Biomed. & Pharmacother., 43 (1989) 237-250

Dossier

Oxalato-platinum or l-OHP, a third-generation platinum complex : an experimental and clinical appraisal and preliminary comparison with cis-platinum and carboplatinum

G. MATHÉ[1*], Y. KIDANI[2], M. SEGIGUCHI[3], M. ERIGUCHI[3], G. FREDJ[4], G. PEYTAVIN[4], J.L. MISSET[1], S. BRIENZA[1], F. de VASSALS, E. CHENU[1] and C. BOURUT[1]

[1]*Département des Maladies Sanguines, Immunitaires et Tumorales & ICIG, Hôpital Paul-Brousse, 14 Avenue Paul-Vaillant-Couturier, 94804 Villejuif, France;*
[2]*Nagoya City University, Faculty of Pharmaceutical Sciences, Laboratory of Analytical Chemistry, Tanabe Dori Mizuho-ku Nagoya 467, Japan; and*
[3]*The University of Medical Science, The University of Tokyo 4-6-1 Shirokanedai Minato-ku, Tokyo 108, Japan*
[4]*Pharmacie, Hôpital Paul-Brousse, 14 Avenue Paul-Vaillant-Couturier, 94804, Villejuif, France*

Summary — A new platinum complex, oxalatoplatin or l-OHP, which, at the same metal dose in experimental tests is as efficient as cisplatin, and is more so at a lower metal dose than carboplatin; which is as efficient in human tumors of the testis and ovary as these other analogs, and more so in melanoma and breast cancer; which is not nephrotoxic, cardiotoxic or mutagenic, and hardly hematotoxic and neurotoxic, is described and compared with the above-mentioned platinum complexes.

Combined with 5Fu, it induces a high number of remissions in colorectal cancer, and has brought about cures in inoperable gastric cancers. Combined with carboplatin, it has resulted in a high proportion of cures in L1210-carrying mice, which no other two-by-two combination of these complexes has achieved.

l-OHP / cis-platinum / carboplatin

Résumé — L'oxalatoplatine ou l-OHP, une troisième génération de complexe de platine, bilan expérimental et clinique actuel et comparaison préliminaire avec le cis-platine et le carboplatine. *Un nouveau complexe de platine, l'oxalatoplatine ou l-OHP, qui, pour la même dose de métal, s'est avéré aussi efficace dans les tests expérimentaux que le cis-platine et davantage pour une dose de ce métal plus faible, que le carboplatine; qui est aussi efficace contre les tumeurs humaines du testicule et de l'ovaire que ces deux analogues-là, et davantage sur le mélanome et sur le cancer du sein; qui n'est ni néphrotoxique, ni cardiotoxique, ni mutagénique, et qui est à peine hématotoxique et neurotoxique, est décrit et comparé avec les complexes de platine ci-dessus.*

Combiné avec le 5Fu, il a induit un nombre élevé de rémissions dans le cancer colorectal et a induit quelques guérisons dans des cas de cancers gastriques inopérables. Combiné avec le carboplatine, il permet d'obtenir une haute proportion de guérisons de souris porteuses de leucémie L1210, qu'aucune autre combinaison des sels de platine deux à deux ne permet d'obtenir.

l-OHP / cis-platine / carboplatine

* *Correspondence and reprints.*

Introduction

Since Rosenberg [37] described the oncostatic effect of cisplatin (cis-$PtCl_2$ $(NH_3)_2$, or CDDP), the number of complexes of this metal [30] has increased much more than the precise knowledge of the mechanisms behind their cytostatic effect, which mainly consist of reactions with nucleophilic sites of DNA, causing intrastrand and interstrand crosslinks (Fig. 1), as well as DNA-protein crosslinks [28].

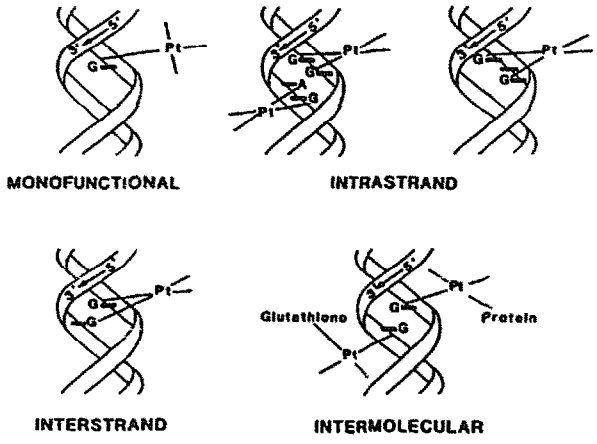


Fig. 1. Structures of the various adducts produced in DNA by afinum complexes [30].

Cisplatin indeed represents major progress in clinical cancer chemotherapy, as its oncostatic potential has been made positive use of, especially in testicular and ovarian carcinomas [43].

Unfortunately it is a rather toxic drug and has two major short-term side-effects : vomiting [43] and kidney lesions [43]. It is also a mutagenic agent [11].

Among the second-generation platinum complexes (Fig. 2; Table I), we have studied CHIP (or cis-dichloro-trans-dihydroxy-bis (isopropylamine) platinum IV) [35], which appeared to be as

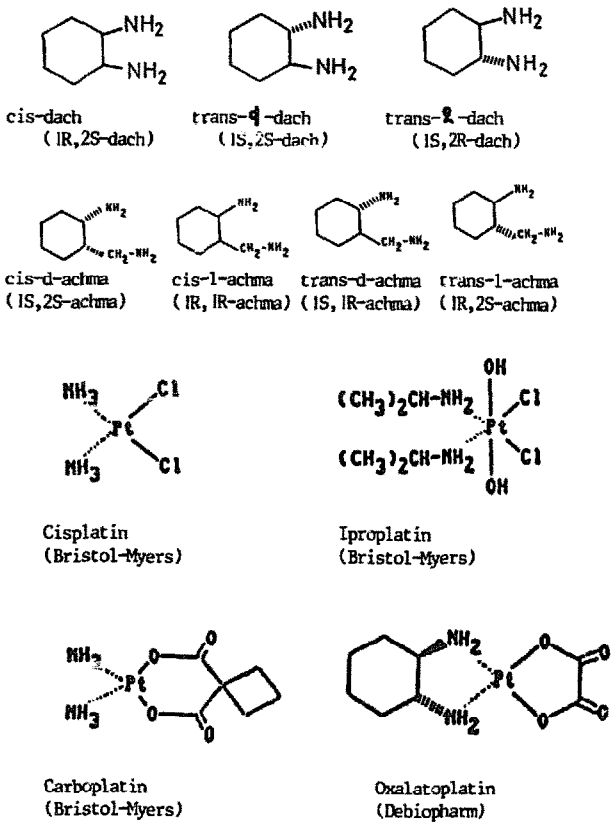


Fig. 2. Principles of platinum complex structures, cisplatin and the second and third generation complexes.

