Amifostine administration during radiotherapy for cancer patients with genetic, autoimmune, metabolic and other diseases

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Amifostine is a broad-spectrum cytoprotective agent approved for protection against cisplatin toxicities and radiation-induced xerostomia; strong clinical evidence exists that amifostine protects normal mucosa and lung from radiation damage. Hypotension, nausea/vomiting, fatigue and fever/rash are the main side-effects associated with amifostine administration. The present study summarizes our experience on daily amifostine administration to cancer patients with various coexisting medical conditions and diseases. The tolerance and the eventual interference of amifostine with the course of the coexisting diseases is reported, providing a core list of medical conditions met in radiotherapy practice, their compatibility with amifostine administration and recommendations on how to deal with these patients. This list comprises genetic diseases (xeroderma pigmentosum, glucose-6-phosphate dehydrogenase deficiency), autoimmune disorders (vitiligo, scleroderma, thyroiditis, perforating collagenosis), metabolic diseases (diabetes mellitus), cardiovascular diseases, neuro/psychiatric diseases and other medical conditions (hypoglycemia, hepatic cirrhosis, alcoholism). A high incidence of fever/rash was noted in patients with autoimmune diseases, while all other conditions did not alter the patterns of side-effects expected following amifostine administration. *Anti-Cancer Drugs* 17:133–138

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Introduction

Amifostine is a broad-spectrum cytoprotective agent approved for the protection against cisplatin toxicities and radiation-induced xerostomia [1,2]. A large number of studies also confirm an important protection against radiation-induced mucositis, esophagitis, diarrhea and pneumonitis [3–7]. As a disadvantage, several side-effects accompany amifostine administration and 15–20% of patients will have to discontinue amifostine at some point of their treatment [2,8,9]. Intravenous administration of the drug is linked with a high incidence of clinical hypotension and acute emesis, while protracted daily administration results in fatigue and somnolence [2,8,10]. The switch to the s.c. route results in abolishment of hypotension and reduction of acute emesis, whereas protracted nausea and fatigue are not diminished [8,11]. The incidence of 'fever/rash', first reported during s.c. administration [8], ranges between 7 and 10% during daily administration of 500 mg of amifostine [8,9,12] and is not increased when the i.v. [10] or s.c. (study submitted) daily dose is increased to 1000 mg. Recent studies comparing the s.c. to the i.v. administration route show a similar incidence for both routes [9,10]. The report of rare cases with severe skin necrolytic syndromes led to the establishment of guidelines for the prevention of amifostine-related skin toxicities [13].

Although the overall tolerance and side-effects of amifostine are quite well known after 15 years of clinical research and use, dilemmas often emerge when amifostine support to cancer patients is to be decided in the context of certain associated diseases. The complex mechanism of amifostine interference with cellular metabolism [14] and with the immune system [15,16], together with its unpredictable tolerance, justifies such dilemmas. It is also of importance to extract from clinical experience easily recognizable subgroups of patients with increased likelihood to exhibit poor tolerance to amifostine, so that such patients either will not receive amifostine or will be strictly observed for eventual side-effects.

The present study summarizes our experience on amifostine administration to cancer patients with various concurrent diseases. The tolerance of amifostine under such conditions is reported. A core list of medical conditions met in radiotherapy practice is provided together with their compatibility with amifostine

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administration and recommendations on how to deal with these patients.

Genetic diseases

Xeroderma pigmentosum (XP)

XP is a genetic spectrum of diseases associated with mutations in various genes [XPA, ERCC3 (XPB), XPC, ERCC2 (XPD), DDB2 (XPE), ERCC4 (XPF), ERCC5 (XPG) and POLH]. The common characteristic is oversensitivity to sunlight, and 1000-fold increased risk for cutaneous and ocular neoplasms. Cells from patients with XP bear a defective nucleotide excision repair and are hypersensitive to UV radiation. Patients with this disorder are often admitted to radiotherapy departments for treatment of multiple skin carcinomas. In a review from St Bartholomew Hospital, London, UK, over a period of 20 years, four out of 2000 children treated with radiotherapy exhibited an extreme radiation hypersensitivity, one of which with XP [17]. Nevertheless, a small number of case reports in the literature suggest that radiotherapy can be tolerated by these patients with acceptable acute effects, although the severity of late sequels is unknown [18,19]. Cytoprotection with amifostine may prove of benefit for such patients.

