ORIGINAL ARTICLE

Use of amifostine in the treatment of recurrent solid tumours in children

Sidi V[1], Arsos G[2], Papakonstantinou E[1], Hatzipantelis E[1], Fragandrea I[1], Gombakis N[3], Koliouskas E[1]

[1]Dept of Paediatric Oncology, Hippokration General Hospital of Thessaloniki, [2]Dept of Nuclear Medicine, Aristotle University School of Medicine, [3]1st Paediatric Dept, Aristotle University School of Medicine, Thessaloniki, Greece

Abstract

Aim: Preclinical and clinical evaluation of amifostine (AMI) administration in conjunction with systemic chemotherapy supports its role as a cytoprotective agent of normal tissues without loss of impairing the antitumour effectiveness of chemotherapeutic agents. Since only a limited number of clinical studies has been performed using AMI in paediatric pts with malignancies we investigated the protective effect of AMI against carboplatin-induced myelotoxicity and nephrotoxicity in a paediatric group of patients. Material and results: AMI was administered in 18/28 paediatric patients with reccurent solid tumours along with ICE (ifosfamide, carboplatin, etoposide) chemotherapy. A significant ($p<0.05$) decrease in GFR was observed in the control group whereas it was maintained at pre – treatment levels in the AMI-treated group. Leukopenia and neutropenia were significantly ($p<0.05$) less in AMI-group. No protective effect of AMI was shown concerning thrombocytopenia. Conclusions: AMI was generally well tolerated at the dose of 740 mg/m^2. Side effects including nausea, vomiting, hypotension, flushing and rigors were moderate and reversible and the interruption of infusion was never required. *Hippokratia 2007; 11 (1):25-29*

Key words: *recurrent solid tumours, paediatric neoplasms, chemotherapy, cytoprotection, amifostine*

Corresponding author: Sidi V, Kapetanidou 26, 55131, Thessaloniki, Greece, e–mail: paedonc@ippokratio.gr, tel: 00302310/413482

The toxicity associated with chemotherapeutic agents and radiation therapy used in the treatment of malignancy is generally severe and may affect the patient's quality of life or even be life-threatening. As chemotherapeutic agents can not distinguish between normal and neoplastic cells, a broad range of tissues, including primarily the bone marrow, the gastrointestinal epithelium, the kidneys and bladder, the lungs, the nervous and cardiovascular systems, may be adversely affected[1].

Therefore, a concept of selective cytoprotection of normal cells and tissues form the cytotoxic effects of chemotherapeutic agents and radiation therapy has emerged. Systemic approaches have included the administration of compounds such as sodium thiosulphate, diethyl dithiocabamate and AMI. Among the various agents that have been tested amifostine seems to be the most effective and the one having the greatest clinical potential[1-3].

AMI protects normal tissues against chemotherapy and radiation – induced toxicity without loss of antitumour effects. AMI is a potentially important adjust for optimizing the dose of intensive chemotherapy. The prodrug is dephosphorylated by membrane – bound alkaline phosphatase to its active free thiol metabolite, WR – 1065, which is taken up rapidly into normal tissues (Fig 1). Uptake of WR – 1065 is negligible in tumour tissue, because tumour tissue contains less membrane bound alkaline phosphatase, typically has a lower pH than normal tissues, and tumour tissue lacks the

