Therapeutic Efficacy of Various Dosages and Modalities of Administration*

M. DE LENA, V. LORUSSO, A. PARADISO and S. TOMMASI
Istituto Oncologico, Via Scipione L'Africano 191, 70124 Bari, Italy

Abstract

Cisplatin is one of the most effective agents available for cancer chemotherapy. This drug showed noteworthy activity in several tumor types but, in particular, in genitourinary, gynecologic and head and neck cancer. In each of these tumors, cisplatin has become a focal point for combination chemotherapy studies. In fact the low to moderate hematologic toxicity of conventional doses and the possibility of preventing the renal toxicity by adequate hydration allows cisplatin to combine well with other myelosuppressive agents. Nowadays in testicular cancer, platinum-based combinations are able to cure also disseminated disease, and a high percentage of stage III–IV ovarian cancer patients submitted to debulking surgery and chemotherapy including cisplatin, may have a long survival and possibly a cure. A good palliation is also possible in bladder cancer, head and neck tumors and in advanced osteosarcoma: in these tumors new opportunities for treatment are offered employing cisplatin-containing regimens in neo-adjuvant chemotherapy. Activity for cisplatin has also been reported in cervix or endometrial cancer, prostate and lung cancer, pediatric solid tumors and lymphomas. While waiting for new platinum analogs with more therapeutic activity and less toxicity to be introduced in clinical practice, oncologists are trying to enhance the therapeutic efficacy of the drug by particular 'schedules' of administration. These efforts led to very interesting results: loco-regional infusions, continuous intravenous and intracavitary administrations or high dose cisplatin in hypertonic saline have been shown to be able to improve the results of cisplatin conventional doses consisting of 100 mg/mq i.v. every 3 weeks or 20 mg/mq i.v. for 5 consecutive days every 3 weeks. The purpose of all these modalities is to expose the tumor to very high drug concentrations which usually cannot be achieved by intravenous administration. In fact a very steep dose–response correlation was demonstrated for cisplatin-sensitive tumors. Loco-regional infusion has been used preoperatively in head and neck cancer and osteosarcoma in order to shrink tumor masses. Intracavitary cisplatin has major indications in tumors confined to peritoneal cavity, such as ovarian cancer, provided sodium thiosulfate administration is used to avoid systemic toxicity. Finally, high dose cisplatin in hypertonic saline seems to be very promising, but relevant myelotoxicity and neurotoxicity are still related to the treatment.

Introduction

In 1965, Rosenberg and coworkers observed that platinum ionic complexes were able to inhibit the replication of *Escherichia coli* in a solution containing ammonium and chloride ions [1]. Several platinum compounds were then synthesized and tested in experimental tumors before *cis*-diamminedichloroplatinum (cisplatin) was introduced in clinical trials. This drug showed noteworthy activity in several tumor types (Table I) but the major impact occurred in the treatment of genitourinary, gynecologic and head and neck cancer. In each of these tumor types cisplatin showed activity as a single agent and was induced in many combination regimens in order to enhance the therapeutic efficacy. The moderate hematologic toxicity of conventional doses and the possibility of preventing the renal toxicity by adequate hydration, allowed cisplatin to be combined with other myelosuppressive agents. Moreover, in experimental studies *in vitro* or in animal models, cisplatin showed synergism with several drugs, such as cyclophosphamide, 5-fluorouracil, etoposide (VP-16) and Ara-C [3–5]. The only side effect that seems

TABLE I. Antitumoral Activity of *cis*-Diamminedichloroplatinum(II) (Cisplatin)

High	Moderate	Limited
Testicular	Lung (oat cell)	Breast
Ovary	Lung (non oat cell)	Prostate
Head and neck	Bladder	Esophagus
Osteosarcoma	Cervix	Stomach
	Lymphomas	

*Paper presented at the Symposium on Cisplatin and Inorganic Anticancer Drugs, Bari, Italy, November 6–7, 1986.

0020-1693/87/$3.50

difficult to manage is the gastrointestinal toxicity with intense nausea and vomiting present at the time of administration and lasting for several hours: however, the most recent antiemetic combinations, including dexametasone, metoclopramide and diphenidramine, are able to diminish the patients' distress from cisplatin-induced emesis [2] and improve treatment compliance.