A 19-year-old patient with XP was admitted to our department for re-irradiation of a skin carcinoma of the nose that recurred after two surgical excisions and one course of radiotherapy (30 Gy in 10 fractions) delivered 2 years before admission. An additional course of 10 radiotherapy fractions (3 Gy per fraction), using 8-MeV electrons, was offered, supported with gradually increasing doses of amifostine delivered s.c. (starting from 250 mg and increasing by 250 mg dose increments up to 1000 mg). The patient tolerated well the dose of 1000 mg without any nausea or fatigue. No skin reaction was noted at the site of injection. Following the sixth amifostine injection, he developed fever (39°C) and skin rash. The fever dropped rapidly with paracetamol and the rash regressed completely within 24 h, after oral administration of methylprednisolone (16 mg twice a day for 2 days). Radiotherapy was accomplished as scheduled, without further administration of amifostine. Of interest, no signs of acute skin reactions were noted in the radiation field.

This case may indicate that high-dose daily amifostine could be safely administered s.c. to patients with XP. As the incidence of fever/rash is 7%, it may be that fever/rash is a more frequent event in XP patients, but symptomatology regresses rapidly just like in non-XP patients.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

G6PD deficiency is the most common enzyme defect in humans associated with hereditary hemolytic anemia. The functionally decreased G6PD causes increased susceptibility to oxidative stress, as a result of diminished ability to generate sufficient NADPH required for production of reduced glutathione in red cells. Exposure of G6PD-deficient individuals to oxidizing substances (phenacetin, sulfonamides and sulfones, nitrofurans, chloramphenicol, nalidixic acid, quinine, chloroquine, primaquine, probenecid, vitamin K analogs, dimercaprol, methylene blue, naphthalene, etc.) results in hemolytic anemia. Although G6PD deficiency predicts for cellular-defective response to oxidative stress, it is unclear whether G6PD-deficient patients are more sensitive to radiotherapy. Ayene *et al.* using Chinese hamster ovary G6PD-null mutant cells showed that exposure to hydroxyethyldisulfide (a thio-specific oxidant) leads to enhanced radiosensitivity [20]. No experience has been reported with amifostine administration in G6PD deficient patients.

A 55-year-old woman with G6PD deficiency was admitted to our department for treatment of an unknown primary squamous cell carcinoma of the neck. Standard fractionation radiotherapy was offered. Amifostine was administered s.c. starting at a dose of 250 mg. The day after the first injection the patient reported sever fatigue, nausea and vomiting. The next dose of amifostine (250 mg s.c.) was injected in combination with 8 mg of dexamethasone i.m., but intolerable symptoms were reported once again. A third injection of 250 mg resulted to unacceptable fatigue and vomiting, and amifostine was interrupted. Hematological and biochemical tests showed no evidence of hemolysis. Mucositis grade 3 appeared at a total dose of 14 Gy, which is much earlier than the onset expected in G6PD-normal patients. Long splits were necessary for the accomplishment of a course of 60 Gy of radiotherapy that lasted 60 days, suggesting that G6PD-deficient patients may be hypersensitive to radiation.

It is evident that amifostine is not a hemolysis-inducing agent in G6PD-deficient patients and this drug should be of value in avoiding acute toxicity that, at least in this patient, was more severe than the one expected in G6PD-normal patients. Whether the poor tolerance of amifostine noted in this patient is a consequence of G6PD deficiency or was just a random event is unclear. According to our experience, 3% of patients receiving amifostine show poor tolerance to very low amifostine doses.

