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SHORT COMMUNICATION

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Lack of nephrotoxicity of new oral platinum drug JM216 in lung cancer patients

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Abstract *Purpose*: The purpose of this study was to assess renal function in patients treated with the oral platinum drug JM216 [bisacetato-ammine-dichloro-cyclohexylamine-platinum(IV)], since the effects of JM216 on renal function have only partly been investigated using serum parameters or ^{51}Cr-EDTA clearance. We used a sensitive method that assessed glomerular filtration rate (GFR), effective renal plasma flow (ERPF), and indicators of tubular and glomerular damage. *Methods*: A group of 24 patients with either non-small-cell lung cancer (NSCLC) stage IIIb/IV or small-cell lung cancer (SCLC), limited disease (LD) or extensive disease (ED), treated with JM216 were studied. All patients had no prior chemotherapy, a performance score <2, a life expectancy of more than 3 months and normal liver, renal and bone marrow functions before treatment. All patients received oral JM216 120 mg/m^2 per day for 5 consecutive days, repeated every 21 days with a maximum of six cycles. In six SCLC patients the dose was escalated to 140 mg/m^2 per day after the first cycle. Prior to treatment, after the first cycle and after the end of treatment renal function was assessed by ^{125}I-sodium thalamate and ^{131}I-hippurate clearances to determine acute and cumulative changes in GFR and ERPF, respectively. Furthermore, tubular and glomerular damage were assessed by urinary excretion of β_2-microglobulin, lactic dehydrogenase (LDH), alkaline phosphatase (ALP), gamma-glutamyltransferase (GT) and albumin. *Results*: In 20 evaluable patients no significant acute impairment of renal function was observed. Median (range) GFR, ERPF and filtration fraction (FF) before treatment were 101 ml/min (53–164 ml/min), 417 ml/min (227–719 ml/min), and 0.25 (0.19–0.33), respectively. After the first cycle values were 117 ml/min (71–189 ml/min), 418 ml/min (228–709 ml/min) and 0.28 (0.21–0.33), respectively. Also, no indications of tubular or glomerular damage were found. In four patients renal function was evaluated at the end of treatment (one after three cycles, one after five cycles and two after six cycles). Median (range) GFR, ERPF and FF were 99 ml/min (74–139 ml/min), 401 ml/min (277–496 ml/min) and 0.26 (0.23–0.30), respectively, revealing no delayed nephrotoxicity. *Conclusion*: We conclude that oral JM216 shows no nephrotoxicity.

Key words Nephrotoxicity · JM216

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Introduction

JM216 [bisacetato-ammine-dichloro-cyclohexamine-platinum(IV)] is a novel oral platinum(IV) drug. JM216 has shown activity against several platinum-sensitive and also platinum-resistant cancer cell lines [20, 22, 23, 25]. In these cell lines JM216 can partly circumvent platinum resistance. In vivo oral JM216 shows activity comparable to that of intravenous cisplatin against human ovarian carcinoma xenografts, and shows even better activity against murine ADJ/PC6 plasmacytoma in mice [11]. The antitumour activity of oral JM216 is currently under investigation in phase II trials for several types of cancer. The drug has been developed in the search for new platinum drugs with a milder toxicity profile than cisplatin, because the use of cisplatin is often limited by its toxicities, especially nephrotoxicity [12, 13, 19]. Cisplatin is nephrotoxic probably because of its effects in changing renal perfusion and injuring tubules [7, 19]. The principal route of excretion of cisplatin is renal, by