Table I. Second-generation platinum complexes.

Internationally recognised name	*Laboratory of origin*	*Abbreviation*	*Chemical name (m.w., water solubility)*
Cisplatin	Bristol-Myers	CDDP NSC 119875	Cis-diammino-dichloro-platinum (II) m.w. = 300.1 w. sol. = 1 mg/ml
Carboplatin	Bristol-Myers	CBDCA NSC 241240	Cis-diammin(cyclobutane-dicarboxylato-1, 1(2-0)-0,0) platinum (II) m.w. = 371.1 w. sol. = 17 mg/ml
Oxalatoplatin	Debiopharm Roger Bellon Rhône Poulenc	1-OHP ICIG 2036	Oxalato (1R, 2R-cyclohexane-diammine) platinum (II) m.w. = 397.1 w. sol. = 7.9 mg/ml

efficient as CDDP and no more toxic. CBDCA or carboplatin (or cis-diammino-1, 1-cyclobutane dicarboxylato platinum II) (in which the bidentate dicarboxylate chelate ligand replaces the 2 chlorine atoms of cisplatin) has however, found preference; it induces the same molecular lesions as the latter in L1210 cells, but is much less active (45 times less) as it is much slower to induce DNA-interstrand and DNA-protein crosslinks [28]. Thus a higher dose of the metal platinum has to be applied than with CDDP to obtain the same effect. Experimental tumors, expecially L1210 leukemia, which are resistant to cisplatin are also resistant to carboplatin [42]. CBDCA causes less toxicity for the kidney than CDDP [3], which may increase anthracyclin toxicity in the case of their combination.

Hence we have concentrated our efforts on the search for non-nephro-toxic, non-mutagenic, less hemato- and cardiotoxic and, of course, more active platinum complexes.

In the "carrier ligand-Pt-leaving group", the group dach (1,2-cyclohexamediamine) (Fig. 2) appeared to be one of the most active ligands. As we had previously studied malonate 1R, 2R-dach Pt (IV) complex [1], which was very active but unfortunately not water-soluble enough to be used in humans, we focussed our interest on oxalate 1R, 2R-dach Pt (IV), being l-OHP, which appeared to us to be as or more experimentally effective than CDDP and much less toxic.

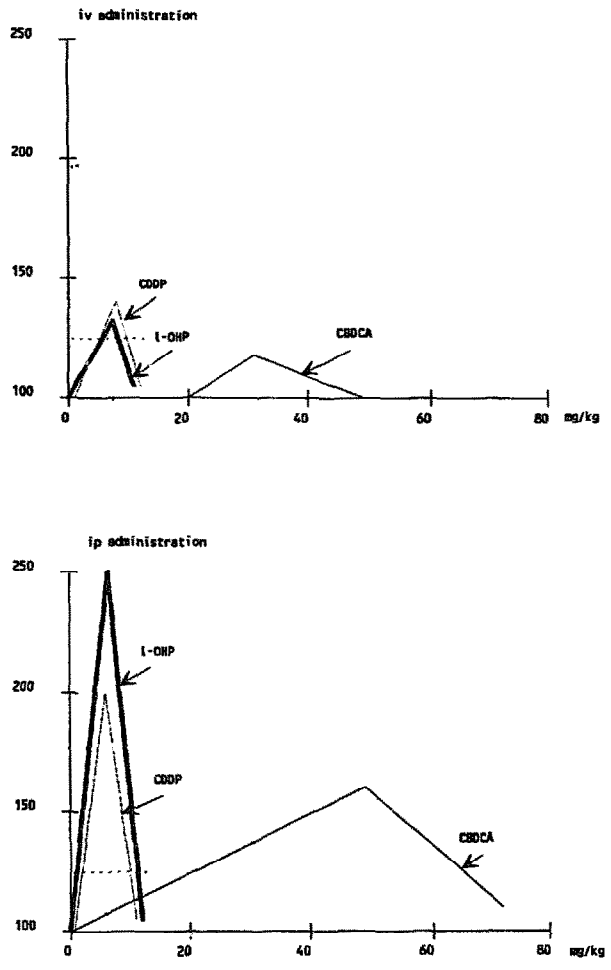


Fig. 3. Comparative curves of the maximally efficient dose ranges (MEDR) of the 3 studied platinum complexes [24].

Murine tumors

Leukemia-lymphomas

The cytostatic effects of l-OHP on L1210 leukemia expressed by the MEDR (maximally efficient dose range) appeared to us [24] to be equal to that of CDDP and higher than that of CBDCA applied at a much higher dose (Fig. 3). The i.p. administration for the 3 complexes is significantly more active than the i.v. (Fig. 3).

l-OHP is of particular interest as it works on the T-leukemia-lymphoma L40 AKR [24] and on the B large-cell lymphoma LGC [24], while CDDP has no effect on the latter [24] (Table II). According to Tashiro [41], l-OHP works as well as CDDP on the histiocytic sarcoma M5076.

Brain neoplasias

l-OHP is active on brain injected L1210 leukemia, while CDDP is not (Table II) [24].

Table II. a) Effects of l-OHP and CDDP on L40 AkR grafted leukemia and LGC lymphoma.

	mg/kg i.v.	*I*[a]	
		l-OHP	*CDDP*
L40 AkR leukemia	5	144	194
	7.5	177	Toxic
LGC lymphoma	5	∞[c]	NA
	7.5	NA[b]	NA

Tumor graft (10^6 cells, i.p.) on day 0.
Treatment i.v. on days 1, 5 and 9.
[a] $I = T/C \times 100$.
[b] NA, not active.
[c] ∞, more than 50 % of mice were cured.

Table II. b) Comparison of the effect of l-OHP and CDDP on intracerebrally grafted L1210 leukemia (10^4 cells) [24].

	I^a	P^b
l-OHP	165	0.02
CDDP	100	

Dose 5 mg/kg i.p.
[a] $I = T/C \times 100$.
[b] *P*, statistical significance.

Solid tumors
Table II summarizes the results with l-OHP on different murine solid tumors studied by us [24] and by Tashiro [41].