Immunity-related diseases

Vitiligo

Vitiligo is a skin disease characterized by depigmented demarcated, often symmetric, areas caused by lack of melanocytes. It is a quite frequent disease affecting 1–2% of the general population, with no particular sex-related prevalence. Although the disease is not inherited, there is certainly a family predisposition. The pathogenesis is unclear, but there is strong evidence that vitiligo should

be classified as an autoimmune disorder [21]. Increased HLA-DR4 in blacks and HLA-B13 in Moroccan Jews or HLA-B35 in Yemenite Jews [22] as an association of vitiligo with other autoimmune diseases (i.e. thyroid diseases or diabetes mellitus) has also been reported [23]. Vitiligo has been also reported to occur after radiotherapy [24–27], but there are no data regarding the relative radiosensitivity of patients with vitiligo.

Two patients with vitiligo have been referred for radiotherapy to our department. The first suffered from a bladder carcinoma and the second from a non-small cell lung carcinoma. Both patients were recruited in a protocol of hypofractionated and accelerated radiotherapy supported with a high daily dose of amifostine administered s.c. The daily dose of 1000 mg was well tolerated by both patients with only mild nausea, fatigue and minimal local reaction at the site of the s.c. injection. However, following 6–8 administration days both patients displayed fever/rash and amifostine was discontinued.

It is suggested that patients with vitiligo have a high likelihood of developing fever/rash during amifostine-supported radiotherapy, which renders the use of amifostine in these patients questionable. However, fever/rash regressed easily within 2 days following cortisone treatment and none of these patients progressed to a skin necrolytic syndrome.

Scleroderma

Scleroderma is a disease with a strong autoimmune background [28]. It has been associated with exposure to many agents including chemicals (vinyl chloride, silicon dioxide), chemotherapy (e.g. taxanes) and ionizing radiation [29–40]. Despite the relatively low number of reported patients with scleroderma undergoing radiotherapy, it seems that these patients are more sensitive to irradiation compared to normal subjects [41]. In a study by Ross *et al.*, reporting on four cases with scleroderma undergoing radiotherapy, radiation early and late effects seemed not to be worse than other patients [42]. In contrast to this study stands a study by Morris *et al.* on patients with connective tissue diseases including 16 patients with scleroderma [43]. The authors noted that, excluding rheumatoid arthritis, patients had a significantly higher incidence of late sequel. In a study by Phan *et al.*, scleroderma was the only connective tissue disease associated with severe radiation sequel [44]. This study is also in full agreement with a study from Yale University [45]. The guidelines from the Canadian Association of Radiation Oncology stress that scleroderma is a relative contraindication for breast-conserving treatment [46]. It seems, therefore, that amifostine could be of value for scleroderma patients undergoing radiotherapy. However, the effects of amifostine administration to patients with autoimmune diseases such as scleroderma are unknown.

A 65-year-old woman with high-risk breast cancer and history of scleroderma was referred for radiotherapy of the thoracic wall and axilla, following modified radical mastectomy. Large-field electron fields for the thoracic wall and X-ray irradiation of the axillary supraclavicular area were scheduled, together with s.c. administration of amifostine at a dose up to 1000 mg, depending on tolerance. The patient tolerated well the dose of 1000 mg, with mild nausea and fatigue. No local erythema was noted at the site of injection. After the fifth injection, however, she developed fever (39°C) without rash, which rapidly regressed with paracetamol. Amifostine was immediately discontinued.

This case may indicate that patients with scleroderma can be treated with amifostine, but should be thoroughly observed for the development of fever/rash symptomatology.

Reactive perforating collagenosis (RPC)

RPC is a rare skin disorder characterized by umbilicated papules with a central adherent keratotic plug located throughout the body, particularly in the upper and lower limbs [47,48]. It is accompanied by general pruritus and scratching. This can be either inherited or acquired, and it is often associated with diabetes mellitus, renal diseases and malignancy. Histologically, it is characterized by transepidermal elimination of altered dermal collagen bundles into a cup-shaped epidermal depression.

