Cancer Chemother Pharmacol (1990) 27: 234–238

Cancer Chemotherapy and Pharmacology

Carboplatin-based chemotherapy with pharmacokinetic analysis for patients with hemodialysis-dependent renal insufficiency

Robert J. Motzer, Donna Niedzwiecki, Marion Isaacs, Celia Menendez-Botet, William P. Tong, Carlos Flombaum, Howard I. Scher, and George J. Bosl

Genitourinary Oncology Service, Division of Solid Tumor Oncology and the Nephrology Service, Department of Medicine and the Department of Clinical Chemistry, Memorial Sloan-Kettering Cancer Center and the Department of Medicine, Cornell University Medical College, New York, New York 10021, USA

Received 15 June 1990/Accepted 14 August 1990

Summary. Three patients with renal insufficiency requiring hemodialysis were treated with carboplatin at 100 mg/m^2 in combination with etoposide for advanced germ-cell tumor (GCT, two cases) or Adriamycin + vinblastine for a transitional-cell carcinoma of the ureter (one case). Hemodialysis was performed 24 h after the administration of carboplatin. Both patients with GCT achieved a complete response, and the patient with transitional-cell carcinoma of the ureter was inevaluable for response but his disease has not progressed. The dose of carboplatin was increased in one patient as renal function improved on therapy. In two patients, the pharmacokinetics of carboplatin were determined; the pre-dialysis half-lives, AUC, and total body clearances of free carboplatin-derived platinum were estimated to be 32 and 18.3 h, 4.93 and 6.17 mg ml^{-1} min, and 18.2 and 18.7 ml/min, respectively. The dialysis elimination half-lives ($t_{1/2\beta}$) of 2 and 3 h, respectively, for these two patients were markedly lower than the predialysis values, indicating that carboplatin was dialyzed. In summary, carboplatin can be given to patients with severe renal insufficiency. Adequate AUCs were achieved and dialysis limited systemic exposure to free carboplatin.

Introduction

Cisplatin-based regimens have played a central role in the treatment of advanced germ-cell tumors (GCT) [3, 8, 26] and transitional-cell carcinoma of the urothelial tract [23]. Carboplatin lacks the nephrotoxicity, neurotoxicity, and ototoxicity of cisplatin [4, 6]; has demonstrated antitumor activity in phase II trials in GCT [2, 18] and transitional-cell carcinoma of the bladder [2]; and has been investigated as an alternative to cisplatin as first-line therapy for GCT [15, 16, 19]. As thrombocytopenia is the major dose-limiting toxicity and carboplatin is largely excreted by the kidney, nomograms have been developed for calculation of the dose of carboplatin given alone or in combination with etoposide to patients with impaired renal failure based on glomerular filtration rate and change in platelet count [5, 7, 13].

The optimal management of GCT and urothelial tract carcinoma with platinum-based chemotherapy is dependent on adequate renal function. In patients with renal failure requiring dialysis, both the experience with and the success of cisplatin-based chemotherapy are limited [12, 22]. The use of carboplatin in patients with severe renal insufficiency may preserve borderline renal function, particularly if improvement is anticipated, and lessen the likelihood of neurotoxicity and ototoxicity. One patient with seminoma and transient renal failure requiring dialysis was successfully treated with carboplatin- and etoposide-based chemotherapy [9]. Herein, we report three patients, two with GCT and one with a urothelial tract carcinoma who were treated with carboplatin while undergoing hemodialysis for acute or chronic renal insufficiency. The pharmacokinetics of carboplatin were analysed on two patients before, during and following hemodialysis.

Patients and methods

Patients and drug administration. Three patients were treated with carboplatin-based chemotherapy while receiving hemodialysis for acute (one case) or chronic (two cases) renal failure. The dose of carboplatin selected and the timing of hemodialysis were based on experience published about one patient [9]. The carboplatin was reconstituted in 250 cc of 5% dextrose in water and was given by i. v. infusion over 30 min. The carboplatin for patient 3 was kindly provided by the Bristol-Myers Corporation. In patients 1 and 3, etoposide was injected as an i. v. bolus given over 60–90 min. Patient 2 received vinblastine and doxorubicin, both of which were given as an i. v. bolus over 5 min.