Test for efficiency of adjuvant therapy
We have submitted the mammary tumor MA16c (which carries sex hormone receptors) to l-OHP as post-surgical adjuvant therapy; this platinum complex is efficient, as it cured >43 % of mice (Table IV) [24].

Cross-resistance
All tumor lines studied by Saijo *et al.* [39] and resistant to CDDP are also cross-resistant to CBDCA. On the contrary, l-OHP is, according to Kidani [19], active on the CDDP resistant L1210 leukemia (Fig. 4).

5-Fluorouracil (5-Fu) potentiation and cross-synergism
Figure 5 shows the dose variable, but considerable synergistic action between 5Fu (modulated by folinic acid) and l-OHP [22].

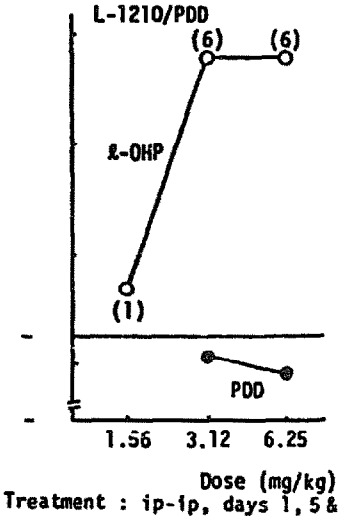


Fig. 4. l-OHP is active on a CDDP-resistant L1210 leukemia [19].

Table IV. Percentage cured animals at day 60 after CT, HT, IT and surgery alone [24].

	Treatment alone	*Neo-adjuvant*	*Adjuvant*	*Neoadjuvant + adjuvant*
CT	40	62	66	43
HT	10	55	40	50
IT	0	0	6	21
Surgery	0			

CT = Chemotherapy : *l*-OHP 5 mg/kg i.p., days 1, 5, 9 neoadjuvant (N); days 21, 25, 29 adjuvant (A), or days 1, 5, 9, 21, 25, 29 (N + A).
IT = Immunotherapy : Zinc gluconate : 6 mg/kg p.o. + bestatin 6 mg/kg p.o. days 1—21 for N, 21—42 for A, or 1—42 (N + A).
HT = Hormonotherapy : D-Trp-6-LH-RH 100 µg/kg i.p. days 1—21 for N, 21—42 for A, or 1—42 (N + A).

Table III. Experimental antitumor activity [24, 41].

Reference screening center	*Tumor graft criteria of evaluation*	*Treatment schedule*	*Daily dose range (mg/kg)*	*Optimal T/C (%)*	*Drugs compared*	*Daily dose range (mg/kg)*	*Optimal T/C (%)*
24	MA 16-C	1, 5, 9	7.5—5.0	206	CDDP CBDCA	5 50	inactive inactive
41	B_{16} melanoma sc survival	1, 5, 9 i.p.	10—2.5	128	CDDP CBDCA	10—2.5 12.5—2.5	139 170
41	Lewis lung sc survival	q2d, d1—19 i.p.	5—1.25	159	CDDP CBDCA	2.5—1.25 60	184 245
41	C_{26} colon carcinoma survival	1.5 i.p.	12.5—3.12	143	CDDP CBDCA	12.5—1.56 25	322

l—OHP = oxalatoplatin; CDDP = cisplatin; CBDCA = carboplatin.

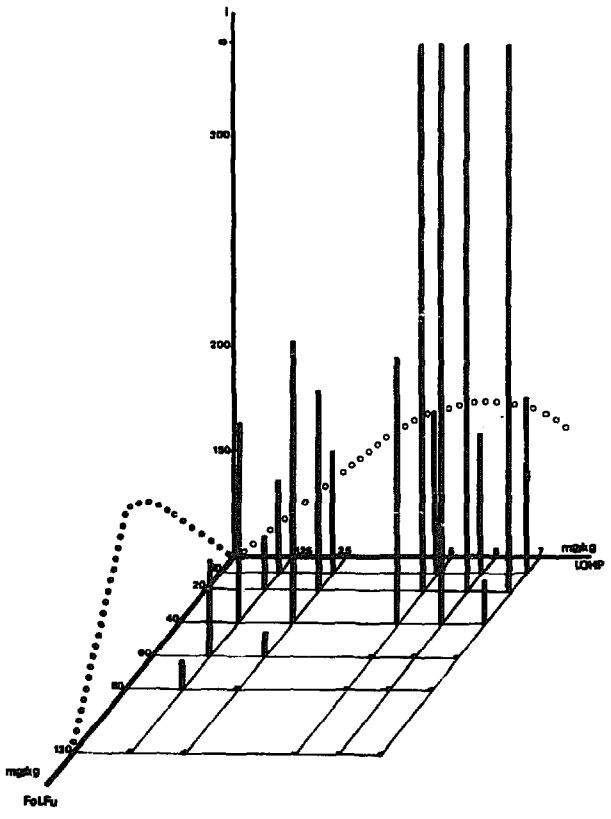


Fig. 5. Synergism between fluorouracil (modulated by folinic acid) and l-OHP studied on L1210 leukemia [22].

Table V. Simultaneous association of the two platinum complexes in the therapy of L1210 leukemia (unpublished).

Platinum complexes	*Dose (mg/kg/d)*	*Injection (day)*	*I*
Half optimal doses			
CBDCA	25		
+		1,5,9	200
l-OHP	3		
CBDCA	25		
+		1,5,9	233
CDDP	3		
CDDP	3		
+		1,5,9	188
l-OHP	3		
Optimal doses			
CBDCA	50		
+		1,5,9	100 Tox.
CDDP	6		
CBDCA	50		
+		1,5,9	∞
l-OHP	6		
CDDP	6		
+		1,5,9	100 Tox.
l-OHP	6		

Still more interesting is the effect of the exclusive combination of l-OHP and carboplatin, as it cured 70 % of the L1210-carrying mice, *versus* no cure with either compound administered alone, and no cure by any other possible two-by-two combinations of the 3 compounds studied (Table V) [22].

Comparative species toxicity

Table VI shows the non-toxicity of l-OHP registered with the 3 doses of the MEDR in mice and with those extrapolated to baboons and humans. This contrasts with CDDP which is highly toxic for the kidney (Table VII), and with carboplatin, which is less toxic for the kidney than CDDP, but more toxic for hemopoiesis (Table VIII). In electron microscopical study, we have observed cardiac toxicity [3] for CDDP but not for l-OHP.

CDDP [11] and carboplatin [6] are mutagenic by the conventional test, while l-OHP is not [41] (Table IX).

