Amifostine-induced Toxic Epidermal Necrolysis during Radiotherapy: a Case Report

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Amifostine is a phosphorylated aminothiol prodrug that can selectively protect normal tissues against the toxic effects of chemotherapy and radiotherapy. In clinical use amifostine is well tolerated and may rarely cause allergic reactions. Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are two closely related entities that present with severe acute mucocutaneous reactions most often triggered by drugs. There are only two case reports related to the use of amifostine during radiotherapy, one case with SJS and the other with SJS–TEN overlap. In this paper, a case with amifostine-induced TEN during radiotherapy is presented.

Key words: amifostine – toxic epidermal necrolysis – radiotherapy

INTRODUCTION

Amifostine is a phosphorylated aminothiol prodrug that can selectively protect normal tissues against the toxic effects of chemotherapy and radiotherapy (RT). In clinical use amifostine is well tolerated and may rarely cause allergic reactions. Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are two closely related entities that present with severe acute mucocutaneous reactions most often triggered by drugs (1,2). SJS refers to cases with <10% of body surface involvement and TEN to those with >30% involvement; those with cutaneous detachment between 10 and 30% are termed SJS–TEN overlap (1).

In the literature there are only two case reports related to the use of amifostine during RT, one case with SJS and the other with SJS–TEN overlap (3). In this paper, a case with amifostine-induced TEN during RT is presented.

CASE REPORT

A 56-year-old male patient with stage IIB nasopharyngeal carcinoma was planned to have curative RT. The RT was given with conventional fractionation combined with daily amifostine as radioprotectant. Radiotherapy was delivered using two lateral parallel opposed fields including nasopharynx and cervical lymphatics and an AP field covering the supraclavicular area. External irradiation was performed using daily fractions of 200 cGy up to a total dose of 6400 cGy to the primary tumor, 6000 cGy to the cervical lymphatics and 5000 cGy to the supraclavicular region. After the completion of external RT, two fractions of intracavitary brachytherapy (ICBT) were added. Amifostine was administered as daily 200 mg/m² IV infusions 30 min prior to RT with the aim of decreasing RT side effects. Intravenous hydration was performed with a 500 ml 0.9% NaCl infusion in 60 min. In the middle of this infusion, 8 mg of dexamethasone and 2 mg of tropisetron were given as an intravenous push before each amifostine course against its emetogenic and hypotensive effects.

RT was tolerated well until the middle of the fourth week. Famotidine, sucralfate and dipyrone (for difficulty in swallowing), nystatin and fluconazole (for mucositis) and benzydamine HCl (for oropharyngeal inflammation) were administered to the patient during RT. There was no other drug use other than those mentioned above. In the middle of the fourth week the patient experienced itching erythematous lesions on the legs, trunk and face and also severe acute mucositis. Because of severe mucositis, RT was interrupted at the beginning of the fifth week. The lesions were evaluated as ‘drug eruption’ and all of the drugs were terminated. A gradual decrease of the eruptions with time was observed. One week later, RT with amifostine was restarted without any accompanying drug when mucositis decreased. Then it was observed that the eruptions increased and skin sensitivity emerged at the fourth fraction of the new RT course with amifostine and the
patient had to be hospitalized immediately. The patient had received 24 times daily amifostine infusion until that time.

Dermatological examination revealed large flaccid blister formations and detachments on the arms and legs which encompassed ~30% of the body surface area. In addition, erythematous macular lesions and some atypical targetoid lesions located especially on the trunk and shoulders were seen, which increased the body surface area involved to a total of 60% (Fig. 1). The patient also had conjunctivitis and extensive oral mucosal ulceration.

Histopathological examination of a 4 mm punch biopsy taken from the right thigh showed subepidermal bullae formation and necrosis of the epidermis that involved predominantly the basal layer.

Amifostine was terminated and RT was stopped with the diagnosis of TEN. Methylprednisolone (2 mg/kg, daily) was started and continued for 5 days. Topical treatment for skin and mucosal lesions was given. By the second day of treatment new lesion development ceased and his general condition improved within 10 days.

**DISCUSSION**

Amifostine is a thiol that can protect cells from damage due to chemotherapy and RT by scavenging oxygen-derived free radicals. Amifostine, formerly known as WR-2721, has been regarded as a broad-spectrum cytoprotective agent. Preclinical studies showed that amifostine was able to protect selectively almost all normal tissues except the central nervous system against the toxic effects of chemotherapeutic agents and irradiation (4,5).

