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Letter to the Editor

Chemotherapy Induced Emesis may Exacerbate the Nephrotoxicity of Combined Ifosfamide/Mesna and Cisplatin Chemotherapy

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A RECENT comment on the nephrotoxicity of chemotherapy in this journal does not mention ifosfamide nephrotoxicity [1]. Both clinical and subclinical nephrotoxicity caused by ifosfamide has been described, and prior or concomitant treatment with cisplatin may potentiate the clinical or subclinical toxic effects [2–4]. Although mesna can largely prevent the urothelial toxicity of ifosfamide the influence of mesna on the nephrotoxicity of ifosfamide is uncertain [2]. We observed two young patients who developed acute renal failure and myelosuppression after combined cisplain and ifosfamide/mesna. Although patients had potentially nephrotoxic chemotherapy before the combination of cisplatin and ifosfamide/mesna, both had good renal function immediately before the latter combination. Despite antiemetic drugs, both patients had prolonged vomiting of delayed onset after cisplatin plus ifosfamide/mesna leading to dehydration which we considered to be an important contributing factor in the development of renal failure.

A 23-year-old man with unilateral renal agenesis and compensatory hypertrophy of the contralateral kidney, developed a right testicular teratoma, with extensive lymph node mestatases. He was given intravenous (i.v.) cisplatin 20 mg/m^2 daily for 5 days and etoposide (VP16) 120 mg/m^2 on days 1, 3 and 5 of cisplatin therapy and treatments were repeated at 21 day intervals to a total of four cycles. In addition bleomycin 30 mg was infused i.v. once weekly to a total of 12 infusions (BEP), and his cancer responded completely. Six months later, because of tumour relapse, he was given cisplatin 100 mg/m^2 once and vinblastine 10 mg i.v. each day for 2 days, with i.v. hydration and he was also given ifosfamide and mesna 5 g/m^2. Ifosfamide was given as a 24 h i.v. infusion of 5 g/m^2 in 3 l of normal saline preceded by 1 g/m^2 i.v. bolus of mesna. Four grams of mesna per square metre were then given by i.v. infusion over a 32 h period starting at the same time as ifosfamide. Immediately before this combination chemotherapy 24 h creatinine clearance was >80 ml/min and serum urea and creatinine were normal. Five days after leaving hospital the patient represented with severe anorexia and continuous nausea with multiple daily vomits and he was clinically dehydrated and oliguric. Serum urea was >40 mmol/l (normal ≤7 mmol/l) and serum creatinine was 1075 μmol/l (normal ≤124 μmol/l). The patient had a total white cell count of 100/mm^3 and a platelet count of 19,000/mm^3. Following i.v. fluid and electrolyte replacement and platelet transfusions the patient entered into the polyuric phase of renal recovery. Chronic renal and bone marrow failure subsequently ensued, and further cytotoxic therapy was not possible.

A 17-year-old male had widespread non-Hodgkin's lymphoma. Doxorubicin, vincristine, bleomycin and cyclophosphamide all i.v. were given on day 1 and cycles were repeated at 21 day intervals. On day 15 of each cycle a 4 h i.v. infusion of methotrexate 200 mg/m^2 was given, and on day 16, folinic acid rescue was administered. Four cycles were given and chemotherapy was then changed to

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vindesine, methyl prednisolone and VP16 i.v. on day 1 with oral VP16 on days 2 and 3 and oral chlorambucil on days 1, 2 and 3. A total of three cycles was given at 21 day intervals. Because of persisting lymphoma cisplatin 100 mg/m^2 i.v. with i.v. hydration was then given. Ifosfamide and mesna were also given as previously described. Three such courses of cisplatin and ifosfamide/mesna were given each at 21 day intervals. Serum urea and creatinine were normal and 24 h creatinine clearances were >80 ml/min during chemotherapy and immediately before the third course. Seven days after leaving hospital following the third course of chemotherapy the patient represented with severe anorexia and continuous nausea with multiple daily vomits and was dehydrated and oligouric. Serum urea was >40 mmol/l and creatinine was >900 μmol/l, and a total white cell count was 1300/mm^3. Intravenous rehydration and two episodes of haemodialysis resulted in an improvement in renal function and serum creatinine and urea became normal 1 month later.

There are current EORTC sponsored studies assessing the combination of ifosfamide/mesna with cisplatin and VP16 (VIP) to treat high volume metastatic germ cell cancer. In contrast to the mode of administration of ifosfamide/mesna and cisplatin in our report, these drugs are fractionated over 5 days in the EORTC studies and this may be less toxic than 24 h continuous infusions of ifosfamide/mesna [2, 4, 5]. Furthermore fractionated ifosfamide/mesna and also cisplatin over 5 days allows for both a longer duration of intravenous hydration and observation for toxic effects. Nonetheless patients should be frequently reviewed during the first week after combined ifosfamide/mesna and cisplatin therapy to ensure that emesis is not causing dehydration and for some patients prolonged i.v. hydration may be necessary.

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