Robert J. Motzer, M. D., is a recipient of an American Cancer Society Career Development Award

Offprint requests to: R. J. Motzer, Memorial Hospital, 1275 York Avenue, New York, NY, 10021, USA

Table 1. Carboplatin dose and pretreatment and nadir blood counts

Patient	(cycle)	Carboplatin dose (mg/m^2)	Pretreatment (nadir)		
			WBC ($\times$ 1,000 cm^3 ml^{-1})	Hb (mg/dl)	Plts ($\times$ 1,000 cm^3 ml^{-1})
1	(1)	100	8.8 (1.1)	9.6 (8.3)	356 (33)
	(2)	100	6.8 (1.5)	8 (6.7)	558 (171)
	(3)	100	10.7 (1.3)	8.4 (9.1)	290 (32)
	(4)	100	8.3 (1.5)	7.4 (7.1)	398 (55)
2	(1)	100	4.7 (0.8)	7.8 (6.6)	286 (83)
	(2)	100	5.7 (2.1)	7 (9.6)	355 (82)
	(3)	100	5.4 (NA)	7.2 (NA)	172 (NA)
3	(1)	150	24.4 (0.7)	8.8 (7.5)	356 (19)
	(2)	300	6.9 (1.2)	10.9 (7.3)	505 (10)
	(3)	300	8.1 (0.3)	11.7 (8)	479 (10)

Hb, Hemoglobin; Plts, platelets; NA, not available

Hemodialysis. Hemodialysis was performed 24 h after the administration of carboplatin using Cuprophane, hollow-fiber dialyzers and Drake-Willock model 480 volumetric machines. Patients were dialyzed for 4 h using a bicarbonate-based dialysate with potassium, magnesium, and calcium concentrations of 2, 1, and 3.5 mEq/l, respectively, adjusted according to each patient's needs. Fluid removal was individually programmed to attain a desired dry weight. In two patients heparin anticoagulation was used. Patient 3 was dialyzed without anticoagulants. In patients 1 and 2, ultrafiltration was performed simultaneously with hemodialysis during the first 30 min of treatment. Patient 1 underwent hemodialysis on the 2 subsequent days after administration of carboplatin in each cycle.

Sample collection. In patients 1 and 2, heparinized (10 IU/l) blood samples (5 ml) were collected from an indwelling i. v. cannula placed in the arm opposite to that receiving carboplatin and were placed on ice. Samples were taken prior to drug administration; at 0.5, 1, 2, 4, 5, and 6 h after administration of carboplatin; at 24 h (immediately pre-hemodialysis); at 24.5, 26, 26.5, 27, 27.5 and 28 h (during hemodialysis); and at 28.5, 29, and 30 h (after dialysis). A 48-h sample was obtained from one patient.

Drug analysis. Plasma carboplatin levels were measured by analysis of plasma platinum concentration, since most of the platinum exists as unchanged carboplatin [14]. The specimens were centrifuged immediately at 2,740 *g* at 4° C for 20 min. The supernatant was separated, part of it was frozen at –20° C until platinum analysis (for determination of total platinum), and the rest was filtered in a Centricon-3 filter and then centrifuged for 5 h at 4° C and 2,740 *g*. The filtered plasma was frozen until analysis, for which it was used to calculate free platinum levels. Carboplatin-derived platinum was determined in filtered and unfiltered plasma by flameless atomic absorption spectrophotometry using a 5000 Perkin Elmer spectrometer (Norwalk, Conn.) equipped with graphite-furnace attachments, an HGA 500 programmer and an AS40 sampler.

Pharmacokinetic analysis. Pharmacokinetic parameters were estimated using standard methodology [10]. The area under the concentration-time curve (AUC) was estimated using the log-trapezoidal approximation. Estimates of AUC were obtained over all time points and separately for the pre-dialysis, dialysis, and post-dialysis intervals. Elimination rates (β) were estimated using linear regression, with log concentration as the outcome variable. The serum half-life ($t_{1/2\beta}$) of platinum was estimated by:

$t_{1/2} = 1n\ 2/\beta$.

Pre-dialysis total body clearance (Cl_{TB}) was estimated by:

$Cl_{TB} = D/AUC$,

where D represent the total amount of carboplatin ultimately eliminated, and AUC was extrapolated to infinity. The percentage of protein-bound platinum was determined by:

(Total – free platinum)/total platinum. The average platinum concentration observed post-dialysis is the mathematical mean of the values obtained after dialysis.

