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A strategy for the development of two clinically active cisplatin analogs: CBDCA and CHIP

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Summary. The antitumor agent cisplatin has a broad antitumor spectrum and has been incorporated into regimens that are curative for some malignant diseases. However, one of the major limitations to its clinical usefulness is the incidence of severe toxicities involving several major organ systems. Therefore, much enthusiasm has been generated for the development of cisplatin analogs that demonstrate an improved therapeutic index in some preclinical models. The two most promising analogs are CBDCA (carboplatin) and CHIP (iproplatin). The preclinical and early clinical trial results have demonstrated that these two compounds show activity in cisplatin-responsive tumors. The preclinical background providing the rationale for the clinical development of these two analogs is described. We suggest a means of screening for each analog's clinical antitumor activity and determining the analogs' utility against specific malignant diseases compared with that of the parent compound or standard treatment.

Introduction

A report by Rosenberg et al. [52] describing the antitumor activity of platinum compounds led to wide-scale clinical investigations of these and other platinum coordination complexes. From these clinical studies, a role for cisplatin in the treatment of a variety of neoplasms was established [34]. The severity of the gastrointestinal and renal toxicities associated with cisplatin administration encouraged trials with schedule manipulations, antiemetic regimens, hydration schema with and without diuretics, and renal prophylaxis such as hypertonic saline and thiosulfate. In addition, interest was stimulated in the development of alternative platinum compounds with a better therapeutic index and a similar or improved antitumor activity spectrum.

Preliminary results against L1210 leukemia and sarcoma 180 in mice [52] demonstrated that the most efficacious platinum compounds had either a *cis* configuration for the chloride groups [platinum(II) coordinated complexes] or were platinum (IV) coordinated complexes. The three properties required for platinum compounds to have antitumor activity are: (a) neutrality; (b) possession of a pair of *cis* leaving groups that have a lability similar to that of the chlorides; and (c) possession of ligands other than the leaving groups [9, 11, 51]. Two cisplatin analogs with these structural characteristics, CBDCA [diammine 1,1 cyclobutane dicarboxylato Pt(II), JM-8, NSC-241240] and CHIP [bis-isopropylamino-*trans*-dihydroxy-*cis*-dichloro Pt(IV), JM-9, NSC-256927], are shown in Fig. 1. Both are undergoing clinical trials sponsored by the National Cancer Institute (NCI). This paper provides a brief review of the preclinical and phase I data on CBDCA and CHIP to present the background for the development of two first-generation platinum coordination complexes and then describes the NCI's planned development of these two agents.

Mechanism of action

Platinum coordination complexes inhibit tumor growth by their effects on DNA replication. The binding of these complexes to DNA is similar to that of bifunctional alkylating agents and has been shown to correlate with cytotoxicity in intact cells [15, 41, 42, 64]. All platinum(II) analogs (including CBDCA) induce DNA shortening and superhelical conformational changes, whereas platinum(IV) compounds (including CHIP) produce DNA degradation [40].

Guanine residues have been shown to be a site of DNA cross-linking [26, 32, 36, 54]. The kinetics of the cisplatin-DNA cross-link formation in L1210 leukemia, previously reported by Zwelling et al., required 12 h drug incubation for maximal cross-link formation. For the much less cytotoxic *trans* isomer, maximal cross-linking occurred by the end of 1 h drug incubation [63]. Other investigators have also reported differences in DNA-protein cross-link kinetics between the *cis* and *trans* isomers [35, 37, 41, 42, 54].