glomerular filtration and tubular excretion [19], which may contribute to its nephrotoxicity. After 6 h 20% of administered cisplatin is recovered in the urine [3]. Accumulation of cisplatin in kidney tissue has been observed [19]. JM216 shows less urinary clearance with a urinary platinum recovery of 4.5% at a dose of 120 mg/m^2 [16] and 6.2% at 140 mg/m^2 [17] in the first 24 h after intake. Nevertheless, renal platinum clearance of JM216 is still higher than the GFR in most patients, suggesting that active renal tubular secretion of platinum is also an elimination mechanism for JM216 [16]. Thus, renal platinum clearance of JM216 is lower than that of cisplatin but it may still be capable of inducing vascular, glomerular or tubular renal damage. Although in some studies measurements of serum creatinine or GFR by ^{51}Cr-EDTA clearance have have not been able to show changes in renal function, the evidence that JM216 has no nephrotoxic side effects is still weak, and urinary excretion of tubular enzymes has not been investigated [1, 16, 17]. Therefore, we investigated whether any acute or cumulative nephrotoxicity of JM216 could be detected using a very sensitive method for measuring glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), and in addition measuring urinary excretion of tubular enzymes as indicators of tubular damage.

Patients and methods

Patients and study drug

A group of 24 patients (15 male, 9 female, median age 64 years, range 37–75 years) with histologically confirmed lung cancer were studied. Of the 24 patients, 13 had non-small-cell lung cancer (NSCLC), 3 stage IIIb and 10 stage IV. The remaining 11 patients had small-cell lung cancer (SCLC), 9 with extensive disease (ED) and 2 with limited disease (LD). None of the patients had been treated with prior chemotherapy. All patients had a performance status (PS, ECOG) <2 and normal liver, renal, and bone marrow functions. Treatment consisted of oral JM216 at a dose of 120 mg/m^2 once daily for 5 consecutive days every 3 weeks, for a maximum of six cycles. In six patients with SCLC, the JM216 dose was escalated to 140 mg/m^2 after the first cycle. Four patients received the maximum six cycles. JM216 was provided by Bristol-Myers Squibb (Brussels, Belgium) in capsules containing 10, 50 or 200 mg with excipients (lactose, sodium starch glycolate, microcrystalline cellulose and magnesium stearate). The study was approved by the local medical ethics committee and written informed consent was obtained from all patients.

Renal function studies

During the 10 days prior to treatment, during the 12 days after the first cycle, and after the end of treatment, GFR and ERPF were determined simultaneously by measuring the clearance of ^{125}I-iothalamate and ^{131}I-hippuran, respectively. This method has been described previously by Donker et al. [4]. In brief, a standard primary dose was administered followed by a 2-h sustaining intravenous infusion of the radioisotopes. Urine collection was started 2 h later. Urine was collected in two 2-h periods and clearances of both radioisotopes were determined. GFR and ERPF were calculated as the mean of the two 2-h clearances, corrected for body surface area. The intrapatient day to day variation of this method is 2.2% for GFR and 5% for ERPF [4]. Filtration fraction (FF) was calculated from GFR divided by ERPF. Lactic dehydrogenase (LDH), alkaline phosphatase (ALP), gamma-glutamyltransferase (GT), β_2-microglobulin and albumin were also determined in the urine samples. Creatinine from serum and 24-h urine was used to determine creatinine clearance. Furthermore, urine analysis for pH, red blood cells, urobilin, and glucose was performed once every cycle. Serum creatinine was determined with an automated multianalyser (SMA-C; Technicon, Tarrytown, N.Y.). Urinary ALP, LDH, and GT were determined using a Vitros analyser (Johnson & Johnson). Urinary creatinine was determined using an SMA-6 analyser (Technicon). Urinary β_2-microglobulin was determined by the radioimmunosorbent technique described by Evrin et al. [5]. To exclude the possibility that JM216 itself interferes with kinetic enzyme detection, urine from three healthy volunteers was incubated at 37 °C for 1 h without and with 0.005, 0.010 and 0.015 mg/ml JM216. Urinary albumin concentration was measured in a 24-h urine collection using an ELISA and total protein using a pyrogallol red molybdate method [26].

Statistics

Statistical analysis was performed by Wilcoxon's test for paired samples for all parameters; $P < 0.05$ was considered as statistically significant.

