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Renal toxicity of the anticancer drug fostriecin

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Abstract *Purpose*: Fostriecin is an inhibitor of topoisomerase II catalytic activity. In a phase I trial we observed renal toxicity, documented as a rise in serum creatinine, which was reversible and non-dose-limiting. The purpose of this study was a detailed analysis of this toxicity. *Methods*: A total of 20 patients received fostriecin as a 1-h i.v. infusion daily × 5 at doses ranging from 2 to 20 mg/m^2 per day. Serum creatinine determination and urinalysis were performed daily during drug administration. Renal hemodynamics were measured by means of clearance studies using ^{125}I-iothalamate and ^{131}I-hippuran in eight patients at doses of ≥4 mg/m^2 per day at baseline, on day 3 or 4 during the first course, and 3 weeks after the second course. *Results*: The rise in serum creatinine was maximal after one to two doses despite continued administration. This increase showed no correlation with the dose level at fostriecin doses of ≥4 mg/m^2 per day. Urinary β_2-microglobulin concentrations increased 150-fold (median), which is compatible with impaired tubular reabsorption. The median change in the glomerular filtration rate (GFR) was −36% (range −28% to −44%), that in effective renal plasma flow (ERPF) was −23% (range −11% to −36%), and the filtration fraction (FF) decreased in all patients during the first course of treatment. The values measured 3 weeks after the second course, however, did not differ from baseline. *Conclusions*: Fostriecin induces reversible renal hemodynamic changes compatible with renal tubular damage.

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Introduction

Fostriecin is a novel antitumor antibiotic with a chemical structure unrelated to that of other drugs [18]. In vitro it has shown activity against murine leukemias P388 and L1210 and against human solid-tumor cell lines in a clonogenic assay [9, 17]. Its clinical development was initiated particularly because fostriecin is an inhibitor of the catalytic activity of DNA topoisomerase II (topo II) [2]. Catalytic inhibitors of topo II are considered to be of potential value for use against tumors with specific drug resistance to classic topo II-directed drugs, such as etoposide and doxorubicin, because of decreased topo II levels [11]. Other possible mechanisms of action of fostriecin include the inhibition of nuclear protein phosphatases involved in cell-cycle regulation and of histone phosphatases involved in chromosome condensation [8, 12].

Renal toxicity has been observed in animal studies [19], but the toxicity profile of fostriecin in humans has thus far remained unknown. We recently performed a clinical phase I trial, and as early as at the lowest doses tested we observed remarkable renal toxicity, documented as a rise in serum creatinine [4]. The overall results of the phase I trial will be reported separately. The purpose of this report is to provide a detailed analysis of the renal toxicity. For further documentation and analysis of this side effect we performed accurate studies on renal hemodynamics in eight patients.

Patients and methods

Patients and drug administration

A total of 20 patients (13 men and 7 women) with advanced malignant disease no longer amenable to established forms of

treatment were entered in the phase I study. The median age was 50 years (range 23–71 years). All patients had solid tumors, and the most common primary disease involved colon or rectal cancer in ten patients and non-small-cell lung cancer in four. None of the patients was known to have renal disease or urological disorders. The mean baseline serum creatinine level was 81 μmol/l (range 42–113 μmol/l). The mean baseline creatinine clearance, based on a 24-h period of urine collection, was 120 ml/min (range 73–190 ml/min). No patient had proteinuria at baseline. One patient had non-insulin-dependent diabetes mellitus as a risk factor for renal disease. No patient had received platinum chemotherapy. Written informed consent was obtained from all patients, and the protocol was approved by the Medical Ethics Committee of the Groningen University Hospital.

Fostriecin (supplied by the National Cancer Institute, Bethesda, Md., USA) was diluted in 0.9% NaCl to a total volume of 50 or 100 ml and was given as a 1-h i.v. infusion daily for 5 days (days 1–5) every 4 weeks. Each infusion started at 2:00 p.m. A total of 42 courses were given at the scheduled dose to the 20 patients. Six patients received one course; ten patients, two courses; and four patients, four courses. For 5 days, four patients received daily doses of 2 mg/m^2; five, 4 mg/m^2; three, 6.6 mg/m^2; three, 10 mg/m^2; three, 12.2 mg/m^2; and two, 20 mg/m^2 (the protocol was amended during the study to allow more rapid dose escalation).