Phase I studies and human pharmacokinetics

The phase I trials have indicated that the dose for phase II trials was 100 mg per cycle every 3 weeks for CDDP, the dose limiting factor being renal, hematopoietic and neurotoxic [20], 400 mg per cycle every 3 weeks for carboplatin [42], the limiting dose factor being hematopoietic [7, 15, 27], and 100 mg per cycle every 3 weeks for l-OHP (Tables X and XI) [23], the only dose-limiting factor being neurotoxicity, which Marty [14] induced by increasing the cycle dose to 200 mg/m^2, well above our recommendations.

Comparative pharmacokinetics of CDDP, CBDCA and l-OHP are given in Tables XII and XIII and in Figure 6 [33].

Phase II trials in human tumors

The object of our phase I trails, which use the intra-patient escalation method rather than the

Table VI. I-OHP : Grading of histologic toxicity in mice and baboon, and of clinico-biologic toxicity in man. Doses indicated by the MEDR in mice : 45—56—67 mg/m² [24, 25].

Species	*Dose (mg/m²)*	*Hemopoiesis*				*Liver*			*Kidney*		*Heart (μ M)*
		Hb	*WBC*	*PMN*	*Plat.*	*SGOT*	*SGPT*	*Al.Ph.*	*Urea*	*Creat.*	
Mice	45		0				0		0	0	0
	56		0				0		0	0	0
	67		0				0		0	0	0
Baboon	45	0	0	0	0	0	0	0	1	0	0
	56	0	0	0	0	0	0	0	1	0	0
	67	0	0	0	0	0	0	0	0	0	0
											Cardio-echography
Human	45	0	0	0	0		0	0	0	0	0
	56	0	0	0	0		0	0	0	0	0
	67	0	0	0	0		0	0	0	0	0

Table VII. CDDP : Grading of histologic toxicity in mice and baboon, and of clinico-biologic toxicity in man. Doses indicated by the MEDR in mice : 45—56—67 mg/m² [24].

Species	*Dose (mg/m²)*	*No. of doses*	*Hemopoiesis*			*Liver*		*Kidney*	
			WBC	*PMN*	*Plat.*	*SGOT*	*SGPT*	*Urea*	*Creat.*
Mice	45								
	56			1		0		2	3
	67								
Baboon	57	1	0	2	0	0		1	0
		3	1	2	3	0		3	2
Human	4	1			0				0
	56	1		0(0—3)	0				⩾2
	67	1		1(0—3)	0				>2
	100	1		0(0—3)	0				>2

Table VIII. CBDCA : Grading of histologic toxicity in mice and dog, and of clinico-biologic toxicity in man. Doses indicated by the MEDR in mice : 360—450—540 mg/m² [10]*.

Species	*Dose (mg/m²)*	*No. of doses*	*Hemopoiesis*				*Liver*			*Kidney*	
			Hb	*WBC*	*PMN*	*Plat.*	*SGOT*	*SGPT*	*Al.Ph.*	*Urea*	*Creat.*
Mice	360			3		ND		ND		ND	
Dog's	400			2		2		ND		ND	
Human	200	7		3		4					
(minimum	300	5		0		1		ND		ND	
nadir)	350	4		1		0					
	400	6		1		0					
	500	5		4		3					
	520	5		3		4					

ND : Not determined.

* The data presented by Carter and Hellman are incomplete in mice and large animals.

Table IX. Non-mutagenicity of Pt oxalato DACH isomers for *S. typhimurium* [19]*.

Pt complex		*Revertant/plate*				*Mutagenicity*
		TA 100		*TA 98*		
Isomer	*μg/plate*	*+ S-9 mix*	*— S-9 mix*	*+ S-9 mix*	*— S-9 mix*	
Trans-l	1	93	70	23	13	(—)
(l-OHP)	5	46	57	22	18	
	10	46	57	25	25	
	50	12	13	10	7	
Trans-d	1	74	93	36	14	(—)
	5	52	76	28	20	
	10	36	50	12	8	
	50	0	0	0	0	
Cis	1	60	71	28	15	(—)
	5	80	68	27	26	
	10	52	60	36	28	
	50	13	22	5	14	
Control		74	75	27	16	

* Mutagenicity of l-OHP for *S. typhimurium* strains TA 100 and TA 98 was determined together with its stereo isomers. None of them were mutagenic for both *Salmonella* strains.

Table X. Phase I study of l-OHP (intra-patient dose escalation method) : toxicities [25].

Dose Level	*No. patients*	*Toxicity*							
		Nausea, vomiting	*Lung*	*Heart*	*Liver*	*Kidney*	*Hematopoiesis*		
	N = 23						*Hb*	*WBC*	*Platelet*
0.45	21	—	—	—	—	—	—	—	—
4.5	21	—	—	—	—	—	—	—	—
9	9	—	—	—	—	—	—	—	—
15	12	—	—	—	—	—	—	—	—
22.5	8	—	—	—	—	—	—	—	—
30	9	1/9	—	—	—	—	—	—	—
45	19	19/19	—	—	—	—	1/19 Gr1	—	—
56	15	15/15	—	—	1/15	—	1/15 Gr1	—	—
67	11	11/11	—	—	—	—	1/11 Gr2	—	1/11 Gr1
100	25	60 %					4 %	4 %	4 % [23]

Parameters evaluated :
Liver : transaminases, alkaline phosphatase.
Kidney : area, creatinine.
Cr : grade according to WHO [8].

Table XI. Phase I study of l-OHP (intra-patient dose escalation method) : anti-tumor activity for the cycle maximum doses ≤ 67 mg, for 100 mg [25].

Response	*No. patients*	*Tumor + target*	*Total dose received*	*Imaging*
Progressive disease	16/23			
		1 prostate + liver and bone metastasis	798 mg	Echo + PAP
Stabilisation	3/23	2 liver	843 mg	
		3 liver	943 mg	αFP
Minor response	1/23	Lung	740 mg	Tomo-scan
Partial response	1/23	Breast carcinoma + bone metastasis	473 mg	Scintigraphy
Complete response	1/23	Melanoma + metastases of the lung and parotid	297 mg*	Scan (of the head and lung)

* *NB* : This patient is still under study. Although he has reached only a low level (45 mg/m²) at the time of this report, the results as evidenced by scan of the and the head confirmed a complete disappearance of the metastases of the lung and the parotid seen before treatment.

