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The Late Effects of *Cis*-platinum on Renal Function

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Abstract—*The combination of bleomycin, etoposide and* cis-*platinum (BEP) is an effective treatment for germ cell tumours. To help define the role of recently developed non-nephrotoxic analogues of* cis-*platinum we have analysed the long term renal damage caused by this agent. We report on* 22 *patients studied* 8–60 *months following BEP chemotherapy. In the* 17 *cases with no pre-chemotherapy renal impairment there was a fall in mean glomerular filtration rate from* 132 ml/min (95% *confidence interval* 123, 141) *pre-chemotherapy to* 103 ml/min (95% *confidence interval* 94, 113) *on late follow up.*

The overall pattern is one of initial fall of glomerular filtration rate during chemotherapy, and no consistent evidence of late recovery or further deterioration; considerable individual variation is observed.

INTRODUCTION

MALIGNANT non-seminomatous germ cell tumour (NSGCT) of the testis is predominantly a disease of young men, most commonly presenting in the third decade of life [1]. The use of *cis*-platinum containing chemotherapy regimens is associated with cure rates which approach 100% in patients presenting with stage I disease [2] and are about 80% in patients with metastatic disease [3]. The acute nephrotoxicity of cisplatin is well documented [4] and can be reduced by measures such as adequate hydration and forced diuresis [5].

The combination of bleomycin, etoposide and cisplatin (BEP) was introduced in the Royal Marsden Hospital (RMH) in 1979 [6] and recent comparative studies have emphasized its efficacy and relative lack of toxicity [7]. However, now that non-nephrotoxic analogues of cisplatin are available [8] it is important to evaluate the long term renal damage caused by this agent. We have investigated the renal function of 22 patients followed up for 8–60 (median 31) months after completion of BEP chemotherapy for NSGCT.

PATIENTS AND METHODS

Between July 1979 and December 1986 171 patients with germ cell tumours were treated by the Testicular Tumour Unit of the RMH utilizing the BEP regimen (Table 1). Between December 1985 and May 1986 22 of these patients consented to further studies of renal function. The selection criteria were treatment with BEP chemotherapy completed more than 6 months previously, no renal irradiation, no bypass surgery for obstructed ureters, no other nephrotoxic drug administration and informed consent.

All patients had received chemotherapy with BEP given with hydration on a 21 day cycle (Table 1) and all patients were disease free at the time of reassessment and had been continuously disease free since their chemotherapy. Patient details are shown in Table 2. The age range of the 22 patients was 18–56 years (median 28 years). Seventeen patients had 'normal' pre-treatment renal function, i.e. normal glomerular filtration rate (GFR), no evidence of obstructive uropathy on intravenous urography, no past medical history of renal disease and no exposure to therapeutic irradiation. Five patients did have pre-chemotherapy renal abnormalities (four cases unilateral hydronephrosis and one case of renal vein thrombosis). The following assessments were routinely performed prior to starting chemotherapy: physical examination including blood pressure estimation, chest X-ray, computerized tomographic scan of thorax and abdomen, lymphangiogram and intravenous urography, serum urea and electrolytes, serum creatinine and GFR. Assessment of renal function including GFR were assessed before each course of chemotherapy. These data were collected retrospectively from the patients' case notes.

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Table 1. BEP regimen

Cisplatin	20 mg/m²/day (total 100 mg/m²)	Days 1, 2, 3, 4, 5
Etoposide	120 mg/m² (total 360 mg/m²)	Days 1, 2, 3
Bleomycin	30 mg i.v.	Days 2, 9, 16 (21 day cycle)
	Hydration	
1 l N saline + 20 mmol KCl (hydration) 6-hourly × 2		Day 0
Mannitol 10%, 200 ml over 30 min pre-chemo		Day 1
Cisplatin 20 mg/m² in 1 l N saline + 20 mmol KCl over 6 h		
1 l N saline + 20 mmol KCl 6-hourly × 3		
As Day 1		Days 2–5
1 l N saline + 20 mmol KCl 6-hourly × 2		Day 6

The prospective investigations of renal function included GFR serum creatinine, magnesium, calcium and β2 microglobulins. Blood pressure (BP) was recorded. The GFR was measured using the single injection method with radioactive chromium labelled ethylenediamine tetraacetic acid ([^{51}Cr]-EDTA) [9] and was corrected for standard body surface area (1.73 m²). Isotope renograms using technetium labelled diethylenetetramine-pentaacetic acid were performed in the five cases with known pre-chemotherapy renal impairment to estimate the relative contribution of each kidney to current renal function [10].

