Preclinical Studies of Cisplatin Analogs*

G. PRATESI
Istituto Nazionale Tumori, Milan, Italy

Abstract

The rationale for the development of new analogs of antitumor drugs is based on the identification of compounds endowed with reduced toxicity and/or increased antitumor effects, *i.e.* higher efficacy on sensitive tumors, wider or different activity spectrum, activity on resistant tumors. The choice of suitable experimental models still represents a challenging point for the experimental researcher, since no model is totally representative of the clinical situation. In the cisplatin area more than a thousand analogs have been screened and less than twenty have been selected for clinical evaluation. This communication deals with an analysis of the experimental models used for the choice of potentially useful drugs. From this retrospective analysis it can be seen that a selection based on few experimental tumors yielded compounds often disappointing at the clinical level, as for the DACH derivatives series showing high activity on L1210 leukemia made resistant to cisplatin. The importance of studying toxicity and antitumor activity on a wide panel of experimental models is stressed. Data on the effects of selected cisplatin derivatives on human xenografts and on primary murine tumors will also be presented.

Introduction

cis-Diamminedichloroplatinum(II) (cisplatin), first identified as an antitumor drug in the late 60's [1], has now been proved to be effective for the treatment of a wide variety of solid cancers in man [2]. It is reasonable to expect that analogs of this drug may be found with superior activities in animals studies, and with either less toxicity or a different spectrum of toxicities. Indeed, more than 200 such analogs out of over 1000 tested have met the criteria of activity against one or more tumor screen systems.

As of late 1979, the success rate for finding active platinum coordination complexes in experimental models is far higher (about 18%) than for the purely organic chemicals (about 5%), and does suggest that we should intensify the search in this field [3]. Fifteen analogs have been tested in phase I clinical trials up to now. However eight of these analogs have been withdrawn during the 70s and four during the early 80s. High toxic effects were usually responsible for stopping the study. Only three analogs still survive in clinical trials, namely cyclobutanedicarboxylate-Pt(II) (carboplatin, CBDCA, JM8) in phase III, isopropylamine-Pt(IV) (iproplatin, CHIP, JM9) in phase II, and *trans*-l-diaminocyclohexaneoxalato-Pt(II) (l-OHP) in phase I.

Results and Discussion

The aim of this presentation is to look back to the experimental results determining the choice of these few selected platinum compounds. JM8 and JM9 were first screened at the English Institute of Cancer Research where hundreds of analogs have been examined and 40 identified as active moieties. Eight compounds of the JM series were selected for more preclinical studies [4]. As well as antitumor activity, other considerations guided the selection, such as aqueous solubility, reactivity of the leaving groups and lack of crossresistance to cisplatin. All of them were compared to the parent drug in respect of several biological properties, as reported in Table I. Investigations for a potential biochemical selectivity is based on the ability of cisplatin to bind to nuclear proteins [5] with consequent enhancement of non-histone protein phosphorylation that has been reported to correlate with cell kill. JM8, JM9 and

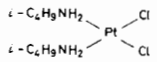
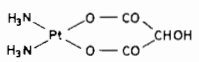
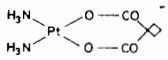
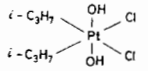
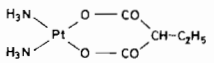
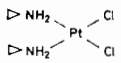
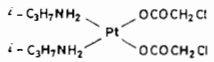
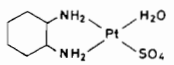
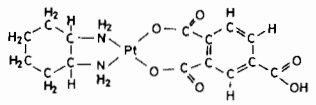
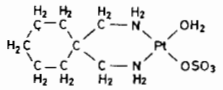
TABLE I. Biological Evaluation of Analogs

Biochemical selectivity	ability to elevate nuclear protein phosphorylation in tumor, liver and kidney
Toxicity	lethal, hematological, renal, emetic
Antitumor activity	effect on L1210/DDP, effect on spectrum of tumor sensitive to cisplatin