Results and Discussion

The conventional doses of cisplatin are 15–20 mg/mq i.v. daily for 5 consecutive days or a single dose of 50–120 mg i.v. every 3 weeks (Table II). With these dosages no particular precautions are needed in order to avoid renal toxicity other than hydration from the day before the treatment to the day after (Table III). The question as to whether mannitol and/or furosemide added to hydration fluids improves renal toxicity amelioration has still not been resolved. Vogl [6] reported a 'short hydration' scheme with forced diuresis (Table IV) useful in the outpatient clinic but in our experience and in that of other authors [7], the need for forced diuresis with drugs is not mandatory provided there is adequate hydration and normal renal function. The hydration modalities utilized in our institute are shown in Table V. The same modalities were also used in the outpatient clinic.

Cisplatin is the most effective single agent that has been discovered for the treatment of metastatic testicular tumors, and platinum-containing regimens have provided the field of chemotherapy with some of its most spectacular results. The most popular of these regimens is called PVB (Table VI). with this regimen Einhorn [8] (from Indiana University) reported 71% complete responses and 25% partial responses in 47 evaluable patients affected by metastatic germ cell tumors of the testis. Bone marrow toxicity was dose-limiting: seven patients had documented sepsis and one of them died. Many other regimens have been proposed by other authors for testicular cancers but up to date no combination regimen has shown a clear superiority to PVB in randomized studies.

Interesting but less exciting results were obtained in studies on ovarian cancer. In this type of tumor the combination of platinum, adriamycin and cyclophosphamide (PAC) has been the most widely used (Table VII). In patients not previously treated with chemotherapy complete response was achieved in 37% and partial response in 31.5% of the cases [9]. There is the possibility that many patients obtaining complete pathological remission can be cured of their disease.

In bladder cancer, cisplatin is the most active single agent and no combination has been found with clear superiority to platinum alone in randomized studies. An objective response of 40–50% of 6 to 12 months duration is achievable with 100 mg/mq every 3 weeks, but in the literature there are rare reports of long-lasting responses [10]. A strict correlation between surgery and chemotherapy consisting of platinum, methotrexate, adriamycin and vinblastine (M-VAC) has recently shown relevant activity in bladder cancer that warrants further investigation [11].

In head and neck cancer, the combinations of platinum with 5-fluorouracil [12] or with methotrexate and bleomycin [13] have been used in advanced disease as a palliative and also in less advanced cases in order to shrink the tumor and facilitate surgery or radiotherapy (neo-adjuvant setting). The results were satisfactory in terms of clinical response (60–80% tumor shrinking) but poor regarding survival or cure [14] (Table VIII).

Rosen [15] has reported significant activity for cisplatin in osteogenic sarcoma patients heavily pretreated with chemotherapy (4 responses out of 20

TABLE II. Conventional Doses of Cisplatin

Daily × 5 consecutive days	15–20 mg/mq i.v. in 15 min every 3 weeks
Single dose	50–120 mg/mq i.v. in 30 min every 3–4 weeks

TABLE III. Hydration Schemes

Low doses (15–20 mg/mq die)	Medium doses (80–120 mg/mq die)
Day before treatment: oral hydration (at least 1000 ml)	Day before treatment: oral hydration (at least 1000 ml)
Day of treatment: cisplatin in 250 ml of normal saline i.v. followed by 1000–1500 ml of dextrose 5%	Day of treatment: 500 ml normal saline + 15 mEq/l magnesium sulfate; cisplatin in 250 ml normal saline i.v. followed by normal saline 1000 ml + 20 mEq/l KCl; dextrose 5% 1000 ml
	Day after treatment: dextrose 5% 2000 ml i.v. + oral hydration

TABLE IV. Short Hydration

Time (min)	
0	dextrose 5% 500 ml + 20 mEq KCl + 72.5 mEq Na, 2.5 mEq K, 50 mEq Cl, 20 mEq lactate, 5 mEq phosphate (basal solution) + furosemide 40 mg
30	basal solution mannitol 12.5 mg
45	cisplatin in 100 ml of normal saline
60	basal solution
90	basal solution

TABLE V. Hydration Modalities Utilized in the Oncologic Institute of Bari

Day before treatment	oral hydration 1000–1500 ml
Day of treatment	dextrose 5% 500 ml; normal saline 500 ml + metoclopramide; cisplatin in 100 ml of normal saline; normal saline 500 ml + Na 72.5 mEq, K 2.5 mEq, Cl 50 mEq, lactate 20 mEq, phosphate 5 mEq; normal saline 500 ml + KCl 20 mEq

TABLE VI. Cisplatin in Testicular Cancer

Platinum	20 mg/mq daily X 5 i.v.	
Vinblastine	0.4 mg/kg days 1 and 2 i.v.	every 3 weeks
Bleomycin	30 U days 2, 9, 16 i.v.	

