropenic fever. This regimen was highly active, with 64% of patients achieving a partial response. Survival measured by the Kaplan–Meier technique was 85% at six months and 65% at 12 months [19].

Overall, amifostine is generally well tolerated. Reversible and manageable side effects most frequently experienced include nausea and vomiting on the day of therapy and transient hypotension during infusion. Therefore, patients must have their blood pressure monitored frequently during amifostine therapy. A significant drop in blood pressure (decrease in systolic pressure $>$ 20 mm Hg for $>$ 5 min or syptomatic hypotension) [2] occurs in $<$ 5% of patients, is evident early in the infusion and is rapidly reversible with treatment discontinuation. Other side effects, such as sneezing, somnolence, dizziness, flushing, hiccups and chills are generally episodic and do not require interruption of therapy. Most side effects are transient, of mild to moderate severity, and do not increase in either frequency or severity with repeated cycles of amifostine therapy.

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