Two patients, one male with nasopharyngeal and one female with vulva carcinoma, were treated with hypofractionated accelerated radiotherapy supported with 1000 mg amifostine injected s.c. before each radiotherapy fraction. During the second week of therapy (after amifostine injections 8–10) skin lesions (to hands, feet and body) suggestive of perforating collagenosis appeared. The diagnosis was histologically confirmed. Both patients reported that they had repeated incidence of this skin disease in the past, although they had never looked for a medical opinion, as lesions were self-regressing with time. Regarding tolerance of amifostine, both patients received the prescribed dose, complaining only of mild nausea. Lesions gradually disappeared within 2–3 weeks after the end of radiotherapy.

These cases demonstrate that it is important to distinguish between amifostine-related rash and recurrent perforating collagenosis, which is accentuated during amifostine therapy. The disease, however, is probably naive by its nature and there is no need to interrupt amifostine therapy.

Autoimmune thyroiditis

Three patients under medication with thyroxin for autoimmune thyroiditis were treated with radiotherapy supported with 1000 mg s.c. amifostine. Although tolerance was

good (lack of nausea or fatigue), two of them developed fever/rash during injections 9–11. Despite the low number of cases, it is suggested that patients with autoimmune thyroid diseases must be carefully observed during treatment with amifostine for the eventual development of fever/rash.

Drug allergy

Four patients with known history of sever anaphylactic episodes with shock after exposure to antibiotics, including cephalosporins and ampicillin, were treated with amifostine administered s.c. without any complications.

Metabolic diseases and other conditions

Diabetes mellitus

A total of 16 patients with diabetes mellitus under therapy with oral hypoglycemic agents or insulin were treated with 500–1000 mg daily amifostine s.c. and were prospectively observed. The tolerance of amifostine seemed not to differ from that of non-diabetic patients. Ten of them received the 1000 mg dose level without any side-effects and one patient developed fever/rash symptomatology.

Hypoglycemia

Subclinical drop of glucose levels about 30 min after i.v. administration of amifostine is a common finding, presumably due to a switch of the cellular metabolism to anaerobic glycolytic pathways [14]. These are normally restored within 30–60 min.

One woman with a known history of idiopathic hypoglycemia was treated with adjuvant radiotherapy for breast cancer, supported with i.v. administration of 1000 mg of amifostine. This represents the only patient with confirmed clinical hypoglycemia after the administration of amifostine. The glucose levels dropped from 80 down to 40 mg/dl, the patient exhibiting a full clinical image of hypoglycemia (loss of contact, sweating, cold skin and fainting). Symptoms were rapidly restored with hypertonic glucose solution injection. The patient was recommended to eat a good portion of Greek sweets half an hour before amifostine and no signs of hypoglycemia or other toxicity appeared on the subsequent days of therapy.

It is recommended that any history of hypoglycemia be recorded in all patients considered for amifostine therapy. Clinical hypoglycemia can be easily misdiagnosed as severe nausea or hypotension, leading erroneously to the diagnosis of poor tolerance. This condition can be easily prevented by recommending consumption of sweets before the amifostine injection.

Hepatic cirrhosis

One patient with hepatic cirrhosis (Child–Pugh class B) and stage III nasopharyngeal cancer was treated with hypofractionated accelerated radiotherapy supported with 1000 mg of daily amifostine. The patient showed an excellent tolerance of amifostine and accomplished his treatment of 80 Gy biological equivalent dose within 3 weeks with mild radiation mucositis. Hepatic function was not deranged.

Alcoholism

Three patients with alcoholism (one with bladder cancer and two with lung cancer) were treated with radiotherapy supported with amifostine. The patients did not interrupt alcohol consumption during therapy. All three exhibited poor tolerance to higher than 500 mg daily dose of amifostine. One of them developed fever/rash.

Cardiovascular diseases

Coronary heart disease

Eight patients with coronary disease, three of them with a 'bypass' cardiovascular operation and four of them with established myocardial infarction within the previous 6–24 months before referral for radiotherapy, were treated with daily amifostine before every radiotherapy fraction. Five of them received a daily dose of 750–1000 mg and three a dose of 500 mg without any side-effects from amifostine.

