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TOXICITY PREVENTION WITH AMIFOSTINE IN PEDIATRIC OSTEOSARCOMA PATIENTS TREATED WITH CISPLATIN AND DOXORUBICIN

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□ *Amifostine has emerged as a pancytoprotectant shown protection against nephrotoxicity, neurotoxicity and ototoxicity in preclinical studies. Methods: We designed a prospective comparative randomized trial to evaluate the cytoprotective effects of amifostine in patients with osteosarcoma receiving cisplatin and doxorrubicin. Patients were evaluated for renal, hearing and cardiac toxicity. Results: We included 28 patients, mean age was 11.6 years, five had metastatic disease. Fifteen patients received amifostine and 13 did not. 20% of patients receiving amifostine developed renal toxicity compared to 30% in the control group ($p = 0.318$). Grade 1 and 2 audiologic toxicity was present in 100% of the experimental group against 85% of the controls ($p = 0.501$). Grade 1 cardiac toxicity was present in 2 patients in the control group ($p = 0.175$). There were no statistical significant differences between the two groups for chemotherapy-related toxicity. Response to chemotherapy was significantly better in the amifostine group. Conclusion: amifostine did not reduce the ototoxicity and nephrotoxicity of our treatment regime. It was not well tolerated due to emesis. It is a selective cytoprotectant without reducing the effect of chemotherapy.*

Keywords osteosarcoma, amifostine, chemotherapy-related toxicity

Survival has improved in most pediatric cancer patients. To achieve that, protocols with intensive chemotherapy and radiation therapy are used.

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Their success is often limited by toxicity to normal cells, which leads to reduction of doses and interruption in treatment. Another concern is the sequelae, which diminish the quality of life of survivors. A substance that would protect normal cells from the toxic effects of therapy without reducing its effectiveness would be ideal. Amifostine (WR-2721) has emerged as an effective and tolerable pancytoprotectant [1, 2]. Amifostine and its active metabolite WR-1065 protect normal cells without reducing the effectiveness of chemotherapy. The protective effect of amifostine is present in normal cells of multiple tissues [3–7]. Preclinical studies have shown protection against nephrotoxicity, myelosupression, neurotoxicity, and ototoxicity [8–11].

We designed a prospective comparative randomized trial to evaluate the renal, hearing, and cardiac protection and side effects associated with amifostine in pediatric patients with osteosarcoma treated with cisplatin and doxorubicin as neoadjuvant therapy at Hospital Infantil de Mexico Federico Gómez and Hospital General de México.

METHODS

Patients

We evaluated 28 consecutive patients diagnosed with osteosarcoma without prior therapy from March 1999 to December 2002. The protocol was approved by the institutional research and ethics committee; informed consent was obtained from parents of each patient.

Treatment Regime

All patients received 4 cycles of intra-arterial cisplatin 150 mg/m^2/dose every 2 weeks and intravenous doxorubicin 75 mg/m^2/dose every 4 weeks before surgery. The intra-arterial form of cisplatin has been used in our institution since 1996 to achieve higher concentrations of cisplatin at the primary site and to evaluate angiographic response to chemotherapy [12, 13]. The intra-arterial administration was carried out under sedation. Hyperhydration at 3000 mL/m^2/day, manitol 12.5 g/m^2/dose 4 times a day, potassium 30 mEq/m^2/day, and magnesium sulfate 16.5 mg/kg/day were supplemented for 72 h. All patients received ondansetron 4 mg/m^2/dose 3 times a day and dexamethasone 6 mg/m^2/day to prevent nausea and vomiting.

Patients were randomly assigned to receive or not to receive amifostine. Amifostine was administered to 15 patients (740 mg/m^2/dose) as a 15-min intravenous infusion immediately prior to any cisplatin administration. During the infusion, nausea, vomiting, hypotension, abdominal

pain, and other related symptoms were documented. Blood pressure was monitored before and every 5 min for 30 min. In case of a decreased of 20 mm Hg or more, amifostine infusion was held and saline administered as 30 mL/kg per dose; if there was a recovery, amifostine was reinitiated. Serum calcium was monitored every 24 h; if symptomatic hypocalcemia developed, 200 mg/kg of calcium gluconate was administered as an IV bolus.

Toxicity Evaluation

Baseline evaluation included complete physical examination, blood counts, chemistry, audiometry and tympanometry, urianalysis, and ejection fraction by echocardiography. This evaluation was repeated before each chemotherapy cycle and after completion of the 4 neoadjuvant cycles. Toxicities were graded according to the World Health Organization (WHO) Common Toxicity Criteria. The evaluated parameters do not differ from the NCI system.

Extension of disease was evaluated at the primary tumor by simple X-ray, and magnetic resonance, lung tomography, and nuclear bone scan were performed for metastatic disease.

Response to neoadjuvant chemotherapy was graded according to necrosis percentage after tumorectomy. Response was considered good if more than 90% necrosis was obtained, partial for 60–90%, and poor for less than 60%.