For this study the initial GFR, the one prior to the last course of BEP and the one obtained at most recent follow up were compared. It is assumed that important changes in renal function following chemotherapy would occur during the first 6 months, therefore 'late' renal function assessed 8–60 months after treatment is not analysed as a time dependent variable. GFR readings were compared using paired *t*-tests.

Table 2. Impact of BEP chemotherapy on GFR

	Patient age (years)	Number of courses of BEP	Pre-treatment GFR (ml/min)	GFR before last course of BEP (ml/min) (% of presenting GFR in brackets)	Late follow up GFR (ml/min)	Period between last BEP and late renal assessment (months)
	21	4	141	119 (84)	140 (99)	50
	18	4	138	98 (71)	117 (85)	31
	24	4	162	106 (65)	113 (70)	30
	23	4	134	99 (74)	117 (87)	31
	27	4	108	95 (88)	106 (98)	57
Patients	35	4	114	79 (69)	82 (72)	8
with 'normal'	21	4	126	117 (93)	116 (92)	28
pre-treatment	28	4	112	93 (83)	89 (79)	23
renal function	56	6	101	105 (104)	97 (96)	30
	38	4	142	117 (82)	109 (77)	51
	28	4	135	115 (85)	109 (81)	22
	33	4	134	101 (75)	101 (75)	13
	32	4	126	101 (80)	89 (71)	25
	28	4	155	133 (86)	117 (75)	30
	23	4	138	123 (89)	109 (79)	24
	37	4	157	116 (74)	73 (46)	24
	51	4	123	96 (78)	72 (59)	59
Patients	18*	4	127	73 (57)	87 (69)	60
with 'abnormal'	31*	3	68	32 (47)	68 (100)	34
pre-treatment	33*	6	85	78 (92)	81 (95)	38
renal imaging	23*	6	98	82 (84)	87‡ (89)	18
	34†	4	74	83 (112)	73‡ (99)	23

*Unilateral hydronephrosis.
†Renal vein thrombosis.
‡Equal function of kidneys with isotope renogram.

RESULTS

Table 2 shows the GFR before therapy, during therapy, and at the last follow up in the 22 patients studied. Results on the 17 patients with normal pre-treatment renal function are shown in Fig. 1. For these 17 patients the mean GFR at presentation was 132 ml/min [95% confidence interval (CI): 123, 141]. During therapy this fell significantly to a mean of 107 ml/min (95% CI: 100, 114) and after a follow up period of between 8–59 months (median 30 months) showed no evidence of recovery, with a mean GFR of 103 ml/min (95% CI: 94, 113). Body weight fell by an average of 3% during treatment (+5% to −8%).

The fall from initial to 'on-treatment' GFR represents a mean fall of 19% [S.E. (mean) = 2.3%] (median 18%) and from initial to late follow up a mean fall of 21% [S.E. (mean) = 3.4%] (median = 21%), suggesting that the loss in GFR is maintained. Formal comparison of the percentage of the initial GFR reading observed on treatment and at follow up indicates no significant difference between the two sets of readings ($t = 0.72$, df = 16, $P = 0.48$) supporting this lack of recovery.

There was no change in serum creatinine concentration during chemotherapy or on subsequent follow up and no change in BP (in particular no change was seen in those whose GFR continued to fall). Serum concentrations of magnesium, calcium and β2 microglobulins were not assessed as a routine before chemotherapy. However, the investigations following chemotherapy showed them to be within normal limits.

Of the five patients with known pre-chemotherapy renal impairment isotope renograms on follow up recorded equal function of both kidneys in only two cases (one unilateral renal vein thrombosis, one unilateral hydronephrosis) and neither case had a marked improvement in GFR. Of the remaining three cass, renal function on the obstructed side contributed 20%, 8% and less than 5% to total renal function on follow up.

DISCUSSION

Cytotoxic chemotherapy has dramatically improved the prognosis for patients with metastatic teratoma and >80% of such patients are expected to become long term survivors [2, 3]. Late toxicity of treatment is thus an important issue. The site of the lesion causing nephrotoxicity from *cis*-platinum is controversial, some suggesting a vasomotor effect on the glomerular tuft [11], and others an effect on renal tubular cells, based on morphological and biochemical signs of tubular damage [12, 13]. In this study the normal serum magnesium and β2 microglobulin obtained on follow up point against long term tubular damage, but do not exclude this as an important event in the acute nephrotoxicity of *cis*-platinum administration.