Aortic aneurysm

Two patients, one with bladder cancer and aneurysm of the abdominal aorta and one with lung cancer and aneurysm of the thoracic aorta, were treated with radiotherapy supported with 1000 mg of daily amifostine injected s.c. There were no side-effects from the amifostine administration.

Arterial hypertension

Twenty-two patients under anti-hypertensive medication were treated with radiotherapy supported with daily amifostine. All patients were recommended to continue their every-morning anti-hypertensive tablets before amifostine s.c. injection. Thirteen (of 20) patients were treated at 1000 mg, four at 750 mg and three patients at 500 mg. Two patients developed fever/rash, but no other side-effects were recorded. Hypotension was not documented.

Neurological/psychiatric diseases

Stroke

Two patients with recent history of ischemic stroke (within 12 months before radiotherapy) were treated with 750 mg daily amifostine delivered s.c., without any side-effects.

Psychosis

Three patients under medical therapy for psychosis (two with breast cancer and one with head neck cancer) were treated with radiotherapy supported with amifostine. All

Table 1 Medical conditions in cancer patients receiving amifostine, tolerance of amifostine and recommendations

Disease	No. patients	Amifostine side-effects	Risk category[a]	Action
Genetic				
XP	1	fever/rash	1a	close observation
G6PD deficiency	1	poor tolerance	2a	starting amifostine dose 250 mg
Immunity related				
vitiligo	2	fever/rash	1a	close observation
scleroderma	1	fever/rash	1a	close observation
perforating collagenosis	2	none	0b	treat 'PC' – continue amifostine
thyroiditis	3	fever/rash	1a	close observation
drug allergy	4	none	0a	none
Metabolic diseases				
diabetes	16	none	0a	none
hypoglycemia	1	hypoglycemia	0b	consumption of sweets
hepatic cirrhosis	1	none	0a	none
alcoholism	3	reduced tolerance	2a	starting amifostine dose 250 mg
Cardiovascular diseases				
coronary heart disease	8	none	0a	none
aortic aneurysm	2	none	0a	none
hypertensive medication	22	none	0a	continue medication
Neurological/Psychiatric diseases				
stroke	2	none	0a	none
psychosis	3	none	0a	none

[a]*Risk scoring*. Amifostine tolerance: 0=no excess risk for side-effects, 1=higher risk for fever/rash, 2=poor tolerance (fatigue, emesis), 3=life-threatening complications: (not observed). Course of the disease: a=unaffected, b=aggravated to an acceptable level, c=unacceptable aggravation: (not observed).

patients received 1000 mg daily amifostine (one i.v. and two s.c.) without any side-effects.

Discussion

The tolerance of amifostine under several medical conditions in patients with cancer is herein reported, providing a core list of diseases and their compatibility with amifostine administration, together with recommendations on how to deal with these patients. Table 1 summarizes the results, indicates the risk, and provides guidelines for action regarding amifostine administration and patient surveillance. It is stressed that this table is based on limited experience for some of the diseases analyzed.

As fever/rash is the most undesirable side-effect of amifostine, enforcing permanent interruption of the drug [13], it is notable that several medical conditions identified herein are presumably linked with a high risk for development of this symptomatology. It is strongly recommended that patients with autoimmune diseases, such as vitiligo, scleroderma and thyroiditis, be closely observed for the development of amifostine-related fever/rash. G6PD deficiency, XP, diabetes and hepatic cirrhosis are compatible with amifostine administration. One should stress, however, the very poor tolerance of one patient with G6PD deficiency, due to emesis and fatigue that was noted at very low dose levels (250 mg). Patients under anti-hypertensive and anti-diabetic medication can continue their therapy as amifostine administration is expected to show the standard patterns of tolerance. Similarly, it seems that coronary heart disease, recent stroke and psychosis are not contraindications for the administration of high-dose s.c. amifostine. Accentuation of RPC is expected in patients receiving amifostine.

Collection of data is ongoing to expand the list of medical conditions radiation oncologists often deal with when treating patients with amifostine. The clinical experience could therefore be enriched with a larger number of patients in order to strengthen the evidence herein provided.

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