Although both CBDCA and CHIP have been shown to react with DNA [8, 20, 40], Mong et al. [40] reported differences in the types of changes induced in PM-2 DNA by these agents. Cisplatin and CBDCA, both platinum(II) compounds, produced alterations in tertiary DNA conformations but had little effect on linear PM-2 DNA; indeed, superhelical structure was a prerequisite for their cytotoxicity. The activity of both compounds was inhibited by

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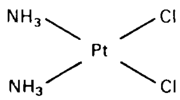
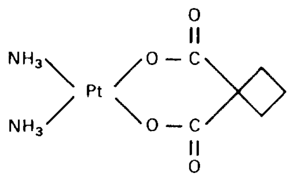
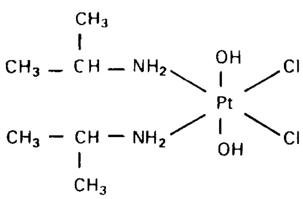
CHEMICAL STRUCTURE	COMMON NAME	NSC #	JM #
	Cis Platinum, Cisplatin	119875	—
	CBDCA, Carboplatin	241240	8
	CHIP, Iproplatin	256927	9

Fig. 1. Structures, names, and NSC numbers of cisplatin and two analogs

Table 1. Antitumor activity of cisplatin, CBDCA, and CHIP against the tumor panel

Tumor system	Treatment schedule (i.p.)	Cisplatin:			CBDCA:			CHIP:		
		Dose range[b] (mg/kg)	T/C ± SE[a] (%)	Score[c]	Dose range (mg/kg)	T/C ± SE (%)	Score	Dose range (mg/kg)	T/C ± SE (%)	Score
Murine tumors:										
i.p. B16 melanocarcinoma	q1d, days 1–9	0.2–4.0	178 ± 2	++	12.5– 25.0	172 ± 4	++	12.5	166	++
s.c. CD_8F_1 mammary tumor	q7d, days 1–29	4.0–12.5	(1 ± 1)	++	50.0–100.0	(8)	++	50.0	(6)	++
s.c. colon 38 tumor	q7d, days 2,9	2.0–16.0	(38 ± 5)	+	100.0–200.0	(33 ± 11)	+	25.0	(46)	–
i.p. L1210 leukemia	q7d, days 1–9	2.0– 4.0	162 ± 2	++	25.0– 64.0	148 ± 7	+	12.5–25.0	183 ± 14	++
i.v. Lewis lung-carcinoma	q1d, days 1–9	0.5– 2.0	153 ± 6	++	6.3– 25.0	119 ± 7	–	6.3–12.5	129	–
Human tumor xenografts:										
s.c. CX-1 colon tumor	q4d × 3, days 14–22	2–4	(81 ± 8)	–	12.5– 50.0	(63)	–	25.0	(41)	–
s.c. LX-1 lung tumor	q4d × 3, days 14	2–8	(69)	–	50.0	(140)	–	25.0	(94)	–
s.c. MX-1 mammary tumor	q4d × 3, days 14	4–8	(3)	++	25.0	(43)	–	25.0	(59)	–
Optima i.p. dose, days 1–9			1.6 mg/kg			16 mg/kg			14 mg/kg	

[a] Antitumor activity expressed as the mean optimal T/C (% indicated) (NIH Publication 84 2635)
[b] Dose range for which optimal activity in a dose response was observed. Minimal criteria for activity: % T/C for survival assays – *L1210, B16*, ⩾125%; *Lewis lung*, ⩾140%; % TC for tumor weight-inhibition assays – *CD_8F_1, colon 38*, ⩽42%; *CX-1, LX-1, MX-1*, ⩽20%
[c] DN2 criteria for activity: % T/C for survival assays, ⩾150%; % T/C for tumor weight-inhibition assays, ⩽10% (values in parentheses). ++, Minimal criteria for activity; –, no activity

Table 2. Comparative activity of cisplatin, CBDCA, and CHIP against mouse leukemias