The patients did not receive premedication or concomitant i.v. hydration. No patient received angiotensin-converting enzyme (ACE) inhibitors or antihypertensive medication. One received a nonsteroidal anti-inflammatory drug continuously. Metoclopramide was given during 12 courses, but this coincided in only 2 patients during the hemodynamics study as described below. Thus, it was unlikely that concomitant medication had a significant influence on the results.

Patient monitoring

Serum concentrations of creatinine, urea, and electrolytes were measured immediately before the start of treatment, daily during treatment (prior to drug infusion), and twice weekly during treatment-free intervals. For evaluation, a >10% increase in serum creatinine from baseline was considered significant, and recovery was defined as a serum creatinine value <10% higher than baseline. Since percentage changes in renal function can more accurately be presented using the inverse of serum creatinine (1/serum creatinine) than by using serum creatinine levels, we used the inverse of serum creatinine for this purpose. Supine blood pressures were measured with a sphygmomanometer immediately before and after each fostriecin infusion. Urinalysis was performed daily during treatment and weekly during treatment-free intervals. Initially, dipstick investigations were performed, with additional microscopic examination being carried out in the case of abnormal test results. Beginning at the dose level of 6.6 mg/m^2 per day, urine microscopy and 24-h collection for proteinalysis was standard in all patients. At doses of ≥6.6 mg/m^2 per day, samples for determination of urinary and serum β_2-microglobulin concentrations were collected daily during treatment. β_2-Microglobulin concentrations (urine and serum) were measured using a particle-enhanced nephelometric assay (Behring, Marburg, Germany).

Renal hemodynamics were measured by means of radioisotopes in 8 of the 16 patients treated at ≥4 mg/m^2 per day (2 at 4 mg/m^2 per day; 1 at 6.6 mg/m^2 per day; 2 at 10 mg/m^2 per day; 3 at 12.2 mg/m^2 per day). Baseline studies were performed within 2 weeks of fostriecin treatment. A second study was performed before drug infusion on day 3 or 4 of the first course because this was nearest the expected serum creatinine peak level. A third study was performed 3 weeks after course 2 (week 8). The glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were measured simultaneously in patients assuming the supine position; the GFR was determined [^{125}I]-iothalamate clearance and the ERPF, by [^{131}I]-hippuran clearance [6]. The filtration fraction (FF) was calculated by the formula $FF = GFR/ERPF$.

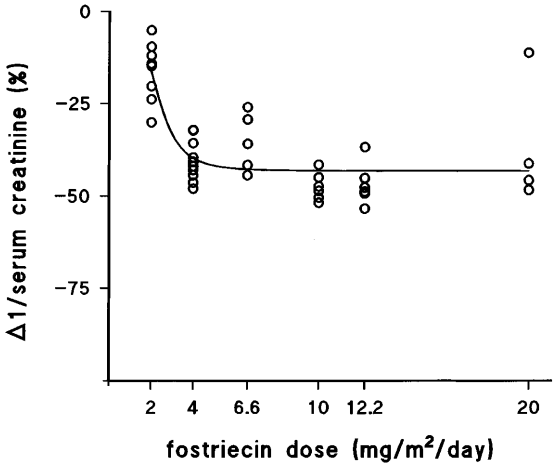

Fig. 1 Maximal change in renal function, expressed as [(*1/peak serum creatinine*)−(*1/baseline serum creatinine*)]/(*1/baseline serum creatinine*) × *100*%, observed during fostriecin administration (42 courses in total) versus the dose. The dose-response curve was fitted to an asymmetric sigmoid model [$y = (E_{max} \times x^s)/(X_{50}^s + x^s)$, $s = 4.20$, $X_{50} = 2.25$ mg/m^2 per day; $r^2 = 0.61$]

Statistical analysis

Wilcoxon's test (two-sided) for paired observations was used to test for differences between measurements within subjects. A P value of <0.05 was considered to be statistically significant. The relationship between the dose and the change in serum creatinine was examined using the sigmoid E_{max} model [14] according to the following equation: $y = (E_{max} \times x^s)/(X_{50}^s + x^s)$, where E_{max} is the maximal change in clearance, X_{50} is the dose that gives 50% of E_{max}, and s is the shape factor that accommodates the shape of the curve. The fit of the model was based on the least sum of squares.