TABLE VII. Cisplatin in Ovarian Cancer

Platinum	50 mg/mq i.v. day 1	
Adriamycin	50 mg/mq i.v. day 1	every 3–4 weeks
Cyclophosphamide	750 mg/mq i.v. day 1	

TABLE VIII. Cisplatin in Head and Neck Cancer

Cisplatin	100 mg/mq i.v. day 1	
5 Fluorouracil	1000 mg/mq i.v. day 1 to 5 (120 h)	every 3 weeks
Methotrexate	40 mg/mq i.v. day 1–15	
Bleomycin	10 U i.m. day 1–8–15	
Cisplatin	50 mg/mq i.v. day 4	

patients). Activity for cisplatin has also been reported in gynecological malignancies, prostate cancer, lung cancer, pediatric solid tumors and lymphomas.

In conclusion, this highly active agent is an important part of the arsenal of the clinical oncologist who now must ask himself if it is possible to enhance the therapeutic efficacy of this drug by particular systems of administration. In fact loco-regional infusions, continuous intravenous and intracavitary administrations or high dose cisplatin in hypertonic saline have been shown to be able to improve the results of cisplatin, although they need further investigation.

Intra-arterial Chemotherapy (IAC)

The rationale behind the use of IAC infusion is based on the exposure of the tumor to very high drug concentrations which usually cannot be achieved by intravenous administration of the same doses of drugs. Stewart and colleagues [16] and Jaffe and colleagues [17] used IAC by inserting percutaneous catheters into epatic, femural, brachial or carotid arteries. They administered cisplatin at the dosage of 120–150 mg/mq over 150 min + 1000–3000 U of eparin every 14 days. A systemic abundant hydration was provided. Phase I studies showed that IAC with cisplatin is well tolerated with acceptable local toxicity. With regard to the therapeutic activity, objective responses were observed also in cases refractory to conventional doses. Poor results were achieved in the treatment of brain metastases by intracarotid administration of cisplatin [18] because of the relevant side effects (headache, lethargy, psychomotor excitment and paresis) and the short duration of responses (Table IX).

TABLE IX. Intra-arterial Chemotherapy (IAC)

Cisplatin dose (mg/mq)	Arteries	Time of administration (min)	Eparin (U)
120–150	epatic brachial	150	1000–3000
150	femural	120	3000
50–100	carotid	50	3000

Nowadays the main indications for IAC with cisplatin are: preoperative neo-adjuvant treatment of osteosarcoma [17] and head and neck cancer [19], or therapy of epatic metastases of tumors sensitive to the drug.

Intraperitoneal Chemotherapy (i.p.)

The goal of intraperitoneal administration of drugs is to expose tumors confined to the peritoneal cavity to drug concentrations higher than those achievable by intravenous delivery. In fact when drugs are administered by peritoneal dialysis, the ratio of total exposure (area under the concentration X time curve AUC) of the peritoneal cavity to that of the systemic circulation is determined by the relative clearances of the drug from these two compartments [20]. Prac-

tically speaking, if a drug is slowly removed from the peritoneal cavity and rapidly eliminated from the rest of the body or extensively metabolized during passage from the cavity to plasma, its concentration in the cavity can be maintained at a higher level than in the plasma [20]. Table X shows the absorption of antineoplastic drugs from the peritoneal cavity over 1 h following administration in rats [21]. Under the conditions of a sufficiently high cavity/plasma concentration ratio, the i.v. infusion of a competitive neutralizing agent may further improve the therapeutic index by blocking the toxicity of the drug reaching the plasma. Howell *et al.* [22] demonstrated that simultaneous administration of sodium thiosulfate protects against nephrotoxicity, thus allowing doses as high as 270 mg/mq of cisplatin to be administered intraperitoneally. Sodium thiosulfate reacts covalently with cisplatin forming a complex that has no toxicity but probably also no activity. Table XI shows the guidelines for i.p. administration of low or high doses of the drug. Pharmacokinetic data show that with i.p. administration the AUC of ascites is 30 times higher than that achievable with the same doses given by the i.v. route (Table XII).

