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Letter to the Editor

Cyclophosphamide Cystitis and Bladder Cancer. A Hypothesis

PETER J. COX

Department of Biochemical Pharmacology, Chester Beatty Research Institute, Institute of Cancer Research, Royal Cancer Hospital, Fulham Road, London, SW3 6JB, United Kingdom

CYCLOPHOSPHAMIDE is the only anti-tumour alkylating agent in common clinical use which causes specific urological damage [1]. In addition, several reports link cyclophosphamide therapy and subsequent bladder carcinoma. A survey of 64 patients, treated with cyclophosphamide and who subsequently developed a malignancy, showed that of those originally treated for primary neoplasm, 32% of the cyclophosphamide-related tumours were in the bladder [2]. Case reports for a total of 14 patients have appeared relating prolonged cyclophosphamide treatment, haemorrhagic cystitis and tumours of the bladder [3–6].

Although cyclophosphamide cystitis was presumed to be due to alkylating metabolites of cyclophosphamide, it has now been demonstrated that acrolein, formed during metabolism, is the causative agent [7]. Alkylating and non-alkylating metabolites or analogues of cyclophosphamide were tested *in vivo* against the rat bladder and only those with the potential for forming acrolein within the bladder were capable of causing oedema and haematuria. Alkylating metabolites in the urine did not cause haemorrhagic cystitis.

It would now appear possible to explain the apparently high incidence of bladder tumours as opposed to other malignancies, secondary to cyclophosphamide treatment, by the following hypothesis. Following administration of the drug, acrolein is released within the bladder and damages the epithelium, causing rapid necrosis and oedema. The subsequent epithelial regeneration and hyperplasia are extremely rapid [8, 9], massive and prolonged [10]. This rapid hyperplasia means that more cells are brought into cycle; thus alkylating metabolites in the urine, including phosphoramide mustard and no < -nitrogen mustard, are able to interfere with nucleic acid replication more effectively than would be the case in the normal bladder epithelium. This in turn leads to an increased probability of clastogenic and carcinogenic changes in the genetic material.

If this hypothesis is correct, even in part, the implications are clear. Firstly, patients suffering haematuria, indicative of haemorrhagic cystitis, may have a higher than average chance of developing secondary bladder cancer; secondly, damage of less severity than that sufficient to cause overt cystitis may be sufficient to promote carcinogenesis by alkylating metabolites; thirdly, every effort should therefore be made to counteract acrolein in the urine, by installation of *N*-acetyl-L-cysteine or other aldehyde-trapping reagent in the bladder, or by their oral or i.v. administration. It is clear that the timing of the trapping agent dose relative to the cyclophosphamide dose is quite critical [7] and depends on the pharmacokinetics of both compounds. It would thus be necessary to study this clinically. However, the possibility of reducing the incidence of bladder tumours secondary to cyclophosphamide seems sufficiently attractive from the patient's point of view to warrant such a study.

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