Results

Serum creatinine, urea, and electrolytes

Significant elevations of serum creatinine were observed in most patients at the starting dose level and in all patients at doses of ≥4 mg/m^2 per day. The maximal decrease in renal function versus the fostriecin dose level during all courses is depicted in Fig. 1. Examination of the dose-effect curve showed that a plateau was reached at daily doses of ≥4 mg/m^2. This allowed the pooling of data from patients who received doses ranging between 4 and 20 mg/m^2 per day for examination of the course of serum creatinine levels measured during fostriecin administration (Fig. 2). Serum creatinine values increased immediately after the first dose, and a maximum was reached on day 3 (i.e., after dose 2) in the majority of courses. Subsequently, serum creatinine values stabilized despite continued drug administration. After drug discontinuation they recovered within 1–2 weeks (median time of recovery, days 10–11; range, day 5 to day 19). In the patients who received at least two courses there was no difference between course 1 and course 2 with regard to the maximal rise in serum creatinine ($n = 12$; $P = 0.13$). Serum urea levels did not increase above

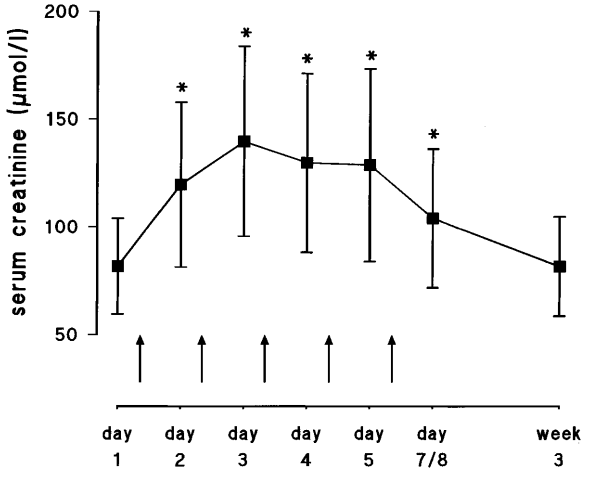

Fig. 2 Mean serum creatinine levels determined for 34 courses at 4–20 mg/m^2 per day (*bars* SD). *Arrows* indicate fostriecin infusion on days 1–5. Mean serum creatinine values recorded on day 1 (baseline), days 2–5, and day 7 or day 8 (whichever available) and the mean of the first value noted between day 15 and day 21 (week 3) are presented

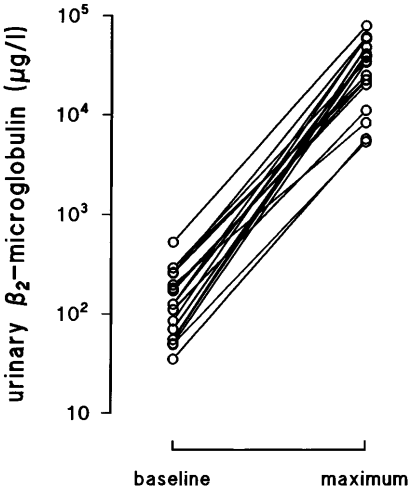

Fig. 3 Maximal increase in urinary β_2-microglobulin excretion as determined during fostriecin administration (data from 18 courses in 11 patients)

7.5 mmol/l during fostriecin administration, and the mean difference between serum urea values recorded on the day serum creatinine reached its peak and those noted at baseline was +1.3 mmol/l. This made a prerenal cause of the renal disorder unlikely. Fostriecin administration was also not accompanied by any consistent change in blood pressure.

In this study, only minor electrolyte abnormalities were encountered during fostriecin administration. Grade 1 hypokalemia was observed in five patients; grade 1–2 hyponatremia, in three cases; and grade 1 hypocalcemia, in four patients. Hypouricemia was not observed.

Urinary abnormalities

No patient developed oliguria (<500 ml/24 h). Transient proteinuria was detected in all patients at doses of ≥10 mg/m^2 per day (median 1.9 g/24 h, range 1.0–3.3 g/24 h). Microscopic hematuria was observed in 7 patients treated at doses of ≥6.6 mg/m^2 per day, and granular casts were found in the urine of 12 patients during drug administration at daily doses of ≥4 mg/m^2. Glucosuria was observed in two patients. Only peak urinary β_2-microglobulin concentrations were considered for this analysis (Fig. 3). Peak urinary β_2-microglobulin concentrations were 10- to 900-fold those measured at baseline (median 150-fold). The corresponding serum β_2-microglobulin concentrations increased maximally 2.2-fold relative to baseline (median 1.6-fold; $P < 0.01$). The latter was compatible with the observed reduction in GFR, as β_2-microglobulin is almost completely excreted by glomerular filtration [16]. The much larger increase in urinary β_2-microglobulin concentration was therefore attributable not to increased β_2-microglobulin formation but to renal tubular dysfunction.