Amifostine is a prodrug that is dephosphorylated to its metabolite WR-1065 by the enzyme alkaline phosphatase. Amifostine performs its selective normal tissue protection through the ability of free thiol to be taken up in higher concentration in normal organs than in tumor tissue. Tumors are relatively hypovascular, and thus hypoxic, and have a lower interstitial pH. Both hypovascularity and low pH cause low rates of prodrug activation by alkaline phosphatase. Moreover, this enzyme is found more abundantly in the microenvironment of normal cells than that of tumor cells. As a result, selective protection of normal tissues is due to the reduced metabolism of amifostine and low uptake of its metabolite WR-1065 in tumor tissue (4).

RT to the head and neck region usually leads to some major toxicity such as xerostomia and mucositis. The severity of these side effects is correlated with the volume of the irradiated field, dose-fractionation scheme and whether RT is combined with chemotherapy (6).

In a phase III randomized trial of radiation ± amifostine in patients with head and neck cancer, Brizel et al. (7) used daily 200 mg/m² amifostine 30 min prior to RT (total RT dose 60–70 Gy). In that study RTOG ≥ 2 acute and late xerostomia were significantly reduced in those patients treated with amifostine. Also in a phase II randomized trial, Buntzel et al. (8) tested the ability of amifostine to reduce the toxicity of carboplatin plus RT (RCT) in patients with head and neck cancer. Radiotherapy was given up to a total dose of 60 Gy concomitantly with carboplatin 70 mg/m² on days 1–5 and days 21–26. The first arm of the study was with RCT alone and the second arm was with RCT preceded by 500 mg of amifostine on the days of chemotherapy only. Mucositis and xerostomia were significantly reduced in the second arm (8). There have also been other phase II and III studies related to the use of amifostine during RT or radiochemotherapy in head and neck cancer (9–13). These studies showed that amifostine decreased acute and late xerostomia and/or mucositis induced by therapy.

In the light of these studies, it is recommended that the use of amifostine should be considered to decrease the incidence of acute and late xerostomia in patients receiving fractionated RT to the head and neck region (4). Also, in our patient amifostine was given with this rationale. In the setting of amifostine administered with RT, the recommended dose is 200 mg/m² given as a slow intravenous push over 3 min, 15–30 min before each fraction of RT (4). The same administration schedule was applied in our patient.

In clinical use, amifostine is well tolerated but may cause transient side effects as nausea, vomiting, flushing, sneezing, mild somnolence, a metallic taste during infusion and occasional allergic reactions (5).

TEN is a rare pattern of cutaneous reaction, which is associated with a number of possible etiological agents, but drugs are the principle cause (1). Among these, sulfonamides, anti-convulsant drugs, antibiotics, allopurinol and non-steroidal anti-inflammatory drugs are those most frequently encountered (14).

RT may be an inciting factor in the production of TEN and SJS (15). In rare cases erythema multiforme-like lesions, of maximum intensity at the sites of exposure, have been reported (16).

In the treatment of intracranial tumors, the use of antiepileptic drugs such as phenytoin, carbamazepine and phenobarbital during RT has been suggested to increase the risk of TEN through synergistic effects. In recent years, increasing numbers of cases with SJS and TEN have been reported (17–20). In
these cases the mechanism of pathogenesis is not fully understood. It is mostly suggested that immunological mechanisms might be responsible.

In the literature, only two cases have been reported with severe skin reactions thought to have developed due to amifostine (3). The two cases of SJS and SJS–TEN overlap both developed skin reactions 4 weeks after the start of radioprotective agent amifostine. In the first case with SJS, the symptoms increased despite the cessation of drugs other than amifostine and vanished only after the cessation of amifostine.

In our patient, the drugs used other than amifostine were those frequently used in clinical practice and with no reported relationship with TEN or SJS development until now. Moreover, after the cessation of all drugs, the symptoms and the severity of the lesions increased and finally TEN developed when amifostine was restarted during RT. For these reasons, we suggest that TEN was induced by amifostine use during RT when amifostine was restarted during RT. For these reasons, severe of the lesions increased and finally TEN developed over, after the cessation of all drugs, the symptoms and the relationship with TEN or SJS development until now. Moreover, after the cessation of all drugs, the symptoms and the severity of the lesions increased and finally TEN developed when amifostine was restarted during RT. For these reasons, we suggest that TEN was induced by amifostine use during RT in our patient. Therefore, it should be noted that amifostine, which is increasingly used as a cytoprotective agent for in our patient. Therefore, it should be noted that amifostine, which is increasingly used as a cytoprotective agent for in our patient. Therefore, it should be noted that amifostine, which is increasingly used as a cytoprotective agent for patients receiving RT, should be considered in the etiology of SJS and TEN.

References