Results

Of the 24 patients, 20 were evaluable for renal function after the first cycle. Four patients were considered not evaluable because either no renal function measurement prior to chemotherapy or no measurement after the first cycle was performed. Median (range) GFR, ERPF and FF before treatment were 101 ml/min (53–164 ml/min), 417 ml/min (227–719 ml/min), and 0.25 (0.19–0.33) respectively. After the first cycle values were 117 ml/min (71–189 ml/min) ml/min, 418 ml/min (228–709 ml/min) and 0.28 (0.21–0.33), respectively. Individual values of GFR, ERPF and FF before and after the first cycle are shown in Fig. 1. No impairment of renal function was observed after the first cycle. There were no significant decreases in GFR and ERPF. FF showed a small increase after the first cycle. Creatinine clearances estimated from 24-h urine, also showed no significant changes after the first cycle. Both baseline 24-h urine creatinine clearance and clearance after cycle 1 were often lower than GFR as measured by ^{125}I-iothalamate. In four patients renal function was also evaluated at the end of treatment (one after three, one after five and two after six cycles). Median (range) GFR, ERPF and FF were 99 ml/min (74–139 ml/min), 401 ml/min (277–496 ml/min) and 0.26 (0.23–0.30), respectively. No significant impairment of renal function at the end of treatment was observed in these patients.

Median values (range) of urinary excretion of tubular enzymes β_2-microglobulin, LDH, ALP and gamma-GT as indicators of tubular damage, and microalbuminuria as an indicator of glomerular damage are shown in Table 1. Values were corrected for creatinine excretion as measured in the 24-h urine collection. LDH and ALP showed a significant slight decrease after the first cycle,

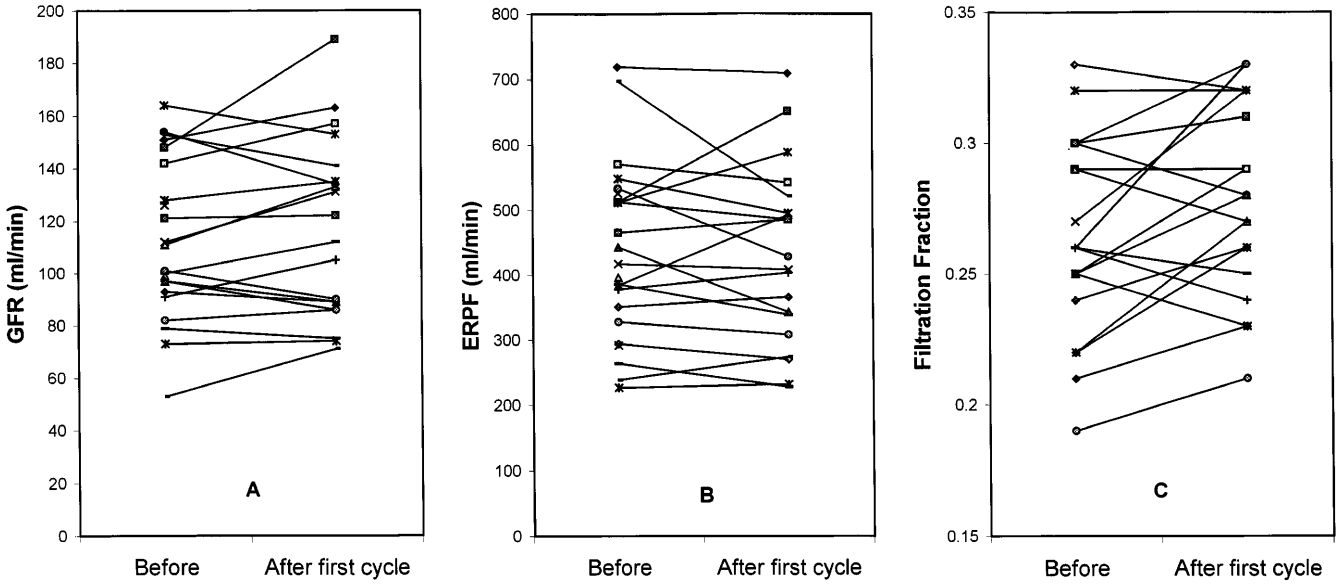

Fig. 1A–C Glomerular filtration rate (GFR) (**A**), effective renal plasma flow (ERPF) (**B**) in millilitres per minute and filtration fractions (FF) (**C**) prior to and immediately after the first cycle of JM216 treatment ($n = 20$)

