Eur J Cancer Clin Oncol, Vol. 25, No. 12, pp. 1903–1904, 1989.
Printed in Great Britain

0277-5379/89$3.00 + 0.00

Letter to the Editor

Can Bismuth Decrease the Kidney Toxic Effect of *Cis*-Platinum?

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THE CHEMOTHERAPEUTIC effect of *cis*-platinum in the treatment of testicular and ovarian cancer is well established. Side-effects in the form mainly of kidney damage are, however, often pronounced and may result in premature termination of treatment resulting in incomplete remission and cure [1, 2].

We therefore found it of considerable interest when a kidney protective effect of bismuth compounds was demonstrated in mouse experiments by Naganuma *et al.* [3]. Experimental evidence in mice points to a mechanism based on the induction in the kidneys of metallothionein by bismuth which in turn, by binding the platinum, obliterates the toxic effect of the latter.

A clinical protocol was set up to test this hypothesis in patients with stage III and IV ovarian cancer given a combination therapy consisting of *cis*-platinum 60 mg/m^2, doxorubicin 40 mg/m^2 and cyclophosphamide 500 mg/m^2, after hydration with 1.5 l 0.88% NaCl. This treatment was given every month for six courses.

Bismuth was given orally as bismuth subsalicylate 1 g times 5 over the 30 h preceding the start of the chemotherapy to allow time for induction of metallothionein synthesis. To monitor the kidney toxic effect of *cis*-platinum and a possible protective effect of pretreatment bismuth, the following tests were carried out:

Accepted 6 September 1989.
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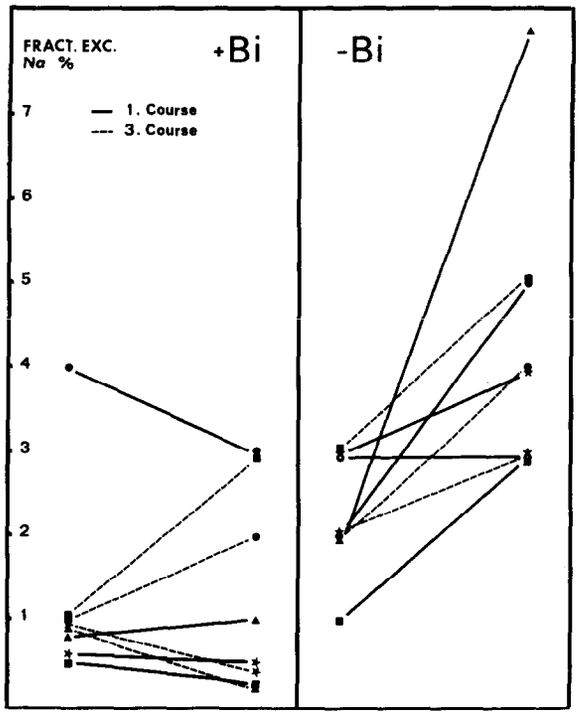
PAH clearance for determining the kidney blood flow, and inuline and creatinine clearances to monitor the glomerular filtration rate. Lithium clearances were used to determine the tubular location of the damage (and/or protection). Furthermore, the fractional excretion of Mg, Ca, K and Na was calculated based on determinations of the ions in plasma and urine. Lithium carbonate, 600 mg, was given orally 12 h before the start of therapy. Inuline was continuously infused 2 g/h after a bolus injection of 5 g. Urine was collected at timed intervals from a catheter a demeure placed before the start of the infusion.

Ten women with advanced ovarian cancer were randomly allocated to the investigation after informed consent, and the study was approved by the local ethical committee. One was subsequently taken off the protocol due to rapid deterioration of her clinical condition. This left us with four women on bismuth supplement and five controls. In each patient the investigations were carried out on three consecutive series of treatment spaced with 1 month's interval. In all of the patients a moderate to severe kidney toxicity was demonstrated with a marked drop in creatinine and inuline clearance. We found no difference in kidney blood flow and glomerular filtration between the groups. Little or no difference was observed for the excretion of magnesium, calcium, potassium as expressed by the calculated fractional excretion rates. There was, however, a marked difference in the total fractional excretion of sodium (Fig. 1) as well as for the



proximal and distal tubuli taken separately between the group given bismuth and the control group, indicating a protective effect of bismuth.

The effect is small and the clinical relevance may be minimal. It is, however, not improbable that the effect might be optimized by different time schedules for the bismuth dosage (more time for metallothionein synthesis) or by use of other inducer metal ions such as Zn. We found it unrealistic to increase the dose of bismuth over 30 h due to its obstipative effect, which was already pronounced at the given dose. Supplement with selenium has been suggested [4] and should be investigated in more detail.

Fig. 1. Fractional excretion of sodium in bismuth-pretreated and controls before and during the first and third courses.

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