Results

The doses of carboplatin, pre-treatment and nadir white blood counts (WBC), hemoglobin levels, and platelet counts for the three patients are summarized in Table 1. Case histories are summarized.

Patient 1

A 44-year-old man with idiopathic chronic renal failure, requiring hemodialysis 3 days/week for 19 years, presented with a left testicular mass. He underwent an inguinal orchiectomy for a nonseminomatous GCT consisting of embryonal carcinoma and endodermal sinus tumor. The extent-of-disease evaluation included an abdominal computerized tomographic (CT) scan that demonstrated retroperitoneal adenopathy and a chest X-ray that revealed a left lung parenchymal nodule. The patient's serum alpha-fetoprotein (AFP) level was 1,060 ng/ml and his human chorionic gonadotropin level (HCG) was 21.8 ng/ml. He was anuric, with a serum creatinine value of 13.8 mg/dl. He was treated with 100 mg/m^2 carboplatin on day 1 and 100 mg/m^2 etoposide on days 1–4. Four cycles were repeated at 29-, 29- and 31-day intervals. During each cycle, hemodialysis was performed on day 2 of chemotherapy and on day 3 of each cycle.

The patient required transfusion of packed red blood cells but was not hospitalized for nadir fever. A CT chest scan following the first and fourth cycles of therapy demonstrated complete resolution of a lung metastasis; however, the retroperitoneal adenopathy slowly progressed, consistent with the "growing teratoma syndrome" [17]. The patient's serum AFP and HCG values normalized on day 159 and day 43, respectively, at a rate consistent with a prolonged serum half-life [21, 25]. Following completion of chemotherapy, he underwent a retroperitoneal lymph-node dissection with en-bloc left nephrectomy. The pathology was interpreted as being an adenocarcinoma arising from an immature teratoma [1], with no evidence of embryonal-cell carcinoma or endodermal sinus tumor. A follow-up CT scan obtained 2 months after resection demonstrated a persistent retrocrural mass, which was completely resected and interpreted as being a mature teratoma. The patient shows no evidence of GCT at 9+ months after the initiation of chemotherapy.

Patient 2

A 42-year-old man with congenital absence of the left kidney was found to have a right hydronephrosis. An exploratory laparotomy, a ureteral segment excision, and a ureterostomy for transitional-cell carcinoma of the right

Table 2. Pharmacokinetic analyses (relative to dialysis)

	Patient 1	Patient 2
AUC (mg ml^{-1} min):		
Total		
Pre-dialysis	8	7.53
During dialysis	0.93	0.51
Post-dialysis	3.96	0.22
Total	13	8.5
Free		
Pre-dialysis	4.93	6.17
During dialysis	0.47	0.21
Post-dialysis	1.57	0.06
Total	6.9	6.7
$t_{1/2\beta}$ (h):		
Total		
Pre-dialysis	27.4	19.7
During dialysis	6.1	5.4
Free		
Pre-dialysis	32	18.3
During dialysis	3	2
Pre-dialysis Cl_{TB} (ml/min):		
Total	11.4	12.8
Free	18.2	18.7
% carboplatin protein-bound:		
4 h	41.2	18.1
24 h	44.2	41.7
Post-dialysis	70.9	71.7
Average observed platinum concentration post-dialysis (μg/ml):		
Total	2.98	2.4
Free	0.96	0.68

Cl_{TB}, Total body clearance

ureter were performed; 4 months later, locally recurrent disease was debulked. The patient was referred to the Memorial Sloan-Kettering Cancer Center (MSKCC) and was treated with four cycles of methotrexate + vinblastine + Adriamycin + cisplatin (MVAC) [23], achieving a complete response (CR) as determined by exploratory laparatomy. He remained free of disease for 30 months, at which time he presented with a seizure as a consequence of renal failure. Complete ureteral obstruction was noted and a ureteral stent and an arterial venous shunt were placed.