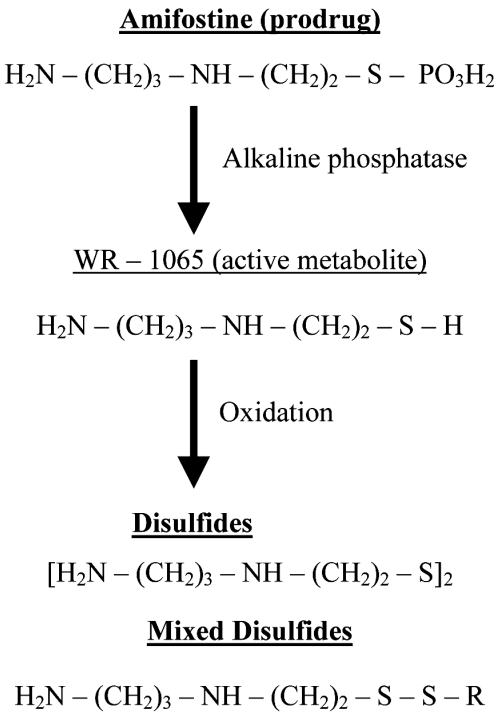

Figure 1: *Amifostine and its metabolites*

WR – 1065 carrier-mediated facilitated diffusion transport mechanism. These factors ultimately lead to a concentration of WR – 1065 in normal tissue, which is 50 – 100 times higher than in neoplastic tissue, even after multiple doses of AMI. The aim of the present study was undertaken in order to expand the clinical experience of AMI in paediatric patients with malignancies and in particular, to investigate the efficacy of AMI in the prevention or limitation of nephrotoxicity after high dose ICE (carboplatin, ifosfamide, etoposide) chemotherapy in paediatric patients with recurrent solid tumours. Only a limited number of studies have been performed in this age group, one which might gain the most from such strategies[1,2].

Patients and methods

From January 2001 to October 2003, 28 pediatric patients (16 boys and 12 girls) of a median age of 6,5 years (range 2 - 14), suffering from recurrent solid tumours, were enrolled in the study. Six out of the 28 patients had Wilms' tumour, six Ewing's sarcoma, one hepatocellular carcinoma, three hepatoblastoma, two nasopharyngeal carcinoma six rhabdomyosarcoma and four neuroblastoma. (Table 1).

Table 1: *Patient Characteristics*

Characteristic	No. of patients	AMI group	control group
No. of assessable patients	28	18	10
Gender			
Male	16	11	5
Female	12	7	5
Age, yrs (median [range])	**6,5 (2-14)**		
Tumor type			
• Wilm's tumour	6/28	4/18	2/10
• Ewing's sarcoma	6/28	4/18	2/10
• Hepatocellular carcinoma	1/28	1/18	-
• Hepatoblastoma	2/18	1/18	1/10
• Nasopharyngeal carcinoma	3/28	2/18	1/10
• Rhabdomyosarcoma	6/28	3/18	3/10
• Neuroblastoma	4/28	3/18	1/10

All 28 patients received 102 courses of the ICE protocol for recurrent paediatric tumours[11]. The ICE protocol included ifosfamide (3gr/m^2) on days 1 and 2, carboplatin (600mg/m^2) on day 3 and etoposide (100mg/m^2) on days 1 and 2 repeated at 3 – weekly intervals. Ifosfamide was administered at a dose of 3.0g/m^2 over a period of 3 hours on days 1 and 2, etoposide at a dose of 100mg/m^2 on days 1 and 2, carboplatin at a dose of 600mg/m^2 over a period of 2 hours on day 3. 2 Mercaptoethane sulphonate sodium [(MESNA) 360mg/m^2] was administered prior to each ifosfamide infusion and was repeated every 3 hours 24 hours after the cessation of the ifosfamide infusion. 18 patients received 62 courses of ICE and AMI (AMI group) whereas 10 patients received only 40 courses of ICE (control group). Patients of both groups were randomly selected. The median number of ICE (couplet with) AMI courses administered to each patient of the AMI group was 3 (range 2 – 6). AMI was administered at a dose of 740mg/m^2 and was being infused for 15 min prior to carboplatin administration.

In our study AMI was administered prior to the infusion of carboplatin only, because we wanted to evaluate its effectiveness in reducing carboplatin toxicity in paediatric patients with recurrent or refractory solid tumours.