TABLE X. Absorption of Antineoplastic Drugs from the Peritoneal Cavity One Hour after Administration in Rats[a]

Drug	Percent absorbed	Molecular weight
1-Asparaginase	9.0	133000
Bleomycin	12.7	1400
Methotrexate	15.0	472
Doxorubicin	20.1	580
5-Fluorouracil	28.4	130
Cytosine arabinoside	29.5	243
Cisplatin	33.0	300
Chlorambucil	69.2	304
Thiotepa	74.4	188
Hexamethylmelamine	91.7	210

[a]Modified and reprinted from ref. 37.

Data regarding activity against ovarian carcinoma are summarized in Table XIII. Five out of seven ovarian cancer patients responded in the studies of Howell [22, 23] but the response criteria were loosely defined (negative cytology or decrease in ascites considered as partial remission). The high pathological complete response (33%) reported by ten Bokkel Huinink [24] is encouraging but the follow-up is too short to reach any definite conclusion. The data of Cohen [25] confirm that i.p.-administered cisplatin may be able to save some patients with microscopical or small macroscopical residual disease following the completion of first-line chemotherapy. The side effects observed were: mild abdominal pain (20%), chemical peritonitis (10%), transcatheter infection (10–15%), nausea and vomiting (100%), mild to moderate myelosuppression.

There are several problems associated with i.p.-administered cisplatin: (1) clinical assessment of response is difficult by physical or cytological examinations without further pathological evaluation either through laparotomy or laparoscopy; (2) some patients who obtained abdominal response relapsed within a few months in extra abdominal sites; (3) it is well documented that thiosulfate protects kidneys from the nephrotoxic effect of cisplatin, probably because it is concentrated extensively in the kidneys neutralizing the cisplatin reaching the renal tubules, but it is possible that thiosulfate also inhibits tumoricidal activity at the cellular level [29].

TABLE XI. Guidelines for Intraperitoneal Administration of Low or High Doses of Cisplatin by Tenckhoff Catheter[a]

Low doses	High doses
Systemic hydration: 200 ml/h of 5% dextrose, starting 2 h before and lasting 4 h after i.p. treatment	Systemic hydration: 1000 ml of normal saline starting 12 h before; 12.5 g of mannitol during the treatment + 20 mg of furosemide i.v. bolus followed by 30 mg in 1000 ml of normal saline (6 h infusion); dextrose 5%: 167 ml/h lasting 12 h
Intraperitoneal (i.p.) treatment: cisplatin 60 mg/mq in 500 ml of normal saline in 15 min, (remove at least 500 ml of ascites if present before cisplatin administration); 1000–1500 ml of normal saline; remove the drug after 2–4 h	Intraperitoneal (i.p.) treatment: cisplatin 90–270 mg/mq in 2000 ml of normal saline in 10 min; remove after 4 h
	Antidote: sodium thiosulfate 7.5 g/mq i.v. bolus followed by 2.13 g/mq in 1000 ml of 5% dextrose (12 h infusion)

[a]From ref. 38.

Further investigations are needed with this very promising experimental technique with emphasis on its possible use in ovarian cancer and gastrointestinal cancers extended to the peritoneal cavity.

Intrapericardial Administration

Neoplastic pericardial effusions rarely respond to conventional therapies Markman and Howell [30] treated 1 patient affected by adenocarcinoma of the lung with pericardial effusion not responsive to systemic chemotherapy, with 50 mg of cisplatin in 5 consecutive days administered in the pericardial sac by Tenckhoff catheter. Complete response was obtained without relevant side effects Fiorentino and coworkers [31] treated 6 patients affected with neoplastic pericardial effusion (2 from Hodgkin disease, 2 from breast cancer, 1 thymoma and 1 mesothelioma). Complete response was obtained in 3 cases (1 Hodgkin, 1 breast cancer and the tymoma) with a duration of 6, 5 and 8 months, respectively (Table XIV).