The patient was put on hemodialysis, which was continued on a weekly schedule; 5 months later, he developed a small-bowel obstruction and at exploration was found to have widely disseminated recurrent tumor. Acute urinary obstruction occurred and a right nephrostomy was placed. His serum creatinine and creatinine clearance values were 13.5 mg/dl and 3 cm^3 min^{-1}, respectively. He was treated with chemotherapy consisting of 100 mg/m^2 carboplatin, 3 mg/m^2 vinblastine, and 22.5 mg/m^2 doxorubicin. Hemodialysis was performed 24 h after carboplatin administration. His course was complicated by *Staphylococcus aureus* and *Klebsiella* septicemia related to an indwelling intravenous catheter. This complication resolved after treatment with appropriate antibiotics and removal of the catheter. The patient received two additional cycles at 36- and 39-day intervals and shows no further complication or evidence of progression of disease at 5 months after the beginning of chemotherapy.

Patient 3

A 35-year-old man presented with a 15-cm, palpable abdominal mass and a right testicular mass measuring 14 cm on a sonogram. A right inguinal orchiectomy was performed and the diagnosis of nonseminomatous GCT was made. An abdominal CT scan revealed a mass in the right lower quadrant, with tumor thrombus in the inferior vena cava extending above the level of the diaphragm into the right atrium as well as into the right renal vein. The patient was transferred to MSKCC due to progressive renal insufficiency despite hydration and placement of a right nephrostomy. At MSKCC he was anticoagulated and hydrated for 2 days, but his serum creatinine value continued to rise to 4.5 mg/dl, with a creatinine clearance of 15 ml/min. He was treated with 20 mg/m^2 cisplatin on days 1–5 and 100 mg/m^2 etoposide on days 1–4. His course was complicated by neutropenia, septicemia, acute renal failure requiring hemodialysis, and a bladder hemorrhage that necessitated a stent placement. An abdominal CT scan demonstrated a minimal decrease in the size of the abdominal mass, although the elevated serum AFP value declined appropriately in half-life.

At 40 days after the initiation of chemotherapy, the patient remained on dialysis and showed recovery of his blood counts. He was treated with 150 mg/m^2 carboplatin on day 1 and 100 mg/m^2 etoposide on days 1–3 (serum creatinine, 3.7 mg/dl; creatinine clearance, 18 cm^3 min^{-1}), undergoing hemodialysis on the day following carboplatin administration. Two additional cycles of 300 mg/m^2 carboplatin on day 1 and 100 mg/m^2 etoposide on days 1–3 were given at 28-day intervals. Serum creatinine and creatinine clearance values prior to these cycles were 1.7 and 1.3 mg/ml and 101 and 51 cm^3 min^{-1}, respectively, as the patient recovered from renal failure and hemodialysis was discontinued. He subsequently underwent exploratory laporotomy, which revealed no viable GCT, and remains in complete remission at 26+ months.

Pharmacokinetics

Total and free platinum levels were obtained prior to, during, and after hemodialysis for the second cycle of therapy in patient 1 (100 mg/m^2 carboplatin; total dose, 210 mg) and the first cycle of therapy in patient 2 (100 mg/m^2 carboplatin; total dose, 160 mg). The pharmacokinetics and the changes versus time in serum total and free platinum levels before and during dialysis are shown in Table 2 and Fig. 1 (patient 1) and 2 (patient 2), respectively. Pre-dialysis elimination rates were prolonged as compared with those obtained in patients with normal renal function [6, 14, 20]. The pre-dialysis half-life observed in patient 2 was shorter than that seen in patient 1, which was most likely a consequence of the residual renal function (creatinine clearance, 3 ml/min) noted in the latter case as