Baseline evaluation included physical examination, complete blood counts and determination at concentration of electrolytes, blood urea nitrogen (BUN), serum creatinine, glucose, total protein, albumine, calcium, phosphate, the activity of AST and ALT.

Plasma calcium levels were determined before and after AMI administration and blood pressure was being measured every 5 minutes during AMI infusion. As antiemetic therapy, all patients received ondansetron, administered intravenously at a 5 mg/m^2 dose from the first day of every cycle of chemotherapy and 8 hourly thereafter until the end of each cycle. In addition, dexamethasone was given at a dose of 8mg/m^2 every 8 hours for 3 days. All patients received granulocyte – colony – stimulating factor (G – CSF) at a daily dose of 5μg/Kg starting 24 hours after completion of chemotherapy and continuing until an absolute neutrophil count (ANC) of 1500/μL was documented for 2 consecutive days after the nadir.

Myelotoxicity and nephrotoxicity were assessed by a total blood count and glomerular filtration rate (GFR) determination by the two – sample ^{51}Cr-EDTA (51 – chromium-ethylenediamino tetraacetic acid) method respectively. For both kinds of test baseline and post – treatment values were obtained. Haematological and GFR values of the AMI – group were compared to those of the control group.

Statistical analysis

The non – parametric Mann – Whitney U test was used for comparisons between AMI- and control groups. The non – parametric Wilcoxon test was applied for paired comparisons (pre – post treatment). Statistical significance was accepted for p values <0.05.

Results

AMI- and control groups did not significantly differ in baseline leukocyte and neutrophil counts, BUN, serum creatinine levels and GFR values. GFR was determined in all patients pre- and post chemotherapy after a median of 3 cycles of chemotherapy. There was a GFR decrease in 7/18 patients (38%) of at the AMI group and in 6/10 (60%) of the control group. There was a statistically significant GFR decrease in the control group as compared to the AMI – group. In the AMI – group mean GFR levels were found after three cycles of che-

motherapy to be 87.2±11.0ml/min/1.73^2 with a difference of 3.1±1.9, whereas in the control group GFR levels were pre treated 84.3±12.9 and a decrease was observed to 72.1±8.0 with a difference percent 13.9±5.7 after three cycles of treatment respectively p< 0.05). (Table 2). The

Table 2: *Change of GFR after ICE chemotherapy with or without AMI coadministration. Values represent mean±SD in cells/μl;*
D%=[(post – treatment – baseline)/baseline]x100;ns, non significant.

	Baseline	Post-treatment	D%	P
Control group	84.3±12.9	72.1±8.0	-13.9±5.7	<0.05
AMI – group	84.5±10.1	87.2±11.0	3.1±1.9	ns

increase also in both the BUN and serum creatinine levels after three cycles of chemotherapy was significantly lower in the AMI as compared to the control group (13.4 ± 5% vs 32.1±9%, P<0.05 and 16±11% vs 31.6±15.3% respectively) (Table 3). Haematological tox-

Table 3: *Change in BUN and serum creatinine levels after ICE chemotherapy with or without AMI coadministration. Values represent mean ± SD in celles/μl; D%= [(post – treatment – baseline)/baseline]x100*

	Baseline	Post-treatment	D%	P
BUN				
Control group	15±4	57±5.8	-32.1±9	<0.05
AMI-group	17±6.1	29.4±7.3	-13.4±5	<0.05
Serum creatinine				
Control group	58.3±12.7	89.9±13.4	-31±15.36	<0.05
AMI-group	52.5±14.8	67.6±17.1	-16±11	<0.05

icity was graded according to the SIOP toxicity grading criteria. Grade IV leukopenia and neutropenia were observed at a median of 7 days after each cycle of chemotherapy in both groups of patients. Conditions potentially leading to neurtropenia such as fever, sepsis or bleeding episodes, did not occur. Leukocyte and neutrophil count were significantly reduced after chemotherapy in both the control and the AMI-group. The decrease however, in both the leucocyte and the neutrophil count was significantly less in the AMI- as compared to the control group (57±12.8% vs 72.5±6.6%, p<0.05 and 52,9 ±16,5% vs 76,7 ±9,3%, p <0.05 respectively) (Table 4). The median platelet nadir was 15 x 10^3/

