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Amifostine Efficacy and Safety in Paediatric Patients with Recurrence Solid Tumours

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S u m m a r y. Preclinical and clinical evaluation of AMI when it is administered in conjunction with systemic chemotherapy supports its role as a cytoprotective agent of normal tissues without impairing the antitumour effectiveness of chemotherapetic agents. We investigated the protective effect of AMI against carboplatin-induced myelotoxicity and nephrotoxicity in 18 children, since only limited studies have been performed for the clinical experience of AMI in pediatric patients with malignacies. AMI was administered in 10 of 18 pediatric patients with recurrent solid tumours along with ICE (ifosfamide, carboplatin, etoposide) chemotherapy. A significant (p<0,05) decrease in GFR was observed in the non AMI group (8 patients) whereas in the AMI-treated group (10 patients) GFR was maintained at its pretreated levels. Leukopenia and neutropenia were significantly (p<0,05) less frequent in AMI-group but there was no difference concerning thrombocytopenia. AMI was generally well tolerated at the dose of 740mg/m^2. Side effects including nausea, vomiting, hypotention, flushing and rigors were moderate and reversible and the interruption of infusion was never required.

INTRODUCTION

Amifostine (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 (1,2).

The aim of the present study was undertaken to expand the clinical experience of amifostine in pediatric patients with malignancies and in particular, to investigate the efficacy of AMI in the prevention or limitation of nepphrotoxicity after high dose ICE (carboplatin, ifosfamide, etoposide) chemotherapy in pediatric 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 (3,4).

PATIENTS AND METHODS

From March 1999 to December 2000 18 pediatric patients (10 boys and 8 girls) of a median age 6,5 years (range 2-14), suffering from recurrent solid tumors, were enrolled in the study. Five patients were affected by Wilms' tumour, five by Ewing's sarcoma, one by hepatocellular carcinoma, two by hepatoblastoma, two by nasopharyngeal carcinoma and three rhabdomyosarcoma. All 18 patients received 64 courses of the ICE protocol for recurrent paediatric tumours. The ICE protocol included ifosfamide (3 g/m^2) on days 1 and 2, carboplatin (600mg/m^2) on day 3 and etoposide (100 mg/m^2) on days 1 and 2 repeated at 3 – weekly intervals. Ten patients received 38 courses of ICE and AMI (AMI group) whereas 8 patients received only ICE (control group). Patients of both groups were by randomisation. The median number of ICE plus AMI courses administered to each patient of the AMI group was 3 (range 2-6). AMI was administered at a dose of 740 mg/m^2 and was being infused for 15 min prior to carboplatin administration. Plasma calcium levels were determined before and after AMI administration and blood pressure was being measured every 5 minutes during AMI infusion.

Myelotoxicity and nephrotoxicity were assessed by a total blood counts and glomerular filtration rate (GFR) determination by the two–sample ^{51}Cr-EDTA 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.

RESULTS

AMI- and control groups did not significantly differ in baseline leucocyte and neutrophil counts and GFR values. GFR was determined in all patients pre- and post chemotherapy after median of 3 cycles of chemotherapy. There was a statistically significant GFR decrease in the control group as compared to the AMI-group. In the AMI-group GFR levels were maintained after three cycles of chemotherapy to 87.2±11.0 ml/min. 1,73 with a difference 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 correspondingly ($p<0.05$). Haematological toxicity was graded according to SIOP toxicity grading criteria. Grade IV leukopenia and neutropenia were observed at a median of 7 days after each cycle of chemotherapy in the both groups of patients. Conditions potentially leading to neutropenia, such as fever, sepsis or bleeding episodes, did not occur. Leucocyte as well as neutrophil counts 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-group 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). The median platelet nadir was $15x10^3/\mu l$ (range $8\text{-}36x10^3/\mu l$) in the control group and $17x10^3/\mu l$ (range $12\text{-}48x10^3/\mu l$) in the AMI group and occurred at a median of 14 days (range 10-20 days) and 12 days (range 10-20 days) respectively.

At the 740 mg/m^2 dose level and 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. No reduction in serum calcium was observed. Hypotension, when noticed, was only slight, not requiring infusion interruption.

CONCLUSION

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 a weighted promising cytoprotective agent and its benefits should be against its potential side effects and its cost. However, larger-scale studies are needed to establish its efficacy (2,3,4).

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