TABLE XII. Pharmacokinetics of Cisplatin (High and Low Doses) Administered by Intravenous or Intraperitoneal Route[a]

Parameters	Low doses		High doses i.p.
	i.v.	i.p.	
Maximal concentration (γ/ml)			
Ascites	0.3	20.5	84.8
Plasma	1.7	0.2	7.5
AUC (γ/ml/h)			
Ascites	1.1	31.5	184.3
Plasma	1.5	8.0	18.4
Urinary excretion in 24 h	41	9	

[a]From ref. 38.

Intrapleural Administration

Also pleural effusions are rarely controlled by systemic chemotherapy. Usually local treatment with sclerosing agents such as tetracycline or bleomycin is employed in order to obtain a complete obliteration of pleural space secondary to fibrinous sclerositis. Recently Markman and coworkers [32] administered intrapleural cisplatin (100 mg/mq) in 250 ml of normal saline plus Ara-C; sodium thiosulfate 4 g/mq i.v. bolus followed by 12 g/mq (6 h infusion) was provided to prevent nephrotoxicity. Five out of seven evaluable patients obtained objective response with mild toxicity.

Intravescical Administration

Cisplatin is the most active single agent against bladder cancer when administered by the i.v. route. Little data are available concerning its activity by intravescical administration. An on-going study by EORTC [33] is comparing intravescical thiotepa, adriamycin, or cisplatin against local relapses after TUR. Preliminary results are encouraging. Cisplatin is introduced by transurethral catheter at the dosage of 50 mg in 50 ml of normal saline and removed after about 50 min.

High-Dose Cisplatin (HD-cisplatin) in Hypertonic Saline

The rationale for HD-cisplatin in hypertonic saline is as follows: (1) cisplatin has a steep dose–response curve in sensitive tumors; (2) dose schedules greater than either 100 mg/mq (in 5 divided doses) or 120 mg/mq (as single dose) have not been used due to

TABLE XIII. Activity of Intraperitoneally Administered Cisplatin in Ovarian Carcinoma

Author (references)	Dose	No. Patients	Response (%)	Comments
Howell [23]	90–270 mg/mq	7	5(71)	response loosely defined
ten Bokkel Huinink [24]	60–150 mg/mq	27	9(33)	all minimal residual disease obtained CR
Cohen [25]	50 mg/mq	23	15(65)	minimal residual disease <6 cm
Pretorius [26]	120–180 mg	4	3(75)	1 CR documented by laparotomy
Caspar [27]	60 mg/mq	4	1(25)	clinical response
Lopez [28]	25–60 mg/mq	7	n.a.	response not analyzed

TABLE XIV. Particular Modalities of Administration

Intrapericardial administration	cisplatin 50 mg in 5 days by Tenckhoff catheter
Intrapleural administration	cisplatin 100 mg/mq in 250 ml of normal saline; sodium thiosulfate 4 mg/mq i.v bolus followed by 12 mg/mq (6 h infusion)
Intravescical administration	cisplatin 50 mg in 50 ml of normal saline; transurethral instillation lasting 50 min

TABLE XV. High-Dose Cisplatin in Hypertonic Saline, PVeBV Scheme Hydration and Toxicity[a]

PVeBV scheme	cisplatin 40 mg/mq continuous infusion for 5 consecutive days; VLB 0.2 mg/kg i.v. day 1; VP-16 100 mg/mq i.v. continuous infusion for 5 days; BLM 30 U/i.v. weekly
Hydration	250 ml/h normal saline + 20 mEq/l KCl, starting 12 h before the treatment and lasting 12 h after; cisplatin 40 mg/mq in 250 ml of hypertonic saline 3% (in 30 min); furosemide 20 mg/i.v. bolus before cisplatin
Toxicity	renal (2/15); severe leukopenia (<1000 w.b.c/mm^3) (15/15); severe thrombocytopenia (<20.000 PP/mm^3) (15/15); ototoxicity (2/15); peripheral neuropathies (6/17); severe nausea and vomiting (17/17)

[a]From ref. 38.

dose-limiting renal toxicity; (3) recent studies of Litterst [34] have demonstrated that cisplatin nephrotoxicity, but not antitumor effect, can be reduced in animals if the drug is administered in hypertonic sodium chloride.