Table 4: *Change in leucocytes and neutrophils count after ICE chemotherapy with or without AMI coadministration. Values represent mean±SD in cells/μl; D%= [(post – treatment – baseline)/ baseline]x100*

	Baseline	Post-treatment	D%	P
Leucocytes				
Control group	3167±565	858±191	-72.5±6.6	<0.05
AMI – group	3233±163	1333±189	-57.0±12.8	<0.05
Neutrophils				
Control group	1167±163	275±121	-76.7±9.3	<0.05
AMI – group	1427±173	567±121	52.9±16.5	<0.05

μl (range 8-36x10^3/μl) in the control group and 17 x10^3/μl (range 12-48x10^3/μl) in the AMI group and occurred at a median of 14 days (range 10-20 days) and 12 days (range 10-20 days) respectively (Table 5).

At the 740mg/m^2 dose level of AMI the side effects were moderate but controllable and interruption of infusion was never required. The principal side effects related to AMI infusions were nausea and vomiting, hypotension and anxiety (Table 6). No reduction in serum calcium was observed. Hypotension, when noticed, was only slight, not requiring infusion interruption.

Discussion

AMI formally known as WR-2721 is a prodrug that forms an activated free thiol, WR-1065 when dephosphorylated by membrane – bound alkaline phosphatase. This metabolite appears to enter nonmalignant cells selectively, by facilitated diffusion, and to create a temporary state of acquired resistance to the cytotoxic effects of chemotherapeutic agents in these tissues. On the other hand the uptake of the drug and its metabolites into tumour tissue is slow or absent. This selectivity probably reflects physiological differences between normal and cancer tissues and cells, such as relatively poor tumour vascularity and more efficient enzymatic dephosporylation of AMI to WR – 1065 in normal tissues. The latter is attributed to a higher relative pH and thereby greater alkaline phosphatase activity in normal tissues as compared to cancer tissues usually exhibiting lower pH values, because of their anaero-

Table 5: *Haematopoietic Toxicity: Thrombocytopenia*

	Dose (mg/m^2)	No of patients	No. of courses	Platelet nadir (x 10^3/μL)	Day	Day at platelet count > 1000.000/μL
AMI group	740	18	62	17(12 – 48)	12(10 – 20)	28(15 – 40)
Control group		10	40	15(8 – 36)	14(12 – 22)	24(14 – 36)

Table 6: *Nonhematologic Toxicities of ICE Plus Amifostine in 18 patients (68 courses)*

Dose (mg/m^2)	No. of courses	No. of patients	Toxicity	Grade 1 and 2	Grade 3 4
740	62	18	Hypotension	5	
			Vomiting	7	5
			Anxiety	4	
			Hypocalcemia	0	
			Flushing	2	
			Rigors	2	

bic metabolism[1,4-7]. The active metabolite WR-1065 provides cellular protection by several mechanisms such as (1) acting as scavenger of oxygen free radicals (derived from radiation therapy or from specific drugs), (2) by reducing availability of dissolved O_2, (3) by deactivating reactive species (H^+ donation), (4) by preventing or reversing cisplatin – DNA adducts and (5) by facilitating DNA repair[5,6,8,9].