The acute nephrotoxicity of *cis*-platinum is well documented and the fall in GFR noted on treatment in the present series is in keeping with previous reports; for example, Meijer *et al.* [11] reported a 23% decrease in median GFR in 24 patients comparing pre-treatment levels with those measured on day 10 of the last course of chemotherapy and Macleod *et al.* a 23% reduction in mean GFR in 22 patients receiving 1–5 courses of *cis*-platinum based chemotherapy [14]. Serum creatinine is an unreliable indicator of renal function [15] possibly due to muscle wasting during therapy and [^{51}Cr]EDTA clearance studies are preferred.

Our study measured GFR prior to the last course, not after the last course, and although the absolute

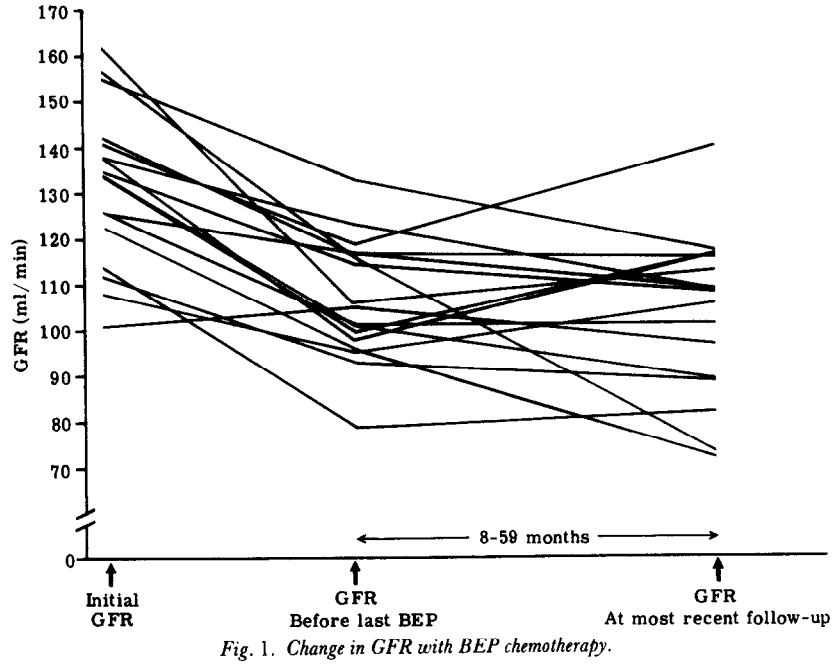

Fig. 1. Change in GFR with BEP chemotherapy.

lower limit of GFR from chemotherapy was not determined, this is unlikely to be more than 5% lower than the recorded on-treatment nadir, since the impact of a single course would be expected to be less than a quarter of the total fall.

The present study shows no overall improvement in GFR with time after chemotherapy, and this overall lack of change is in keeping with both Dentino *et al.*'s study [12] of seven patients followed for 2 years post-*cis*-platinum chemotherapy and with Macleod *et al.*'s study [14] of 22 patients followed for 6–60 months post-*cis*-platinum based chemotherapy suggesting that *cis*-platinum induced renal damage is permanent. However, 4/17 of our cases showed an increase of more than 10% on follow up and both Fjeldborg *et al.* [16] and Macleod *et al.* [14] report 4/22 and 5/22 patients respectively showing an improvement in renal function on long term follow up, implying that recovery of function can occur in some patients. In our series 5/17 patients showed a decline of more than 10% in GFR. The clinical significance of this fall in GFR is not yet apparent, and how much of the fall was a result of the final course of chemotherapy is not known. However, Groth *et al.* [13] suggest that renal function can continue to deteriorate even after *cis*-platinum chemotherapy, possibly due to accumulation of *cis*-platinum in the kidney, or to a rise in intratubular pressure. The five patients we studied with pre-existing renal damage are interesting in that no dose reductions of cisplatin were made and no attempt was made to bypass obstructed ureters. On follow up investigation, renal function recovered only to pre-treatment levels with little function being contributed to by the previously obstructed side in three of four cases, and it may be that in these patients either stenting of the ureters or percutaneous nephrostomy or alternative non-nephrotoxic chemotherapy with carboplatin should be considered [17].

In conclusion, our study suggests that the majority of patients treated with BEP chemotherapy for malignant NSGCT may experience a permanent fall in their GFR. The long term clinical significance of this has not yet been established and further follow up is required.

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