Tumor	Treatment schedule	Cisplatin: Dose (mg/kg)	Cisplatin: Activity	CBDCA: Dose (mg/kg)	CBDCA: Activity	CHIP: Dose (mg/kg)	CHIP: Activity	Reference
L1210	Day 1	4–10	157%–186% T/C	32	171% T/C	50	137% T/C	[2, 7, 8, 41, 45, 46]
	Day 1	8	164%–229% T/C	128	150% T/C	32	171% T/C	
	Days 1–9	2/day	157%–285% T/C	64	157% T/C	16/day	207% T/C	
	Days 1–9 or Days 1, 5, 9	1.6–2.4/day	186%–257% T/C	25/day	152% T/C	25/day	191% T/C	
L1210/CDDP	Day 1	4–8	94%–131% T/C	120	113% T/C	32	118% T/C	[46]
L1210 *in vivo* → *in vitro*	Day 1	9	Surviving fraction = 50%[a]	336	Surviving fraction = 50%[a]	135	Surviving fraction = 50%[a]	[27]
P388	Days 1–9	–	–	25	152% T/C	18	202% T/C	[7, 8]
	Days 1, 5, 9	–	–	–	–	50	154% T/C	

[a] In vitro colony formation assay. Shown is the dose that caused a 50% reduction in the colony formation of tumor cells in vitro following treatment of tumor-bearing mice. %T/C, Median survival time of drug-treated tumor-bearing mice compared with that of mice treated with vehicle only. Drugs were given i.p.

sodium chloride. CHIP, a platinum(IV) compound, caused breakage of covalently closed, circular PM-2 DNA; this breakage was not inhibited by sodium chloride. This suggests involvement of the axial *trans* bonds rather than the equatorial *cis* bonds [40]. In addition, the concentration of CHIP required to produce DNA damage was higher than that required for cytotoxicity [40], suggesting that DNA breakage may not be the primary mechanism of cytotoxicity.

Antitumor activity

CBDCA and CHIP have been tested for antitumor activity against many in vitro and in vivo tumor models, including human tumor xenografts. Comparative results obtained with the analogs and cisplatin at optimal doses against tumors used in a preclinical screen at the NCI are shown in Table 1 [60, 61]. These data are the results of screening carried out under the auspices of the Developmental Therapeutics Program (Division of Cancer Treatment, NCI, Bethesda, Md). Cisplatin showed the broadest ac-

Table 3. Toxicity of cisplatin, CBDCA, and CHIP after a single i.v. dose in male F344 rats

	Cisplatin mg/kg (mg/m²)	CBDCA mg/kg (mg/m²)	CHIP mg/kg (mg/m²)
LD_{10}	6 (36)	52.5 (313.2)	33.4 (200.4)
LD_{50}	8 (48)	60.9 (365.4)	39.0 (234.0)
$\frac{LD_{50}{}^{a}}{LD_{10}}$	1.3	1.2	1.2
$\frac{LD_{50}{}^{b}}{LD_{50}}$	–	7.6	4.9

LD_{10} or LD_{50} is the dose that produced lethality in 10% or 50%, respectively, of the rats treated (data from [58])

[a] $\frac{LD_{50} \text{ compound in mg/kg}}{LD_{10} \text{ compound in mg/kg}}$ = toxicity quotient

[b] $\frac{LD_{50} \text{ analog in mg/kg}}{LD_{50} \text{ cisplatin in mg/kg}}$ = potency ratio

Table 4. (*a*) Comparative toxicity of cisplatin, CBDCA, and CHIP after a single i.v. injection in male F344 rats

Parameter	Cisplatin	CBDCA	CHIP
Hematocrit	1	3	2
WBC	3	2	3
BUN	3	1	1
Creatinine	3	1	1
SGPT	1	1	1
Body weight loss	3	1	2
Histopathology:			
Renal	4	1	3
Lymphatic	4	1	4
Hematopoietic	3	4	3
Gastrointestinal	4	1	1
Total score:	30	16	21

(*b*) Scoring used for comparative toxicity of platinum compounds after single-dose administration

Parameter	Scoring system and definitions
Hematocrit, WBC	1 = <20% decrease
	2 = 20%–50% decrease
	3 = >50% decrease
BUN, creatinine, SGPT	1 = <50% decrease
	2 = 50%–200% increase
	3 = >200% increase
Body weight loss	1 = no weight loss (maybe slowing of growth)
	2 = <10% (or <15% serial bleeding) weight loss
	3 = ≥10% (or >15% serial bleeding) weight loss
Histopathology	1 = no lesions
	2 = mild lesions in few animals
	3 = lesions of moderate to marked severity
	4 = lesions of marked to extreme severity

