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Effects of two pyridinalalkyliminerhodium(I) complexes in mice bearing MCa mammary carcinoma*

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Summary. The examination of the differential effects of two square-planar rhodium(I) complexes on primary tumor growth and on the formation of spontaneous and artificially (i.v. tumor injection) induced lung metastases of MCa mammary carcinoma suggests different mechanisms of action, depending on the chemical characteristics of the compound used. Of the two complexes used, cyclooctadiene(2-pyridinalmethylimine)Rh(I) chloride and cyclooctadiene(2-pyridinalisopropylimine)Rh(I) chloride, the former compound confirmed the antineoplastic action previously shown in the Lewis lung carcinoma model. The activity of this derivative on lung metastasis formation seems to be unrelated to a cytotoxic action for tumor cells localized in the lungs. More likely, it appears that modifications occurring at the primary tumor level, probably different from a tumor-cell-directed lethality, are responsible for the reduction of spontaneous lung metastasis formation observed in treated animals. The hyperplasia of the spleen induced in treated animals seems to suggest that this compound is endowed with properties typical for biological response modifiers.

Introduction

The clinical effectiveness of *cis*-dichlorodiammineplatinum (generic name, cisplatin) in the treatment of human malignancies has evoked great stimuli to seek new analogs [4, 14]. The obvious aim was to explore the possible existence of complexes endowed with higher activity or at least with lower toxicity. Of the several studies made with group VIII transition metals, besides the reports on platinum derivatives, those on rhodium complexes have indicated the occurrence of antitumor effects of some interest in a number of experimental systems; some of them exhibited antitumor activity comparable to that of cisplatin itself [3, 5, 11, 13]. Although none of the complexes studied to date was suggested to deserve clinical evaluation, the results of these studies enable a better understanding of the interactions between transition metal complexes and biological systems such as in vivo growing tumors [13].

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As far as square-planar rhodium(I) complexes of the type $[Rh(chel)(L\text{-}L)]^{+/\circ}$ are concerned, where chel = pyridinalimine (N-N-R) or acethylacetonate (acac) and L-L = *cis,cis*-1,5-cyclooctadiene (COD), 1,5-hexadiene (HD), or norbornadiene (NBD), the antineoplastic activity can be modified by changing the nature of either the diolefinc ligand or the R-group of the pyridinalimine ligand. Pyridinalalkylimine derivatives of rhodium(I) have exibited antineoplastic effects in mice bearing Lewis lung carcinoma and P388 lymphocytic leukemia [12]. The effects on the metastatic tumor depended on the chemical characteristics of the complex used; whereas those on the leukemic tumor were evident with almost all of the compounds and treatment schedules used.

We therefore thought it worthwhile to extend the examination of the antitumor properties of the pyridinalalkylimine rhodium(I) derivatives to another solid malignant neoplasm, the MCa mammary carcinoma of the CBA mouse. The complexes tested, cyclooctadiene (2-pyridinalmethylimine)-rhodium(I) chloride, $[Rh(COD)(N\text{-}N\text{-}CH_3)]^+Cl^-$, and cyclooctadiene(2-pyridinalisopropylimine)-rhodium(I) chloride, $[Rh(COD)(N\text{-}N\text{-}iC_3H_7)]^+Cl^-$, were chosen because of their opposite effects on the Lewis lung carcinoma tumor [12]. In the present investigation, their effects on primary tumor growth as well as spontaneous and i.v.-induced pulmonary metastases were differentially examined at equitoxic doses and compared with the effects on tumor viability and the metastatic capacity of the in vivo treated tumor, examined by vivo-vivo bioassays in intact or immunosuppressed syngeneic mice of the same sex and body weight.

Materials and methods

Synthesis. The samples of $[Rh(COD)(N\text{-}N\text{-}CH_3)]^+Cl^-$ and $[Rh(COD)(N\text{-}N\text{-}iC_3H_7)]^+Cl^-$ used were prepared following previously reported procedures [16].

Animal treatment. Each compound, dissolved by sonication in a cold environment for 10 s, was given i.p. in 0.1 ml/10 g body weight isotonic sodium chloride containing 1% sodium carboxymethyl-cellulose. Animal treatment was carried out at a daily dose of 8.2 μmol/kg $[Rh(COD)(N\text{-}N\text{-}CH_3)]^+Cl^-$ and 15.3 μmol/kg $[Rh(COD)(N\text{-}N\text{-}iC_3H_7)]^+Cl^-$ given for 12 consecutive days; the doses used are the maximum tolerated doses and correspond to the $LD_{0.05}$ extrapolated from plots relating

log(dose) vs probit(lethality), according to the method of Litchfield and Wilcoxon [6]. For the reported experiments, CBA female mice weighing 20–22 g were used. The animals came from a locally established colony derived from inbred litters obtained from Chester Beatty Institute (London, England) and were maintained under conventional procedures for inbred strains.