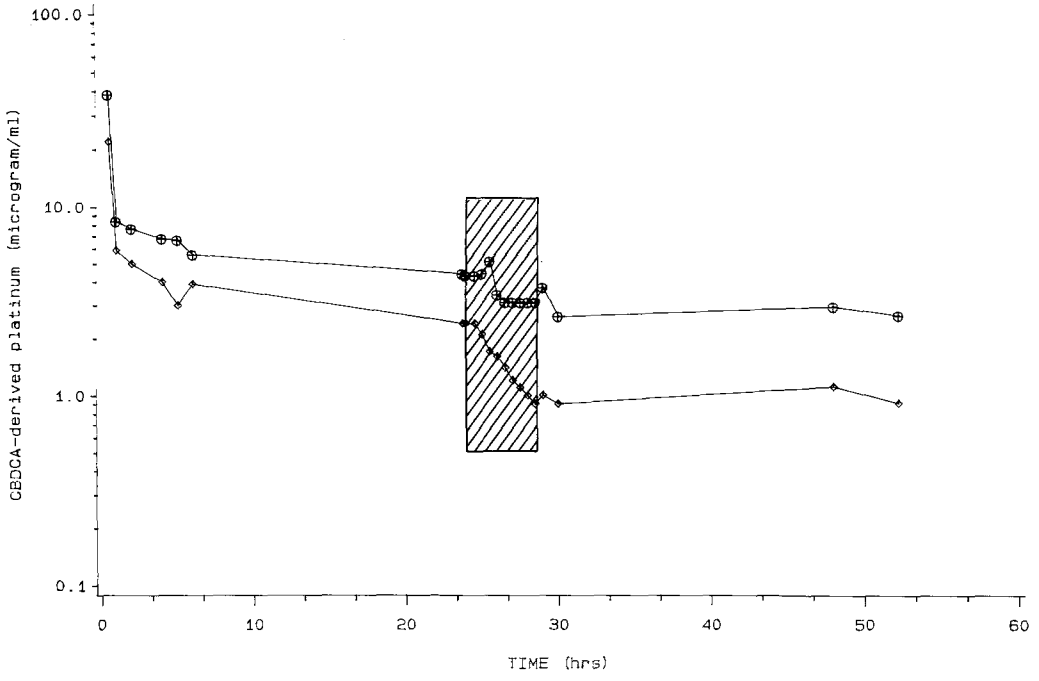

Fig. 1. Total and free concentration of carboplatin-derived platinum (μg/ml) versus time (h) for patient 1. The *hatched area* represents the time on dialysis. ⊕, total platinum; ◇, free platinum

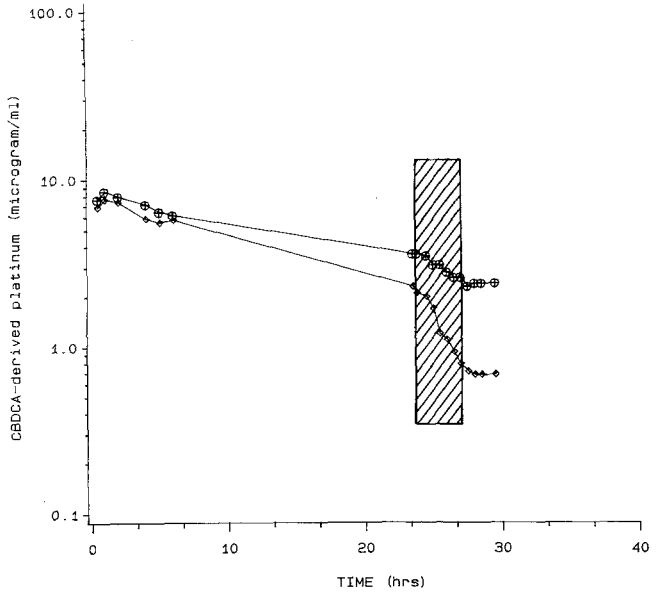

Fig. 2. Total and free concentration of carboplatin-derived platinum (μg/ml) versus time (h) for patient 2. The *hatched area* represents the time on dialysis. ⊕, Total platinum; ◇, free platinum

compared with the anuric renal failure observed in patient 1.

The decline in the concentration of carboplatin prior to dialysis suggested nonrenal mechanisms of elimination. There was an increased rate of drug elimination, particularly of free platinum, during dialysis, and drug was recovered from the dialysate. A high proportion of carboplatin remained free in plasma, and the proportion of protein-bound carboplatin increased with time. The concentration of unfilterable/filterable carboplatin remained relatively stable within the 24 h following dialysis, with the drug being present in plasma up to 48 h post-administration.

Discussion

The present study showed that patients with renal insufficiency requiring hemodialysis may be treated with carboplatin-based chemotherapy at an attenuated dose, yielding both demonstrable efficacy and manageable toxicity. The doses of carboplatin closely approximated the appropriate dose estimated by available nomograms for patients with severe renal insufficiency [5, 7]. Both patients with GCT achieved a complete response, and the patient with transitional-cell carcinoma of the ureter was inevaluable for response but his disease has not progressed. Neither oto- nor neurotoxicity was observed. Dose escalation was not possible in these patients when renal insufficiency was sufficiently severe to require hemodialysis. The carboplatin dose for one patient was escalated in subsequent cycles as renal function improved. The observed myelosuppression emphasizes the importance of attenuation of the carboplatin dose, frequent hematologic monitoring, and early medical intervention for treatment of infectious complications in patients treated with carboplatin in the setting of severe renal insufficiency.