Renal hemodynamics

The course of serum creatinine levels measured during courses 1 and 2 in the eight patients included in the isotope studies is depicted in Fig. 4. The median change observed in 1/serum creatinine during the courses in which the isotope studies were performed was −41% (range −32% to −48%). This indicates that these eight patients were representative for the dose range of 4–20 mg/m^2 per day (also see Fig. 1). In four patients the GFR and ERPF were measured on the same day the peak serum creatinine level was reached; in two patients, 1 day later; and in two cases 1 day earlier. The changes in observed GFR and ERPF in these patients are

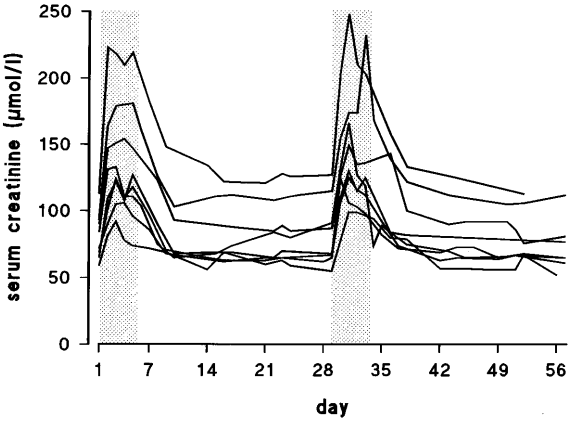

Fig. 4 Course of serum creatinine levels measured during courses 1 and 2 in the eight patients included in the renal hemodynamics studies. The *shaded areas* indicate fostriecin administration on days 1–5 of each course

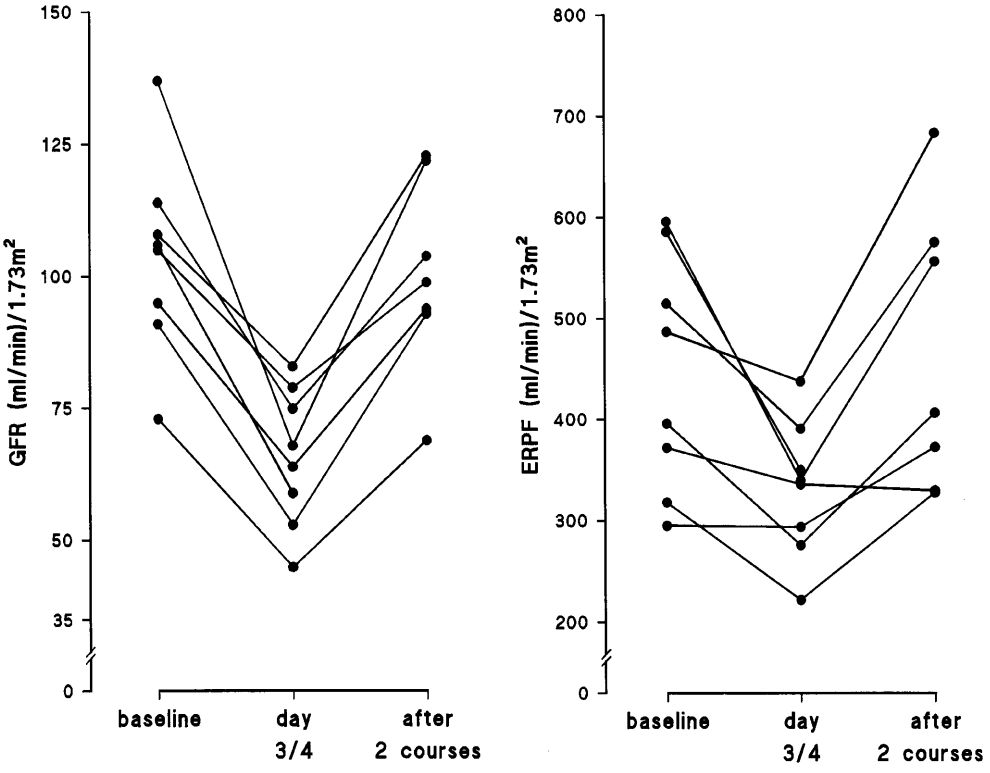

Fig. 5 GFR and ERPF (normalized to body surface area) values relative to baseline as recorded on day 3 or 4 of fostriecin course 1 ($n = 8$) and 3 weeks after course 2 ($n = 7$). The difference after 2 courses was not statistically significant relative to baseline

summarized in Fig. 5. The GFR and ERPF decreased in all patients. The median change in GFR was −36% ($P = 0.01$; range −28% to −44%) and that in ERPF was −23% ($P = 0.01$; range −11% to −36%). The FF also decreased in all patients (median −13%, range −4% to −42%; $P = 0.01$). This implies that the GFR always decreased more than the ERPF. After 2 courses, GFR and ERPF did not differ from baseline ($n = 7$; 1 patient refused follow-up). Thus, no irreversible loss of renal function was detected.