Two randomized groups were formed: 15 patients received amifostine and 13 did not. Toxicity grade was accumulative with each cycle and the final grade was taken as the valid one. The results are presented in percentage of patients with each grade of toxicity.

Statistical Analysis

We used comparison of two proportions for response to chemotherapy and toxicity between the amifostine group and the control group. The comparisons between the two groups for gender, age, and extension of disease were made using the chi-square test.

We considered $p < .05$ as statistically significant.

RESULTS

Patients

Twenty-eight patients diagnosed with osteosarcoma without prior therapy were included in the study. The mean age was 11.6 years (range 7–15). Fourteen were female. Five had metastatic disease. There was no statistical difference between the groups regarding gender, age, or stage of disease.

TABLE 1 Chemotherapy-associated Toxicity

WHO toxicity	Amifostine ($n = 15$)	Control ($n = 13$)
Renal grade		
1	3	1
2	0	1
3	0	1
4	0	1 $p = .318$
Audiologic grade		
1	13	8
2	2	2
3	0	0
4	0	0 $p = .501$
Cardiac grade		
1	0	2
2	0	0
3	0	0
4	0	0 $p = .175$

All patients were evaluated for audiologic, renal, cardiac, and infusion-related toxicities. Histologic examination for response to chemotherapy was available for all patients except one in the control group.

Chemotherapy-Associated Toxicity

Renal toxicity developed in 20% of patients receiving amifostine compared to 30% in the control group ($p = .318$). One patient in the control group required peritoneal dialysis and died of relapse. Audiologic toxicity grades 1 and 2 was found in 100% in the experimental against 85% in the control group ($p = .501$). Grade 1 cardiac toxicity was present in only 2 patients of the control group ($p = .175$). There were no statistical significant differences between the two groups for chemotherapy-related toxicity. Data are presented in Table 1.

Amifostine-Related Toxicity

There was no infusion-related hypotension in any patient in the amifostine group. All patients in the experimental group developed asymptomatic hypocalcemia. Ninety-three percent of patients receiving amifostine developed grade 3 vomiting toxicity against 7% in the control group. ($p = .000$) No other secondary effects were reported.

Response to Chemotherapy

Response to chemotherapy was significantly better in the experimental than in the control group ($p = .043$). Response is summarized in Table 2.

TABLE 2 Response to Chemotherapy

Necrosis	Amifostine ($n = 15$)	Control ($n = 12$)
>90%	8	6
60–90%	6	1
<60%	1	5

DISCUSSION

In this study, we used a high-dose cisplatin-based regimen in a short time, reaching 600 mg/m^2 total dose in 6 weeks. Nephrotoxicity is usually the dose limit toxicity of cisplatin-based therapy, in our study 25% of patients developed it. The toxicity observed was mainly mild but 7% had grade 3 and 4 nephrotoxicities; these 2 cases were in the control group. The nephrotoxicity presented in our study was higher than that reported by Petrilli et al., possibly because we use a higher dose of cisplatin per cycle [14]. There was no significant reduction of toxicity with the use of amifostine.

Another dose-limiting toxicity of cisplatin is ototoxicity. It is reported in 36% of patients receiving 50–100 mg/m^2; in higher-dose regimens it is as high as 90% [15]. Marina et al. reported the use of amifostine in children with germ cell tumors receiving high-dose cisplatin. Of 34 evaluable patients, 75% had significant hearing loss. They concluded amifostine did not protect against ototoxicity produced by high-dose cisplatin combined with etoposide and bleomycin [16]. In our study, we observed ototoxicity in 100% of patients receiving amifostine, and 76% of controls. As reported by Marina et al., amifostine did not protect patients from ototoxicity.

We did not observe significant cardiac toxicity, maybe because the cumulated dose of doxorubicin was 150 mg/m^2, a lesser dose than the known toxic dose. We cannot conclude the role of amifostine in heart protection.

All patients receiving amifostine developed grade 3 and 4 emesis in contrast to 7% in the control group despite the recommended support with ondansetron and dexamethasone. Also, they all presented transient asymptomatic hypocalcemia. We did not observe the commonly reported secondary effects associated with amifostine of slight somnolence, dizziness, sneezing, and facial flushing [17]. It may be due to the fact that our patients are under sedation during amifostine infusion.

Response to chemotherapy was significantly better in the amifostine group, demonstrating that amifostine is a cytoprotective agent not affecting the efficacy of chemotherapy in osteosarcoma. To our knowledge, the are few randomized prospective studies evaluating amifostine in previously untreated children receiving chemotherapy eliminating the possibility of

bias due to previous toxicity. We can conclude that amifostine used in the doses and schedule described here did not reduce the ototoxicity and nephrotoxicity of our treatment regime. It was not well tolerated due to vomiting and it produces transient asymptomatic hypocalcemia that does not require treatment. It is a selective cytoprotectant without reducing the effect of chemotherapy.

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