The pharmacokinetic studies showed that adequate AUCs were achieved before, during, and after hemodialysis [5, 7]. A high proportion of carboplatin remained free in plasma, with increased protein-binding over time being similar to that noted in patients with normal renal function [6, 14]. Since elimination of carboplatin is dependent on glomerular filtration [6, 14], the prolonged half-life of free carboplatin in patients with minimal or absent renal function was expected. The dialysis elimination half-life was markedly shorter than the pre-dialysis value, indicating that some (mostly free) carboplatin was dialyzed. No rebound of free platinum was detected after dialysis, which has been reported with methotrexate and makes dialysis of that drug in the setting of renal insufficiency of uncertain benefit [11].

The paucity of experience on the use and pharmacokinetics of cisplatin in dialysis-dependent patients [12, 22] limits its comparison to carboplatin. The majority of cisplatin is rapidly protein-bound, and renal excretion accounts for a minority of the elimination of free platinum [24]. For patients on chronic dialysis for whom nephrotoxicity is not a consideration, the administration of full-dose cisplatin has been recommended [24]. However, the published experience is limited to two dialysis-dependent patients who were treated with relatively low doses (50 and 30 mg) of cisplatin [12, 22]. Both patients died after a limited follow-up; therefore, the chronic and delayed toxicity could not be fully assessed [12, 22]. The relative lack of nonhematologic toxicity of carboplatin remains an attractive feature of this platinum analogue. Furthermore, in patients with marginal renal function or in whom recovery of renal function is anticipated, the use of carboplatin in the setting of dialysis-dependent renal insufficiency may preserve remaining kidney function and avoid nonhematologic toxicity.

In summary, carboplatin can be given to patients with renal insufficiency. Adequate AUCs are achieved and dialysis limits systemic exposure to free carboplatin. Although data on cisplatin administration under these circumstances is very limited, the greater protein binding of cisplatin makes its acute and chronic toxicity profile uncertain. Carboplatin is preferable to cisplatin in the circumstance of renal failure because of its predictable kinetics and limited toxicity profile.