Ozols *et al.* [35] reported the results of phase I-II trials of HD-cisplatin in hypertonic saline with the combination PVeBV (Table XV). They obtained 88% complete responses in poor prognosis untreated patients with testicular cancer. The dose of cisplatin was as high as two times the conventional dose (40 *vs.* 20 mg/mq daily X 5). The toxicity was severe (myelosuppression, ototoxicity and neurotoxicity).

In ovarian carcinoma [36] 19 patients, pretreated with conventional doses of cisplatin were submitted to HD-cisplatin (40 mg/mq for 5 consecutive days). Objective response was observed in 32% of cases but the incidence of neurotoxicity in these patients was greater than in testicular cancer ones. This was probably due to more advanced age and cisplatin pretreatment.

In conclusion: (1) HD-cisplatin in hypertonic saline with abundant systemic hydration (5000 ml) is an effective regimen without severe nephrotoxicity; (2) HD-cisplatin is more effective than conventional cisplatin; (3) the toxicity of the treatment is still relevant, particularly dose-limiting are myelosuppression, ototoxicity and neurotoxicity; (4) very careful evaluation of pretreatment renal function or neuropathy is needed and very specialized assistance must be provided during drug administration.

Conclusions

Cisplatin is one of the most active agents in the 'arsenal' of the medical oncologist. The low to moderate hematological toxicity allows combination of cisplatin with other myelosuppressive agents. The best results achieved by platinum-based combinations were in testicular and in ovarian cancer with the conventional doses of 100 mg/mq i.v. or 20 mg/mq daily X 5. These are the current doses recommended in clinical practice. Other modalities are utilized only in very specialized centers but must be considered still experimental. Among these the most promising seem to be:

(1) IAC (intra-arterial) which is effective as a preoperative treatment in osteosarcoma or head and neck cancer;

(2) i.p. (intraperitoneal) used for minimal residual disease of ovarian carcinoma;

(3) HD-cisplatin (high dose) that showed activity in patients pretreated with conventional doses but also relevant toxicity.

Even as new platinum analogs loom on the horizon, the clinical research on cisplatin continues to testify to the fact that the medical oncologist does not passively await new discoveries, but continually 'sharpens his present weapons for the fight'.

References

1 B. Rosenberg, L. Van Camp and T. Krigas, *Nature (London), 205,* 698 (1965).
2 M. G. Kris, R. J. Gralla, L. B. Tyson, R. A. Clark, D. P. Kelsen, L. K. Reilly, S. Groshen, G. J. Bosl and L. A. Kalman, *Cancer, 55,* 527 (1985).
3 F. M. Shabel, Jr., M. V. Trader, W. R. Carter, Jr., T. H. Carbett and D. P. Griswold, Jr., *Cancer Treat. Rep., 63,* 1459 (1979).
4 B. Drewinko, C. Green and T. L. Loo, *Cancer Treat. Rep., 60,* 1619 (1976).
5 B. Rosenberg, *Cancer, 55,* 2303 (1985).
6 S. D. Vogl, T. Zavarious and B. Kaplan, *Cancer, 45,* 11 (1980).
7 J. Ortrow, M. J. Egorin, D. Hahn, S. Markus, J. Aisner, P. Chang, A. Le Roy, N. R. Bachur and P. H. Wiernik, *Cancer Treat. Rep., 65,* 73 (1981).
8 L. H. Einhorn and J. P. Donahue, *Ann. Inter. Med., 87,* 293 (1977).
9 C. E. Eherlich, L. Einhorn, S. D. Williams and J. Morgan, *Cancer Treat. Rep., 63,* 281 (1979).
10 D. J. Higby, H. J. Wallace, D. J. Albert and J. F. Holland, *Cancer, 33,* 1219 (1974).
11 C. M. Sternberg, A. Yagoda, H. I. Sher, R. C. Watson, P. S. Hollander, H. W. Her, P. C. Sogani, M. J. Morse, W. R. Fair and W. F. Whitmore, *Proc. ASCO, C409,* 105 (1985).
12 M. Rooney, J. Kish, J. Jacobs, J. Kinzie, A. Weaver, J. Crissman and M. Al-Sarraf, *Cancer, 55,* 1123 (1985).
13 S. E. Vogl and B. H. Kaplan, *Cancer, 44,* 26 (1979).
14 I. F. Tannock and G. Browman, *J. Clin. Oncol., 4,* 1121 (1986).
15 G. Rosen, A. Niremberg, B. Caparres, H. Juergens, C. Tan and R. Gutierrez, in A. W. Prestayko, S. T. Crooke and S. K. Carter (eds.), 'Cisplatin in Metastatic Osteogenic Sarcoma', Academic Press, New York, 1980, pp. 465–475.
16 D. J. Stewart, R. S. Benjamin, S. Zimmerman, R. M. Caprioli, S. Wallace, W. Chuang, D. Calvo III, M. Samuel and J. Bonura, *Cancer Res., 43,* 917 (1983).

