Interleukin-2 Therapy and Renal Enzyme Excretion in Patients with Metastatic Colorectal Cancer

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Dear Sir,

Recent interest in the treatment of malignancy with biological response modifiers has focused on the use of recombinant interleukin-2 (rIL-2). However, one of the major side-effects has been rIL-2-induced nephro-toxicity, which has been assessed previously by using measurements of serum urea, creatinine and less commonly, creatinine clearance rates [1,2]. However, significant renal cell damage must be present before there is evidence of reduced renal function. Recent studies have demonstrated that the release of specific enzymes into the urine is a sensitive indicator of renal cell damage occurring prior to a deterioration in renal function [3]. In particular, N-acetyl-β-D-glucosaminidase (NAG), found predominantly in the lysosomes of the proximal tubular cells, and the brush border enzymes γ-glutamyl transferase (GGT) and alanine aminopeptidase (AAP), have been used as indicators of renal damage [4].

We have evaluated, therefore, 9 patients with metastatic colorectal cancer receiving a constant intravenous infusion of rIL-2 (Pro-leukin®, Eurocetus BV, Amsterdam, The Netherlands; 18×10^6 IU/m² body surface area/24 h for a total of 120 h) and one pulse of 5-fluorouracil (600 mg/m² body surface area), and folinic acid (25 mg/m² body surface area), also given intravenously 48 h later. Prior to commencing any treatment, the activities of NAG, AAP and GGT were measured in the patients urine [5]. In addition, the urinary activities of these enzymes were measured 72 h later, during the rIL-2 infusion (day 3), 48 h after the rIL-2 had finished (day 7) and on a final occasion 3 weeks later (day 28). The results are shown in table 1.

Previous studies have suggested that IL-2-induced nephrotoxicity may be due to a pre-renal component together with an intrinsic renal component [6]. Also, in vitro studies have revealed that rIL-2 is directly toxic to renal tubular cells [7]. Our studies have shown that within 72 h of commencing rIL-2 therapy there were substantial increase in the excretion of both lysosomal and brush border enzymes, which are predominantly located in the proximal tubule. Furthermore,

the activities of AAP and GGT remained elevated 48 h after rIL-2 therapy had finished, but all enzyme activities had returned to normal 21 days after cessation of therapy. We have shown previously that rIL-2 therapy results in disturbances of glomerulotubular function, as assessed by renal tubular handling of sodium and water and NAG enzymuria in vivo, in man

[8]. The increase in enzyme excretion reported here would also be consistent with damage to the proximal tubular cells, either directly by rIL-2 or possibly due to renal ischaemia induced by rIL-2. These changes preceded any deterioration in renal function as revealed by serum urea and creatinine concentrations, and were transitory, with enzyme activities returning to normal within 3 weeks. Enzymuria, therefore, is a sensitive, non-invasive measure of renal dysfunction induced by rIL-2. Such findings, therefore, may alert the clinician, at an early stage, to the possibility of a renal insult prior to overt clinical or biochemical disturbances becoming manifest.

Table 1. Enzymuria and rIL-2 therapy

Pre-rIL-2 Day 3

Day 7

Day 28

AAP, IU/mmol urine creatinine	3 ± 3
GGT, IU/mmol urine creatinine	6 ± 4
NAG, IU/mmol urine creatinine	44 ± 5
Serum creatinine, µmol/l	77 ± 4
18 ± 9**	15 ± 8**
21 ± 11**	22 ± 6**
105 ± 5**	101 ± 19
89 ± 8	84 ± 6
79 ± 6	

Values shown are means ± SEM; * p < 0.05, ** p < 0.01, compared with pre-treatment values.

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