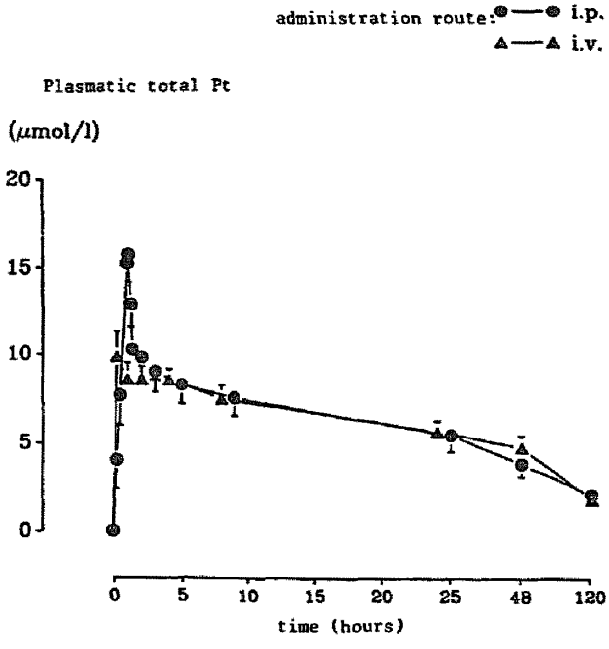


Fig. 6. Comparison of the i.v. and i.p. routes after administration [34].

conventional interpatient escalation type, considered unethical by our Committee of Ethics, Methodology and Economics [4], is to find not the maximally tolerated dose but the active dose, which is lower than the former for most drugs we have studied [26].

Table XII. Compared pharmacokinetic parameters of cisplatin, carboplatin and oxalatoplatin [33].

Pharmacokinetic parameters	*Cis-platin*	*Carbo-platin*	*Oxalato-platin*
$T^{1/2}$ α total Pt (min.)	8.7—912	10.8—98	ND
$T^{1/2}$ β total Pt (h.)	30.5—290.4	16.6—98	70.1
$T^{1/2}$ α free Pt (min.)	2.7—78	5.7—125	ND
$T^{1/2}$ β free Pt (min.)	25.9—226.8	102—436	ND
% Bound protein 4 h. post—infusion	90	24	ND
Excretion units/24 h. (% of dose admin.)			ND
Renal clearance of free Pt/FG count	0.38—3.62	0.7	ND
Plasma clearance of total Pt (ml/min/m²)			5.9
Plasma clearance of free Pt (ml/min/m²)	15.6—658	40—123	ND
Vol. (ml/m²)	52.3—65.6	16.1—24	36.5
total Pt	21.2—50.5	17.3	
free Pt	23.6—81.9	16	
$T^{1/2}$ free Pt *in vitro* (h)	1.5—3.7	30	
C_{max} total Pt plasm. (μmol/l)			16.6
T_{max} total Pt (h)			1
AUC (μmol/l·h)			749.4
MRT (h)			102.5
Biliary excretion (% dose admin.)	< 0.06		

Having observed that the murine MEDR extrapolated to man is perfectly tolerated, we have conducted the first phase II trials by continuing to escalate the dose of the phase I trial [23] without reaching toxic amounts, and have chosen 100 mg per cycle.

Table XIII. Compared pharmacokinetic parameters of carboplatin, cisplatin and oxalatoplatin (by peritoneal administration) [33].

Pharmacokinetic parameters	*Cis-platin*	*Carbo-platin*	
$T^{1/2}$ β of elimination (h)			Mathé 61.8 Fredj 68.8 NS*
Clearance of plasm. of total Pl (ml/min·m²)		16.7	M 7.5 F 6.4 NS*
Renal clearance of free Pt (ml/min·m²)	86—126		
Peritoneal clearance of total Pl (ml/min/m²)		11.3	
Peritoneal clearance of free Pl (ml/min/m²)	43.3	7	
Excretion units·24 h (%) dose admin.)	23—37	64	
Vol. (l/m²)			M 40.3 F 30.6 NS*
C_{max} total Pl plasm. (μmol/l)	50—360	10—30	M 7.35 F 8.9 S*
C_{max} free Pl plasm. (μmol/l)	150—280		
Peritoneal C_{max} (μmol/l)		500	
Peritoneal T_{max} (h)			M 1.25 F 4.65 S*
Peritoneal MRT (h)	0.85	4.7	M 91.8 F 100.7 NS*
AUC (μmol/l·h)			M 553.6 F 857.4 NS*
Peritoneal (4 h)		908	
Plasmatic		50	
R = perit./plasm.	12.4	18.2	
Peritoneal (24 h)		1107	
Plasmatic		173	
R = perit./plasm.		6.2	

* Wilcoxon test : S = $p \leq 0.05$ significant difference from i.v.
NS = no significant difference between i.p. and i.v.

Platinum complexes applied as single drugs. The preliminary results of our l-OHP phase II trial are very promising in testicular and ovarian cancers, non-Hodgkin's lymphomas, gliomas, head and neck tumors, and lung small-cell carcinoma.

We shall only compare here the results for melanoma, ovary and breast cancer, for which we have sufficient patients (Table XIV). The same proportion of responses (complete + "partial > 50 %" remissions) is registered in ovarian cancer previously treated with CDDP, CBDCA or l-OHP (≈ 30 %). We have not conducted phase II trials of l-OHP applied as a single drug in not previously treated patients, as other authors have done with CDDP and CBDCA, since in our opinion, this is highly unethical [4].

In melanoma, we have observed a 33 % response (including complete remissions). l-OHP is the only drug to achieve such remissions and at this incidence.

In breast cancers, we have not obtained more remissions with the usual bolus administration than other authors with CDDP. But by administering l-OHP according to the chronopharmacological modality, we have registered a 20 % response rate (Table XIV).

Combinations of platinum complexes with 5-fluorouracil. These combinations have been studied in colorectal cancer. If we consider the application in a 3—5-day cycle, which is the usual one, one registers between 0 [29] and 25 % [5, 40] for CDDP, between 12 % [18] and 40 % [16] for carboplatin. For l-OHP, if we combine 5-fluorouracil modulated with folinic acid [21], our response rate is 23.5 % for bolus injection, and 60 % when we apply it according to the chronobiologic modality (Table XV).

In gastric cancer, we have not found combinations reduced to 5Fu and CDDP or carboplatin; combined with 5Fu, l-OHP has given us 5 responses out of 8 patients, among which there were 2 complete tumor disappearances in non-operable patients who were checked microscopically at second-look surgical intervention (Figs. 7, 8) (unpublished results).