17 N. Jaffe, J. Knapp, V. P. Chuang, S. Wallace, A. Ayola, J. Murray, A. Cangir, A. Wang and R. S. Benjamin, *Cancer, 51,* 402 (1983).
18 D. J. Stewart, S. Wallace, L. Fevu, M. Leavenus, S. E. Young, S. Handel, G. Mavligit and R. S. Benjamin, *Cancer Res., 42,* 2059 (1982).
19 S. Frustaci, L. Barzan, S. Tumolo, R. Comoretto, G. Quadu, E. Galligioni, M. Lorenzini, D. Crivellari, G. Caruso, G. Piccin, A. Veronesi, U. Tirelli and E. Grigoletto, *Cancer, 57,* 1118 (1986).
20 R. L. Dedrick, C. Myers, P. M. Bungay and V. T. De Vita, Jr., *Cancer Treat. Rep., 62,* 1 (1978).
21 C. L. Litterst, I. J. Torres, S. Arnold, D. McGunagle, R. Furner, B. I. Sikic and A. M. Guarino, *Cancer Treat. Rep., 66,* 147 (1982).
22 S. B. Howell, C. E. Pfeifle, W. E. Wung and R. A. Olshen, *Cancer Res., 43,* 1426 (1983).
23 S. B. Howell, C. E. Pfeifle, W. E. Wung, R. A. Olshen, W. E. Lucas, J. L. Yon and M. Green, *Ann. Intern. Med., 97,* 845 (1982).
24 W. W. ten Bokkel-Huinink, R. Dubbelman, E. Aartsen, H. Franklin and J. G. McVie, *Semin. Oncol. (Suppl. 4),* 43 (1985).
25 C. J. Cohen, *Semin. Oncol. (Suppl. 3), 12,* 53 (1985).
26 R. G. Pretorius, N. F. Hacker, J. S. Berek, L. C. Ford, J. D. Hoeschele, J. A. Bertler and L. D. Lagasse, *Cancer Treat. Rep., 67,* 1085 (1983).
27 E. S. Carper, D. P. Kelsen, N. W. Alcock and J. L. Lewis, *Cancer Treat. Rep., 67,* 235 (1983).
28 J. A. Lopez, J. G. Krikorian, S. D. Reich, R. D. Smyth, B. F. Issel and F. H. Lee, *Proc. ASCO, C122,* 31 (1983).
29 J. Uozumi, M. Ishizawa, Y. Iamoto and T. Baba, *Cancer Chemother. Pharmacol., 13,* 82 (1984).
30 M. Markman and S. B. Howell, *Cancer Drug Delivery, 1,* 49 (1985).
31 O. Daniele, A. Fornariero, S. M. L. Aversa, C. Ghiotto, P. Morandi and M. V. Fiorentino, *Tumori, 195,* 701 (1986).
32 M. Markman, S. Cleary, M. E. King and S. B. Howell, *Med. Pediatr. Oncol., 13,* 191 (1985).
33 L. Denis, *Lancet, 1,* 1378 (1983).
34 C. L. Litterst, *Toxicol. Appl. Pharm., 61,* 99 (1981).
35 R. F. Ozols, B. J. Cordeu, J. Jacob, M. N. Wesley, Y. Oschega and R. C. Young, *Ann. Intern. Med., 100,* 19 (1984).
36 R. F. Ozols, Y. Oschega, C. E. Myers and R. C. Young, *J. Clin. Oncol., 3,* 1246 (1985).
37 D. E. Brenner, *J. Clin. Oncol., 4,* 1135 (1986).
38 G. Gasparini and E. Bajetta, *Argomenti Oncol., 7,* 2 (1986).