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

0020-1693/87/$3.50

TABLE II. List of Platinum Complexes

Number	Structure	Compound name
		*cis*-dichlorodiammineplatinum(II) (cisplatin)
JM 2		*cis*-dichlorodiisobutylamineplatinum(II) (diisobutylamine)
JM 5		*cis*-diamminehydroxymalonateplatinum(II) (hydroxymalonate)
JM 8		*cis*-diammine-1,1-cyclobutanedicarboxylate (CBDCA)
JM 9		*cis*-dichloro-*trans*-dihydroxyisopropylamine-platinum(IV) (CHIP)
JM 10		*cis*-diammineethylmalonateplatinum(II) (ethyl malonate)
JM 11		*cis*-dichlorodicyclopropylamineplatinum(II) (dicyclopropylamine)
JM 16		*cis*-diisopropylaminedichloroacetateplatinum(II) (diisopropylamine chloroacetate)
JM 20		sulfato-1,2-diaminocyclohexaneplatinum(II) (Dac-sulphate)
JM 82		(4-carboxyphthalato)(1,2-diaminocyclohexane)-platinum(II)
TNO 6		aqua(1,1-bis(aminomethyl)cyclohexane)sulfato-platinum(II)

JM20 show a higher enhancement in tumor tissue as compared to normal kidney and liver tissues [4].

Table II shows the list of compounds which we will discuss with respect to toxicity and activity studies.

The different toxicities were evaluated in mice, except the emetic one for which ferrets were used. From Table III it may be seen that most compounds are less potent and less nephrotoxic than cisplatin. Moreover they induce a similar emesis degree and higher myelosuppressive effects than cisplatin does. JM8 had the best pattern of toxicity. The lack of correlation between some experimental and clinical results in toxicity studies will be presented.

As for as antitumor activity, all the compounds except l-OHP, containing the diaminocyclohexane moiety, namely JM20, JM82, TNO6 and PHIC (diaminecyclohexaneisocitrato-Pt(II)) showed activity on the L1210 leukemia resistant to cisplatin (see

TABLE III. Toxicity[a]

	Acute LD_{50} value (i.p.)	Percentage incidence of BUN ⩾ 30%	Maximal percentage decrease WBC (day)	Emetic[b] effects
cisplatin	17.8	80	53 (3)	[c]
JM5	208	10	64 (5)	
JM8	181	0	50 (4)	[d]
JM9	51.5	0	61 (5)	[c]
JM10	120	0	44 (3)	
JM20	22.5	0	67 (5)	
JM82	76.5	45	56 (5)	[c]
l-OHP	20	0		
TNO6	11–20	0	62 (5)	[c]

[a]Values in the Table were obtained from refs. 8, 9, 10 and 11. [b]Observed in ferret. [c]Emesis in the majority of ferrets. [d]Emesis in 50% at highest dose tested.

Table IV). Unfortunately, all these analogs did not overcome phase I clinical trials, mainly for unexpected toxic problems, and therefore could not be adequately evaluated for their therapeutic potential. However, not one compound showed better antitumor effects than cisplatin when tested in a panel of murine solid tumors or in three human xenografted tumor lines (LX, CX and MX), as reported in Table V.

TABLE IV. Activity on L1210 i.p., Single i.p. Treatment[a]

Compound	Optimal dose	Maximum *T/C* (%)	
		L1210/0	L1210/DDP
cisplatin	8	164–229	106–121
JM8	128	150	113
JM9	32	171	118
JM40	34	129	109
JM20	12	200–217	200–370
JM82	59	217–250	290
TNO6	18	233	171
PHIC	169	193	>333 (9 inj)
L-OHP	6–8	245	Not active

[a]Values in the Table were obtained from refs. 8, 9, 12, 13 and 14.

Many studies have dealt with JM8 and JM9 activity on human tumors transplanted in nude athymic mice and some of them are reported in Table VI. In these reports cisplatin seems the better drug, because it induces tumor growth reduction in 11/13 mixed tumors as compared to 10/13 and 4/7 for JM8 and JM9, respectively. Moreover tumor growth reduction higher than 90% was reached in 8/13 cisplatin-treated, and in 3/13 and 2/7 analog-treated tumors. The broad spectrum of human tumors utilized in these experimental studies could possibly make them comparable to a phase II clinical study.