Dose-related nausea and/or vomiting occur in many patients receiving cisplatin (≈ 80 %) and carboplatin (≈ 43 %) [2, 8]. In the latter case it was noted that vomiting was delayed 6—12 h after administration of the drug. The incidence of these side-effects is 60 % in the case of l-OHP (Table XVI).

As far as severe side-effects are concerned, Table XVI shows that l-OHP has never been as clinically nephrotoxic as CDDP is [30b], and that

it is much less frequently hematoxic than CBDCA [9].

At a dose of < 100 mg per cycle, l-OHP is still less frequently ototoxic than cisplatin, but it induces paresthesias more often than the other two platinum complexes : these initial signs of neurotoxicity are in fact useful to indicate the risk of serious manifestations, and prompt an interruption of the treatment before the latter appear.

Table XIV. Efficacity of *l*-OHP *versus* CDDP—CBDCA.

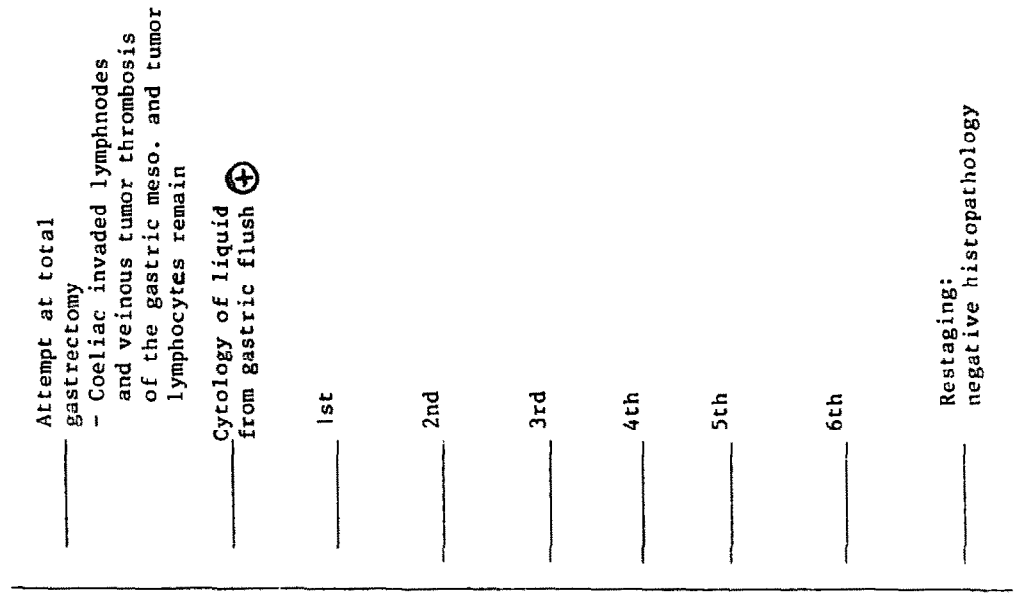
	Melanoma (Previously and not previously treated) (%)	*Ovary*		*Breast Previously treated) (%)*
		Not previously treated (%)	*Previously treated (%)*	
CDDP	10 (a)	57.6 % (b,c,d)	25 (b,c,d)	6 (e)
CBDCA	11.5 (f—g) (4—19)	59 (h)	23 (i)	0 (j)
l-OHP	33	—	28	0 (bolus) 20 (chrono)*

* Pharmacological modality.
(a) Al-Sarraf M. (1982) Cisplatin hydration with and without mannitol diuresis in refactory disseminated malignant melanoma : A. Southwest Oncology Group Study (8b).
(b) Niijima T. *et al.* : Gan to Kagakuryoho 9(1), 46-54 (30b).
(c) Kawai H. *et al.* : Gan to Kagakuryoho 9(3), 433-442 (30b).
(d) Kato T. *et al.* : Gan to Kagakuryoho 9(4), 694-701 (30b).
(e) Ostrow S. *et al.* (1980) High-dose cis-diamminedichloro-platinum therapy in patients with advanced breast cancer : pharmacokinetics, toxicity and therapeutics (8b).
(f) Franks C.R. *et al.* (1986) Randomized phase II trial of carboplatin *vs* iproplatin in solid tumors (8b).
(g) Evans L.M. *et al.* (1987) Phase II trial of carboplatin in advanced malignant melanoma (8b).
(h) Swenerton K.D. (1986) The efficacy and toxicity of carboplatin in previously treated patients with advanced ovarian cancer (8b).
(i) Booth B.W; *et al.* (1985) Phase II trial of carboplatin in advanced breast carcinoma : a cancer and leukemia B. study (8b).
(j) Canetta R.M. *et al.* (1984) Developing new drugs for ovarian cancer : a challenging task in changing reality (8b).
We give as the references a, b, c etc. those articles in which the proportion published corresponds to that of the general means of all the trials.

Table XV. *l*-OHP combination phase II trial.

	Protocol	*Modality*	*PTS*	*CR*	*PR*	*% Response*	*SD*	*PD*
Rectocolon	+ 5-FU folinic acid	Bolus	34	1	7	23.5	19	7
	+ 5-FU follonic acid	Chronotherapy	31 (20*)	—	13 (12*)	42 (60*)	14 (7*)	4 (1*)
Stomach	+ 5-FU	Bolus	8	2	3			

* Among whom 20 had not been previously treated by 5FU chrono-12 PR (60 %).



	20 VI 1988	VII	VII	VIII	IX	X	XI	XII	I 1989
Ag CA 50		60.9		17.9	14.9		7.4		
LASA		29.7		11.5	11.3		9.1		
Day 1 1-OHPmg			100	100	90	100	110	110	
Day 1-5 5FUmg			1000	1000	1000	1000	1000	1000	
i.v.			600	600	600	600	600	600	
i.p.			400	400	400	400	400	400	

Fig. 7. Treatment of an inoperable gastric cancer in a 40-yr old male with 1-OHP combined with 5Fu : complete remission.

Table XVI. Toxicity of LOHP *versus* CBDCA and CDDP.