but no increase in excretion of enzymes, indicating tubular damage, was observed. The control experiment with urine from healthy volunteers revealed no interference of JM216 with enzyme measurement. Microalbuminuria also showed no significant changes.

Discussion

In this study we used a sensitive method to assess renal function after treatment with oral JM216. No acute or cumulative decrease in GFR and ERPF was observed, indicating that JM216 did not impair renal function. Urinary albumin excretion did not change after JM216 treatment, indicating that no glomerular damage occurred. Also, no increase in excretion of tubular enzymes could be observed, indicating that tubular function remained intact during and after JM216 treatment. Animal studies have shown no nephrotoxicity of JM216, as assessed by inulin clearance in mice [15] or by creatinine clearance in rats [14]. Only after chronic daily dosing of JM216 is a slight decrease in GFR observed in mice [15]. Human phase I studies have not been able to establish nephrotoxicity as estimated by serum parameters [1] or assessed by ^{51}Cr-EDTA clearance [16, 17]. The disadvantage of these methods is that they measure only GFR. Previous studies with cisplatin have shown a decrease in GFR and ERPF after treatment [18, 19, 21]. Also, an increase in FF has been observed, implying that ERPF decreases more than GFR [21]. A transient rise in urinary total protein has also been observed after cisplatin treatment [8]. Furthermore, it appears that platinum-induced nephrotoxicity primarily involves degenerative changes in the proximal tubules [7] which can be monitored by excretion of urinary enzymes [2, 7, 10]. Therefore, measuring only GFR or creatinine clearance may underestimate renal toxicity, especially subclinical nephrotoxicity after treatment with JM216.

Our study focused on GFR, ERPF, and indicators of tubular or glomerular damage as well. However, none of the parameters revealed any nephrotoxicity, so our data confirm the earlier findings that JM216 shows no nephrotoxicity. Cisplatin on the other hand, still shows serious nephrotoxicity in a minority of patients, even with hydration- and diuresis-enhancing schedules. Newer platinum drugs such as carboplatin show subclinical nephrotoxicity, especially after multiple chemotherapy cycles [6, 9, 24]. In the present study we showed that the oral drug JM216 does not show any nephrotoxicity. Therefore, oral JM216 can easily be administered to patients at home without the need for hydration

Table 1 Urinary excretion of tubular enzymes and glomerular protein. Values are medians (range)

	Number of patients	Baseline	After cycle 1
β_2-Microglobulin/creatinine (μg/mmol)	8	9.96 (2.78–19.00)	12.68 (3.66–556.5)
LDH/creatinine (U/mmol)	12	4.05 (1.78–10.56)	2.25* (1.52–4.65)
ALP/creatinine (U/mmol)	13	2.00 (0.83–4.49)	1.29* (0.29–2.79)
Gamma-GT/creatinine (U/mmol)	12	5.19 (0.56–22.50)	7.12 (0.49–14.70)
Albumin/creatinine (mg/mmol)	8	1.10 (0.59–5.00)	1.31 (0.40–20.23)

*$P < 0.05$

schedules to reduce nephrotoxic side effects, and might be an alternative for cisplatin or carboplatin in the treatment of cancer patients.

In conclusion, oral JM216 can be safely administered without tubular or glomerular side effects on an outpatient base. As far as safety is concerned, JM216 might be a good alternative for cisplatin.

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