WBC, leukocyte count; BUN, blood urea nitrogen; SGPT, glutamic pyruvic transaminase
Data from [58]

tivity spectrum, with significant activity against i. v. Lewis lung carcinoma and s. c. human mammary xenograft [60, 61], neither of which were affected by CBDCA or CHIP. Both cisplatin and CBDCA showed a similar level of activity against s. c. colon 38, whereas CHIP showed no activity. Cisplatin and CHIP showed quantitatively better activity against i. p. L1210 than did CBDCA [60, 61].

The results of comparative experiments in mouse leukemias are summarized in Table 2 [4, 9, 10, 29, 45, 49, 50, 58]. The L1210 in vivo and in vitro results clearly indicate that cisplatin has the highest potency, followed by CHIP, with CBDCA being the least potent [29]. An L1210 line made resistant in vitro to cisplatin (L1210/CDDP) demonstrated cross-resistance to CBDCA and CHIP [49].

Toxicology

Comparative toxicologic studies showed CBDCA and CHIP to be less potent than the parent compound, as evidenced by the defined toxic doses shown in Table 3 [58]. The severity of myelosuppression, nephrotoxicity, and gastrointestinal toxicity caused by the parent compound was qualitatively different from that observed after treatment with the two analogs, as shown in Table 4 [29, 45, 50, 58]. Both CBDCA and CHIP produced more hematologic toxicity than did cisplatin, but they caused much less renal toxicity than the parent drug. Cisplatin produced more severe histopathologic lesions in the gastrointestinal tract than did either analog.

In summary, toxicologic studies showed the two analogs to be less potent than cisplatin, and, although the same organ systems (hematologic, renal, and gastrointestinal) were affected by all three compounds, the patterns of toxicity were different. The analogs consistently showed less renal and gastrointestinal toxicity but more hematopoietic toxicity than did cisplatin.

Clinical studies results

Phase I trials

Comparative results from phase I studies of cisplatin, CBDCA, and CHIP in adults are shown in Table 5 [5–7, 12–14, 17, 22, 24, 25, 27, 31, 33, 46, 47, 53, 55, 57, 59]. Based on the total dose (in milligrams) tolerated for each drug, cisplatin is the most potent; CHIP, intermediate; and CBDCA, the least potent. CBDCA and CHIP differed from cisplatin in the relative severity of their gastrointestinal, neurologic, renal, and hematologic side effects. Hematologic effects, especially thrombocytopenia, were dose-limiting for CBDCA and CHIP [5, 6, 12, 13, 17, 22, 24, 27, 31, 46, 47, 53, 55, 57, 59], whereas renal, hematologic, and gastrointestinal effects were frequently dose-limiting for cisplatin [12, 22, 53, 57]. Diarrhea was reported from studies of CHIP, but it was not dose-limiting [5, 13, 17, 24, 47]. Renal toxic effects observed in studies of CBDCA and CHIP occurred in patients who had preexisting renal disease or a concomitant nephrotoxic event [6, 14, 17, 27, 47]. No new neurologic toxicity was found with administration of the analogs; however, exacerbations of preexisting neurologic defects were observed following treatment with CBDCA [6, 14, 27, 55]. Antitumor effects were reported from the phase I trials of each compound, particularly in patients with ovarian carcinoma. In summary, less renal toxicity was seen with the analogs and hematologic toxic effects were dose-limiting in phase I testing of CBDCA and CHIP, confirming the results seen in preclinical toxicologic studies.

Clinical pharmacokinetics

The clinical pharmacokinetic parameters of the three compounds after i. v. single-dose administration are summarized in Table 6. Total and filterable (free, non-protein-bound) platinum values were determined using flameless atomic absorption spectrophotometry [18, 19, 21, 24, 43]. Following CBDCA or CHIP administration, the plot of the plasma levels for either total or filterable platinum was most often described as biexponential. The initial half-life ($t_{1/2}$) was usually <1 h, whereas the terminal half-life ($t_{1/2}\,\beta$) ranged from 7 h to over 5 days. This biexponential pattern was not reported for cisplatin. Thus far, no major pharmacokinetic differences have been observed that explain the differences in clinical potency and toxicity of these three analogs.