	1-OHP (%)	*CDDP [30b] (%)*	*CBDCA [9] (%)*
400 mg/m²/4 Wk		*100 mg/m²/3—4 Wk*	
Myelosuppression (> GR II WHO)			
leucopenia	4	31.7	55
thrombocytopenia	4	21	32
anemia	4	28	59
Nephrotoxicity (> GR II WHO)			
creatinin serum	0	9	7
Gastrointestinal (> GR II WHO)			
vomiting	60	78	53
diarrhoea	0	8.6	6
Neurotoxicity—GR III WHO	0	22	2
—GR II WHO	28		
Ototoxicity (> GR II WHO)	0	3.7	1.1
mucositis	0	0.6	2
alopecia	0	2.9	2

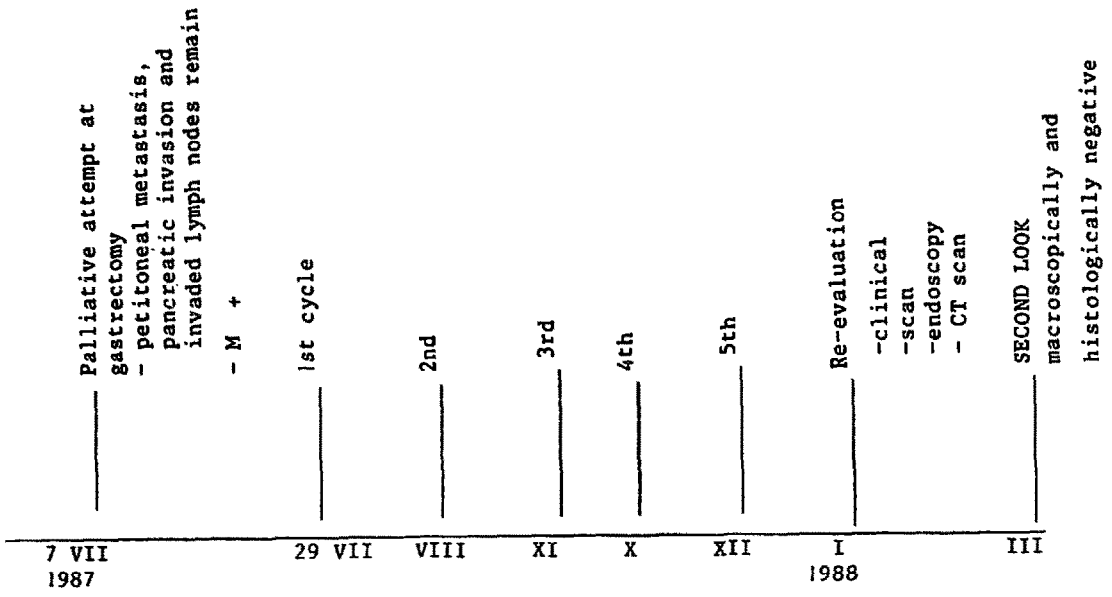


Fig. 8. Treatment of an inoperable gastric cancer in a 43-yr old male with l-OHP combined with 5Fu : complete remission.

References

1 Alcock N., Burchenal J.H., Young C., Muggia F. & Mathé G. (1979) Preclinical trial in baboon and phase I—II trial and pharmacokinetics in man of malonato-platinum. *Med. Oncol.* 5, 40 (abstr. No. 160)

2 Allen J.C., Walker R., Luks E., Jennings M. & Barfoot S. (1987) Carboplatin and recurrent childhood brain tumours. *J. Clin. Oncol.* 5, 459

3 Anjo A., Dantchev D. & Mathé G. (1989) Notes on the cardiotoxicity of platinum complexes (except l-OHP) in ultrastructural study. *Biomed. Pharmacother.* (same issue)

4 Arpaillange P., Dion S. & Mathé G. (1985) Proposal for ethical standards in therapeutic trials. *Br. Med. J.* 291, 887

5 Berretta J.R., Fraschinini P. & Labianca R. (1986) Weekly 5-fluorouracil (F) *versus* combination chemotherapy for advanced gastrointestinal carcinomas : a prospective study program. *Proc. Am. Soc. Clin. Oncol.* (abstr.) 5, 94

6 Bristol Myers Company (1983) Ames assay of JM-8 BMC. Syracuse, New York

7 Calvert A.H., Harland S.J., Newell D.R., Siddik Z.H. & Harrap K.R. (1985) Phase I studies with carboplatin at the Royal Marsden Hospital. *Cancer Treat. Rev.* 12 (suppl. A), 51

8a Calvert A.H., Harland S.J., Newell D.R., Siddik Z.H. & Jones A.C. (1982) Early clinical studies with cis-diammine-1, 1-cyclobutane dicarboxylate platinum II. *Cancer Chemother. Pharmacol.* 9, 140

8b Cancer Treatment Symposia (1985) *Phase II Single Agent Studies.* Vol. 4 (spec. issue)

9 Cannetta R., Rozenweig M. & Carter S.K. (1985) Carboplatin : the clinical spectrum to date. *Cancer Treat. Rev.* 12 (suppl. A), 125

10 Carter S.K. & Hellman K. (eds) (1985) *Paraplatin (Carboplatin) : Current Status and Future Prospects.* Academic Press, London

11 Coluccia M., Correale M., Fanizzi F.P., Giordano D., Maresca L., Mariggio M.A., Natile G. & Tamaro M. (1984) Mutagenic activity of some platinum complexes : chemical properties and biological activity. *Toxicol. Environ. Chem.* 8, 1

12 Eastman A., Schultz N., Sheibani N. & Sorenson C.M. (1988) Mechanisms of resistance to platinum drugs. *In : Platinum and Other Metal Coordination*

Coumpounds in Cancer Chemotherapy (M. Nicolini, ed.), Martinus Nijhoff, Boston

13 Einzig A., Kelsen D.P., Cheng E., Sordillo P. & Heelan R. (1985) Phase II trial of carboplatin in patients with adenocarcinomas of the upper gastrointestinal tract. *Cancer Treat. Rep.* 69, 1453

14 Extra J.M., Cuvier C., Espie M., de Cremoux P., Gourmel B. & Marty M.A. (1988) Phase I study of L-diamino cyclohexane-oxalatoplatinum (l-OHP) in patients with advanced solid tumors. European Society for Medical Oncology, 13th Congress, Oct. 30—Nov. 1, Lugano, Switzerland

15 Foster B.J., Clagett-Carr K., Leyland-Jones B. & Hoth D. (1985) Results of NCI-sponsored phase I trials with carboplatin. *Cancer Treat. Rev.* 12 (suppl. A), 43

16 Gil A., Dy C., Fernandez-Hidalgo O., Sureda M. & Santos M. (1987) Carboplatin and 120 hours 5-fluorouracil in patients with colorectal cancer. *Ecco*, Madrid, (abstr. 161), p. 42