Both preclinical and clinical studies of various alkylating agents and platinum compounds have indicated that AMI can ameliorate drug – induced myelotoxicity and nephrotoxicity without impairing their antitumour efficacy. Cisplatin and carboplatin cause dose-related renal dysfunction in addition to increased serum creatinine levels and uraemia, electrolyte abnormalities such as hypomagnesaemia and hypocalcaemia[10,11]. Carboplatin, an analogue of cisplatin, is less nephrotoxic than cisplatin whereas its haematological toxicity is significant resulting mainly in prolonged thrombocytopenia. The platinum compounds nephrotoxic effect is on the renal tubules with the proximal tubules being most affected[5,12]. Preclinical studies with mice or rats illustrate the nephroprotective effect of AMI, which probably does not fully eliminate nephrotoxicity, but it does significantly reduce the severity and duration of nephrotoxicity[5,13]. Some clinical studies have demonstrated the efficacy of AMI as a nephroprotectant agent[6,10,14]. There are few studies in the literature reporting on a lack of protection of the proximal tubular cells by AMI in children receiving ifosfamide containing regimens. Kraker et al have reported absence of protective effect of AMI and, in some patients even evidence of deterioration in tubular function. However, each group consisted of only 4 patients[15-17]. Nephrotoxicity is a common complication of carboplatin – based regimens and can limit its use. No significant renal toxicity was observed in some studies in either group[16,17]. Glover et al studied AMI in phase I and phase II studies escalating cisplatin doses in patients with melanoma and reported decreased renal toxicity[18].

Although it is known that carboplatin is not as nephrotoxic as cisplatin, our results suggest that AMI reduces the degree of its renal toxicity. Glomerular filtration rate in patients receiving intensive carboplatin – based chemotherapy in combination with AMI were found to be less decreased as compared with the non – protectant group($13.9 \pm 5.73\%$, $p < 0.05$).

Leukopenia, neutropenia and thrombocytopenia are the most common haematologic toxicities associated with the ICE regimen. In our study, the decrease in the leucocytes and neutrophils counts in the AMI group was less statistically significant than the counts in the control group. Petrili et al have reported that there was a statistically significant leukocyte and neutrophil protection with AMI but no significant haemoglobin and platelet protection could be shown. There are some recent studies reporting that AMI is not myeloprotective. The authors suggest that there were no significant differences in the occurrence of neutropenia or thrombocytopenia between the two groups[17,19-23].

The protective dosage of AMI applied in this study was 740 mg/m^2. This accounts for 80% of the dose currently used in adults, is generally in accordance with NCI Cancer Therapy Evaluation Program, Children's Cancer Group, Pediatric Oncology Group and International Society of Pediatric Oncology guidelines or recommendations, and has been proved to be safe with relatively low side – effects[12,19,24,25]. It is important that the recommended dose be infused over 15 minutes or less as a lengthier infusion is associated with a higher incidence of side effects[17,26,27].

The most common side effects associated with AMI infusion are nausea, vomiting, hyprotension in hypocalcaemia, anxiety and facial flushing. However, when these side effects are adequately managed, the drug is well tolerated. The patients in this study tolerated the dose of 740 mg/m^2. Emesis is a common side effect of AMI and occurs more frequently when AMI is combined with highly emetogenic chemotherapeutic agents such as cisplatin or to a lesser extent carboplatin. Effective antiemetic management includes monitoring of the patient's fluid balance and antiemetics administration prior to and after AMI infusion. Therefore vigorous pre - emptive antiemetic treatment is warranted.

Clinical and/or laboratory hypocalcaemia is a known side – effect during AMI therapy, apparently due to inhibiting of parathyroid hormone the secretion[8]. However, in the dose range of 740-910 mg/m^2 symptomatic hypocalcaemia rarely occurs and was not observed in our patients. Patients at risk for hypocalcaemia e.g. those with nephrotic syndrome or those receiving hypocalcaemic agents should be closely monitored[8,22,27,28].

Coadministration of AMI with chemotherapy is feasible and seems to bear a more or less acceptable toxicity profile. The protective efficacy of AMI was demonstrated in our group of patients receiving intensive chemotherapy and was associated with less nephrotoxicity and myelotoxicity. AMI seems to be promising cytoprotective agent and its benefits should be weighed against its potential side effects and its cost. However, larger – scale studies are needed to establish its efficacy.

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