Discussion

The renal effects of fostriecin were characterized by the absence of a clear dose-effect relationship at doses of ≥4 mg/m^2 per day and by a maximal effect after the first or second of five consecutive daily doses. Thus, toxicity did not increase but rather declined after day 3 despite continued drug administration. This renal toxicity of fostriecin was not considered to be dose-limiting because it was rapidly reversible.

The renal hemodynamics studies were scheduled to coincide with the maximal serum creatinine concentration measured during fostriecin administration. Therefore, these studies provide an accurate estimate of the maximal decrease in GFR indicated by the elevated serum creatinine levels. The median decrease of 36% implies a considerable loss of renal function. During fostriecin administration, high urinary β_2-microglobulin concentrations were observed, which indicated a renal tubular abnormality. This is supported by histology studies in rats, where morphological changes in the renal tubular epithelium were observed as soon as 8 h after fostriecin infusion [19]. Although we did not measure the urinary β_2-microglobulin/creatinine ratio, it is unlikely that the observed median 150-fold increase in urinary β_2-microglobulin could be explained by an overall increase in urine concentration. Moreover, diuresis was not decreased during fostriecin administration (data not shown).

A renal tubular abnormality is compatible with the observed renal hemodynamic changes. The observed fall in GFR could have resulted from increased tubular pressure due to narrowing of the tubular lumen because of cellular swelling or interstitial edema. In addition, the presence of casts in the urine suggests that obstruction by cellular debris may have occurred. That the FF decreased in all eight patients further supports a tubular abnormality as the major toxic change. In contrast, no decrease in FF is expected when the primary change is a fall in renal plasma flow, e.g., due to afferent arteriolar vasoconstriction [13]. Tubular epithelial dysfunction might also explain the decreased ERPF, as renal hippuran extraction is a function of tubular secretion. Other observations in the present study that were consistent with a primarily tubular insult include the slight increase in serum urea as compared with creatinine (because filtered urea is normally subject to tubular reabsorption) and the only mild proteinuria. Although electrolyte abnormalities were minimal and were found in only a minority of patients in this study, a detailed analysis of the urinary and the fractional excretion of calcium, phosphate, urate, and other electrolytes should be incorporated in future studies of the renal toxicities of fostriecin.

Toxic nephropathy can be accompanied by a range of microscopic abnormalities, but tubular dysfunction can occur without overt necrosis [3]. The rapid onset of recovery after drug discontinuation suggests that fostriecin induced only limited, or focal, morphological changes, in contrast to its considerable effects on renal function.

Although many anticancer agents, including cisplatin, cause tubular damage [3], comparisons are difficult because fostriecin is structurally unrelated to other drugs and has a novel mechanism of action. Another topo II catalytic inhibitor, merbarone, has shown dose-limiting renal toxicity, and rat studies using this agent have revealed tubular necrosis [5, 10].

One of the mechanisms that might explain why the renal effects of fostriecin appeared to be limited to the first one to two doses and did not increase with further dose escalation would be the interaction of fostriecin with the reduced folate carrier. This carrier has been shown to be responsible for the cellular uptake of fostriecin in in vitro tumor models [7]. Because the drug-carrier interaction appeared to be slowly reversible, fostriecin might block its own uptake due to saturation of this transport mechanism. However, the presence of the reduced folate carrier on human renal tubular cells has not been proven, and evidence of its presence in normal tissues was presented only very recently [1, 15].

In summary, the present study shows that fostriecin can induce a considerable decrease in renal function, which is associated with renal tubular damage. The rapid recovery from and reversibility of this decrease suggests a predominantly functional disorder rather than extensive necrosis. Further investigation to elucidate the exact mechanism and to develop protective measures is needed. There was no indication of cumulative toxicity, but the follow-up studies were performed after only two courses in a limited number of patients. Therefore, future studies should also investigate the risk of irreversible long-term toxicity.

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