Developmental plans

The simultaneous clinical development of CBDCA and CHIP has stimulated many questions regarding the relative utility of each with respect to the other as well as to cisplatin. The scientific questions center around the relative therapeutic index (antitumor effects vs acute and chronic toxic side effects) of each compound relative to the others. This section describes some of the clinical developmental plans for these two analogs as well as giving specific illustrative examples for each of the three main disease categories.

Disease-oriented strategy. To incorporate the concept of *relative therapeutic index* into the phase II and phase III developmental plans, diseases were divided into three major categories according to cisplatin responsiveness and whether or not cisplatin was an important component of currently used standard treatment of the advanced disease. Illustrative examples of these disease categories are given in Table 7 and include the following:

A Cisplatin-sensitive diseases, where standard therapy incorporating cisplatin is curative; examples include germ-cell tumors and epithelial ovarian carcinomas. In this category, it is highly likely that CBDCA and CHIP would have some antitumor activity; in fact, hints of tumor responsiveness were seen in patients with ovarian carcinoma entered in the phase I trials. In this category, the usefulness of a traditional phase II trial was questioned. A phase II trial entering 30–40 patients would delineate an analog's antitumor activity with such broad confidence limits that it would not be possible to determine the activity relative to that of the parent compound. Therefore, the plan was to move directly from phase I testing to phase III comparative trials.

An illustrative example for this category is provided by a comparative trial of one analog with the parent compound. Patients with advanced ovarian carcinoma who had not received prior chemotherapy were randomized to receive a combination of either CBDCA plus cyclophosphamide or cisplatin plus cyclophosphamide [1]. The cyclophosphamide dose (mg/m^2) was the same in each combination. Preliminary results show equivalent activity;

Table 5. Comparative adult phase I studies of cisplatin, CBDCA, and CHIP

Schedule	Cisplatin:				CBDCA:				CHIP:		
	Maximal dose(s) each day (mg/m²)	Major toxicities			Maximal dose(s) each day (mg/m²)	Major toxicities			Maximal dose(s) each day (mg/m²)	Major toxici	
		Dose-limiting	Others	Refer-ence		Dose-limiting	Others	Refer-ence		Dose-limiting	O
Single dose	200, 100	Renal Nausea & vomiting	RBC, WBC, plts Hearing, loss, tinnitus Hyperuricema	[21, 50]	520, 550, 440, 600	↓plts	Nausea & vomiting ↓WBC, RBC Renal Malaise Neuropathy	[4, 24, 26, 29]	350, 350	↓plts	↓V N D H (r
Twice weekly × 2–4 week	15, 60	WBC, RBC, plts Nausea & vomiting	Renal Tinnitus	[5, 53]	–	–	–	–	–	–	–
Daily × 5	40, 24, 15	Renal	Nausea & vomiting ↓RBC, WBC, plts Tinnitus, hearing loss Heart failure with conduction defects	[21, 50, 53]	125, 99	↓WBC, plts	Nausea & vomiting ↓RBC Renal Paresthesias Myalgia, arthralgia	[54]	65, 45	↓plts	↓V R N D H (r
Weekly × 4	55	↓WBC, plts	Renal Nausea & vomiting Tinnitus Hypersensitivity	[10]	150	↓plts	Renal	[42]	95	↓plts	↓V N D
Bolus q4d until toxicity	~80	↓WBC, plts renal	Nausea & vomiting Hearing loss	[31]	–	–	–	–	–	–	–
24-h continuous infusion	–	–	–	–	500, 320	↓plts	Nausea & vomiting Hearing loss ↓Mg ↓RBC Renal	[12, 29]	–	–	–

RBC, red blood cells; WBC, white blood cells; plts, platelets; ↓, decreased; Mg, serum magnesium

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