References

1. Ahmed T, Bosl GJ, Hajdu S (1985) Teratoma with malignant transformation in men. Cancer 56: 860–863
2. Akaza H, Hagiwara M, Deguchi N, Kawai T, Satomi Y, Matsuda T, Miki T, Ueda T, Kotake T, Tazaki H, Aso Y, Niijima T, for the Carboplatin Study Group (1989) Phase II trial of carboplatin in patients with advanced germ-cell testicular tumors and transitional cell carcinomas of the urinary tract. Cancer Chemother Pharmacol 23: 181–185
3. Bosl GJ, Gluckman R, Geller N, Golbey RB, Whitmore WF, Herr H, Sogani P, Morse M, Martini N, Bains M, McCormack P (1986) VAB-6: an effective chemotherapy regimen for patients with germ-cell tumors. J Clin Oncol 4: 1493–1499
4. Calvert AH, Harland SJ, Newell DR, Siddik ZH, Jones AC, McElwain TJ, Raju S, Wiltshaw E, Smith IE, Baker JM, Peckham MJ, Harrap KR (1982) Early clinical studies with *cis*-diammine-1,1-cyclobutanedicarboxylate platinum(II). Cancer Chemother Pharmacol 9: 140–147
5. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME, Wiltshaw E (1989) Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 7: 1748–1756
6. Curt GA, Grygiel JJ, Corden BJ, Ozols RF, Weiss RB, Tell DT, Myers CE, Collins JM (1983) A phase I and pharmacokinetic study of diamminecyclobutane-dicarboxylatoplatinum (NSC 241240). Cancer Res 43: 4470–4473
7. Egorin MJ, Van Echo DA, Olman EA, Whitacre MY, Forrest A, Aisner J (1985) Prospective validation of a pharmacologically based dosing scheme for the *cis*-diamminedichloroplatinum analogue diamminecyclobutanedicarboxylatoplatinum Cancer Res 45: 6502–6506
8. Einhorn L (1981) Testicular cancer as a model for a curable neoplasm: The Richard and Hinda Rosenthal Foundation Award Lecture. Cancer Res 41: 3275–3280
9. Farhangi M, Weinstein SH (1987) Carboplatin, etoposide, and bleomycin for treatment of stage IIC seminoma complicated by acute renal failure. Cancer Treat Rep 71: 1123–1124
10. Gibaldi M, Perrier D (1982) Pharmacokinetics, 2nd edn. Marcel Dekker, New York
11. Gibson TP, Reich SD, Krumlovsky FA, Ivonavich P, Gonczy C (1978) Hemoperfusion for methotrexate removal. Clin Pharmacol Ther 23: 351–355
12. Goutette A, Lemoine R, Adhemar J, Kleinknecht D, Man N, Droz J, Macquet J (1981) Kinetics of cisplatin in an anuric patient undergoing hemofiltration dialysis. Cancer Treat Rep 65: 665–668
13. Harland S, Horwich A (1987) What dose of carboplatin can be combined with etoposide and bleomycin in patients with testicular cancer (abstract 184)? Proc Am Soc Clin Oncol 6: 48
14. Harland SJ, Newell DR, Siddik Z, Chadwick R, Calvert AH, Harrap KR (1984) Pharmacokinetics of *cis*-diammine-1,1-cyclobutanedicarboxylate platinum in patients with normal and impaired renal function. Cancer Res 44: 1693–1697
15. Horwich A, Dearnaley DP, Duchesne GM, Williams M, Brada M, Peckham MJ (1989) Simple nontoxic treatment of advanced metastatic seminoma with carboplatin. J Clin Oncol 7: 1150–1156
16. Horwich A, Dearnaley D, Harland S, Peckham MJ, Hendry WF (1989) Carboplatin-etoposide-bleomycin (CEB) combination chemotherapy is effective in good prognosis metastatic testicular non seminomatous germ cell tumours (abstract 521). Proc Am Soc Clin Oncol 8: 134
17. Logothetis CJ, Samuels M, Trindade A, Johnson DE (1982) The growing teratoma syndrome. Cancer 50: 1629–1635
18. Motzer RJ, Bosl GJ, Tauer K, Golbey R (1987) Phase II trial of carboplatin in patients with advanced germ cell tumors refractory to cisplatin. Cancer Treat Rep 71: 197–198
19. Motzer RJ, Cooper K, Geller NL, Pfister DG, Lin S, Bajorin D, Scher HI, Herr H, Fair W, Morse M, Sogain P, Whitmore W, Bosl GJ (1990) Carboplatin + etoposide + bleomycin for patients with poor risk germ cell tumors. Cancer 65: 2465–2471
20. Newell DR, Eeles RA, Gumbrell LA, Boxall FE, Horwich A, Calvert AH (1989) Carboplatin and etoposide pharmacokinetics in patients with testicular teratoma. Cancer Chemother Pharmacol 23: 367–372
21. Nisselbaum JS, Bosl GJ, Golbey RB, Schwartz DC, Schwartz MK (1984) Changes in serum alpha-fetoprotein and chorionic gonadotropin in response to cancer therapy. Ann Clin Lab Sci 14: 179–188
22. Prestayko AE, Luft F, Einhorn L, Crooke ST (1978) Cisplatin pharmacokinetics in a patient with renal dysfunction. Med Pediatr Oncol 5: 183–188
23. Sternberg CN, Yagoda A, Scher HI, Watson RC, Herr H, Morse M, Sogani P, Vaughan E, Bander N, Weiselber L, Geller N, Hollander P, Lipperman R, Fair W, Whitmore W (1988). M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. J Urol 139: 461–469
24. Sulkes A, Collins JM (1987) Reappraisal of some dosage adjustment guidelines. Cancer Treat Rep 71: 229–233
25. Vogelzang NJ, Lange PH, Goldman A, Vessala RH, Fraley EE, Kennedy BJ (1982) Acute changes of alpha-fetoprotein and human chorionic gonadotropin during induction chemotherapy of germ cell tumors. Cancer Res 42: 4855–4861
26. Williams S, Birch R, Einhorm LH, Irwin L, Greco FA, Loehrer PJ (1987) Treatment of disseminated germ-cell tumors with cisplatin, bleomycin and either vinblastine or etoposide. N Engl J Med 316: 1435–1440