17 Gore M.E., Hills C.A., Siddik Z.H., Sloane J.P. & Winkley A.R. (1987) Priming reduces the bone marrow toxicity of carboplatin. *Eur. J. Cancer Clin. Oncol.* 23, 75

18 Hidalgo O.F., Bilbao I., Gil A., Martin Algarra S. & Campbell W. (1988) Phase II study of intra-arterial carboplatin and 5-fluorouracil 5-day infusion in liver metastasis from colorectal cancer. *Asco* 7 (abstr. 399)

19 Kidani Y. (1988) A coordination chemical approach to prepare organ-specific antitumor platinum complexes in cancer chemotherapy. *In : Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy* (M. Nicolini, ed.), Martinus Nijhoff Publ., Boston

20 Lokich J.J. (1980) Phase I study of cis-diamminedichloroplatinum (II) administered as a constant 5-day infusion. *Cancer Treat. Rep.* 64, 905

21 Machover D., Goldschmidt E., Chollet P., Metzger G., Zittoun J., Marquet J., Vandenbulcke J.M., Misset J.L., Schwarzenberg L., Fourtillan J.B., Gaget H. & Mathé G. (1986) Treatment of advanced colorectal and gastric adenocarcinomas with 5-fluorouracil and high-dose folinic acid. *J. Clin. Oncol.* 4, 685

22 Mathé G., Blazsek I., Florentin I., Orbach-Arbhouys S., Lévi F., Bourut C., Chenu E. & Eriguchi M. (1989) Correlation between oncostatic, differenciating, immunologic and virostatic agents and actions. I. Experimental study. *In : International Interface of Clinical and Laboratory Responses to Anticancer Drugs* (in press)

23 Mathé G., Kidani Y., Misset J.L., Triana K., Machover D. & Musset M. (1986) Phase I trial of oxalato-platinum (l-OHP) : a new trial design with dose escalation in each patient. 7th International Symposium on Future Trends in Chemotherapy, Tirrenia (Pisa), Italy (abstr. p. 65)

24 Mathé G., Kidani Y., Noji M., Maral R., Bourut C. & Chenu E. (1985) Antitumor activity of l-OHP in mice. *Cancer Lett.* 27, 135

25 Mathé G., Kidani Y., Triana K., Brienza S., Ribaud P., Goldschmidt E., Ecstein E., Despax R., Musset M. & Misset J.L. (1986) A phase I trial of trans-l-diamino-cyclohexane oxalato-platinum (l-OHP). *Biomed. Pharmacother.* 40, 372

26 Mathé G. & Triana K. (1989) Lessons drawn from a double intra-patient escalation method phase I trial, of a sermustine, a metabolite of the nitrosourea CNCC (in preparation)

27 McVie J.G., Ten Bokkel Huinink W., Dubbelman R., van der Vijgh F.H. & Klein I. (1985) Phase I study and pharmacokinetics of intraperitoneal carboplatin. *Cancer Treat. Rev.* 12 (suppl. A), 35

28 Micetich K.C., Barnes D. & Erickson L.C. (1985) A comparative study of the cytotoxicity and DNA-damaging effects of cis-(diamino) (1-cyclobutanedicarboxylato)-platinum (II) and cis-diamminedichloroplatinum (II on L1210 cells. *Cancer Res.* 45, 4043

29 Muchmore E.R., Smeets H.J. & Horton M.C. (1985) 5-fluorouracil (5Fu) and cis-platinum (CDDP) chemotherapy for advanced colorectal cancer : a phase II trial. *Proc. Am. Soc. Clin. Oncol.* (abstr.) 4, 81

30aNicolini M. (ed.) (1988) *Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy.* Martinus Nijhoff Publ., Boston

30bNippon Kayaku (1982) *Cisplatinum Injection*

31 Olencki T., Pazdur R., Samson M. & Baker L. (1987) CBDCA (NSC-241240) : phase II evaluation in metastatic colorectal carcinoma. *Am. Assoc. Cancer Res.* 28, 200 (abstr. No 795)

32 Perry D.J., Weiss R.B., Creekmore S.P., Micetich K.C. & Curt G.A. (1986) Carboplatin for advanced colorectal carcinoma : a phase II study. *Cancer Treat. Rep.* 70, 301

33 Peytavin G. (1988) Étude pharmacocinétique comparée de trois dérivés du platine : cisplatine (cysplatyl), carboplatine (paraplatine) et oxaliplatine (non commercialisé) Thèse Hôpital Paul-Brousse, Villejuif

34 Raziz D., Mathé G. & Grymberg M. (1989) *In : Ethics and Methodology of Human Trials.* Elsevier, Amsterdam, (in press)

35 Ribaud P., Gouveia J., Misset J.L. & Mathé G. (1986) Phase I study of cis-dichloro-trans-dihydroxy-bis (isopropylamine) platinum IV (CHIP). *Oncology* 43, 78

36 Rose W.C. & Schurig J.E. (1985) Preclinical antitumor and toxicologic profile of carboplatin. *Cancer Treat. Rev.* 12 (suppl. A), 1

37 Rosenberg B., Vancamp L., Trosko J.E. & Mansour V.H. (1969) Platinum compounds : a new class of potent antitumor agents. *Nature* 222, 385

38 Reizenstein P., Mathé G. & Dicato M. (eds) (1988) *Managing Minimal Residual Malignancy in Man.* Pergamon Press, Oxford

39 Saijo N., Nakagawa K., Bungo M., Sasaki Y., Fujiwara Y. & Hong W.S. (1989) Characteristics of clinical and experimental resistance to cisplatin. *In : International Interface of Clinical and Laboratory Responses to Anticancer Drugs* (in press)

40 Shepard K.V., Bitran J.D., Sweet D.L., Faintuch J., Robin E. & Levin B. (1984) Treatment of metastatic colorectal carcinoma with cis-platinum (DDP) and 5-fluorouracil (5Fu). *Proc. Am. Soc. Clin. Oncol.* (abstr.) 3, 147

41 Tashiro T., Kawada Y., Sakurai Y. & Kidani Y. (1989) Antitumor activity of new platinum complex, oxalato(trans-l-1,2-diaminocyclohexane)platinum (II). *Biomed. Pharmacother.* (same issue)

42 Wagstaff A.J., Ward A., Benfield P. & Heel R.C. (1989) Carboplatin : a preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic officacy in the treatment of cancer. *Drugs* 37, 162

43 Zwelling L.A. (1986) Cisplatin and new platinum analogs. *In : Cancer Chemotherapy* (H.M. Pinedo & B.A. Chabner, eds.), Elsevier, Amsterdam