The antitumor efficacy of JM8 and JM9 was compared to cisplatin against primary colonic tumors chemically induced in outbred mice [6]. all drugs reduced tumor growth but only cisplatin reached statistically significant values, either given alone or in combination with 5-fluorouracil. A comparison with phase II clinical results in colon cancer will be made.

In a recent paper, Rose [7] presented the M5076 murine tumor as a model yielding preclinical data

TABLE V. Xenografted Tumor Lines[a]

Compound	Mouse tumors						Human tumors		
	M109 Lung	B16 Melanoma	CD8F1 Mammary	Colon 38	Lewis Lung	Colon 26	Lung LX	Colon CX	Mammary MX
cisplatin	++	+++	++	+	+++	+++	–	–	+
JM8	↓	↓	↓	=		↓	=	=	↓
JM9		↓	↓	=		↓	=	=	↓
JM40	↓	↓			=	=		=	
JM20		↓							
JM82	↓	↓	↓	=	=	↓		=	
L-OHP		↓			↓				
TNO6	↓	↓			↓	↓			

[a](–) Inactive; (+), ILS = 25–50% or TWI = 25–50%; (++), ILS = 50–100% or TWI = 50–75%; (+++), ILS > 100% or TWI > 75%.

TABLE VI. Activity on Human Xenografted Tumors

Human tumor		Relative tumor growth in treated over control mice						Reference
Type	Number	DDP		CBDCA		CHIP		
		<50%	<10%	<50%	<10%	<50%	<10%	
Yolk SAC	3		3	1	2	1	1	15
Ovarian CA	2	1	1	1	1		1	16
Bladder transitional cell CA	2	1		1		1		17
Urothelial	3	1	2	2		N.D.		18
Pancreas ductal adeno CA	3		2	2		N.D		19
Total	13	3	8	7	3	2	2	

which correlated with evolving clinical results'. Responses of mice bearing subcutaneously implanted M5076 tumors to cisplatin, JM8 and JM9 were observed repeatedly, whereas TNO6 was inactive. This model could then represent an useful tool for the first screening of cisplatin analogs instead of the widely used murine leukemias.

In conclusion, it is generally accepted that preclinical studies on suitable models provide really useful information; specifically, my opinion is that it is incorrect to expect that 'one' experimental model will predict clinical utility of a new antitumor drug, but only careful evaluation of a range of experimental results could lead to the selection of promising derivatives. In the cisplatin area, attention has been focused more on reduced toxicity than on superior antitumor activity in selecting second generation analogs.

In the light of the widely used clinical modalities reducing cisplatin nephrotoxicity, more activity studies should be considered, especially in cisplatin-resistant tumors other than L1210/DDP leukemia, in choosing third generation cisplatin analogs for clinical trials.

References

1 B. Rosenberg *et al., Nature (London), 222,* 385 (1969).
2 S. K. Carter, in M. P. Hacker, E. B. Douple and I. H. Krakoff (eds.), 'Platinum Coordination Complexes in Cancer Chemotherapy', Martinus Nijhoff, Boston, 1984, pp. 359–376.
3 B. Rosenberg, in A. W. Prestayko, S. T. Crooke and S. K. Carter (eds.), 'Cisplatin Current Status and New Developments', Academic Press, New York, 1980, pp. 9–20.
4 K. R. Harrap *et al.*, in A. W. Prestayko, S. T. Crooke and S. K. Carter (eds.), 'Cisplatin Current Status and New Developments', Academic Press, New York, 1980, pp. 193–212.
5 G. Wilkinson *et al., Biochimie, 60,* 851 (1978).
6 G. Pratesi *et al., Fifth NCI-EORTC Symposium,* Amsterdam, 1986, Abstract S1-20.
7 W. C. Rose, *Anticancer Res., 6,* 557 (1986).