Tumor transplantation and evaluation. The MCa mammary carcinoma line used was obtained from Rudjer Boskovic Institute, Zagreb, Yugoslavia [2, 8]; it was locally maintained in vivo by i.m. passages into the calf of the left hind leg of 25–100 mm^3 tumor fragments obtained by mincing (with scissors) 2-week-old tumors in an equal volume of phosphate-buffered saline (PBS). For experimental purposes, single-cell suspensions were prepared. Tumor fragments from about 2–3 donors were minced with scissors in an equal volume of PBS, filtered through a double layer of sterile gauze, and centrifuged at 500 *g* for 10 min. The pellet was resuspended in an equal volume of PBS and cell viability was checked by trypan blue exclusion; only preparations having at least 65% viable cells were used.

Primary tumor and spontaneous metastasis. The effects of drug treatment on the primary tumor and the formation of spontaneous lung metastases were studied in mice inoculated i.m. with 10^6 viable tumor cells into the calf of the left hind leg. Primary tumor weight was determined by caliper measurements, assuming a tumor density equal to 1, as the volume of the rotation ellipsoid having the short and long axes equal to A and B, respectively:

$$\text{Tumor weight} = (\pi/6) \times A^2 \times B. \quad (1)$$

The number of lung metastases on the surface of freshly removed lung was counted by means of a low-power stereomicroscope. The weight of the metastatic tumor per animal was determined as the sum of the individual weight of each metastasis, calculated by means of Eq. 1.

Artificial metastasis. Artificial induction of lung metastasis was achieved by i.v. injection of tumor cells; none of the inoculated mice died within 24 h due to the i.v. injection of tumor cells. The effects of treatment on the number and weight of lung tumor colonies was evaluated as above for the spontaneous metastases.

Tumor viability and metastatic potential. In all, 10^6 tumor cells obtained from primary tumors of CBA mice inoculated i.m. as described above and treated daily with the tested complexes (controls treated with the vehicle) were inoculated i.m. into intact syngeneic recipients or into mice immunosuppressed with 180 mg/kg cyclophosphamide given i.p. 24 h earlier. Primary tumor growth and the development of spontaneous pulmonary metastases were determined as reported above.

Surgery. A radical surgical excision of the whole tumor-bearing leg was carried out with the mice under Ketalar anesthesia (125 mg/kg i.p.).

Results and discussion

The effects of equitoxic doses of $[Rh(COD)(N\text{-}N\text{-}CH_3)]^+Cl^-$ and $[Rh(COD)(N\text{-}N\text{-}iC_3H_7)]^+Cl^-$ on primary tumor growth and the formation of spontaneous pulmonary metastases are illustrated in Fig. 1 and Table 1, respectively. Both complexes significantly reduced primary tumor growth; the effect of $[Rh(COD)(N\text{-}N\text{-}iC_3H_7)]^+Cl^-$ was statistically superior to that of the $[Rh(COD)(N\text{-}N\text{-}CH_3)]^+Cl^-$ derivative. Lung metastases were also statistically reduced by both complexes in mice that maintained their primary tumor in situ until sacrifice. In these animals, the effects of $[Rh(COD)(N\text{-}N\text{-}CH_3)]^+Cl^-$ on the weight of the lung metastasis were slightly more pronounced than those of $[Rh(COD)(N\text{-}N\text{-}iC_3H_7)]^+Cl^-$ (inhibition, 63% vs 41%); the number of animals devoid of large metastases increased from 30% (group of controls) to about 70% in both treated groups. The effects on tumor metastases were completely abolished by surgical removal of the primary tumor at the end of drug treatment. In spite of a reduction in primary tumor weight comparable with that seen in Fig. 1 (statistically significant reduction of 23% and 35% for the methyl and isopropyl derivatives, respectively), lung metastases were not lowered and no significant prolongation of the survival of treated animals was observed (data obtained from the experiment reported in Table 1 using separate groups of ten CBA mice). The absence of inhibition of metastatic growth and of prolongation of survival in mice treated with the rhodium complexes and surgery could be ascribed to the increased formation of lung metastases during the surgical event. This hypothesis is in agreement

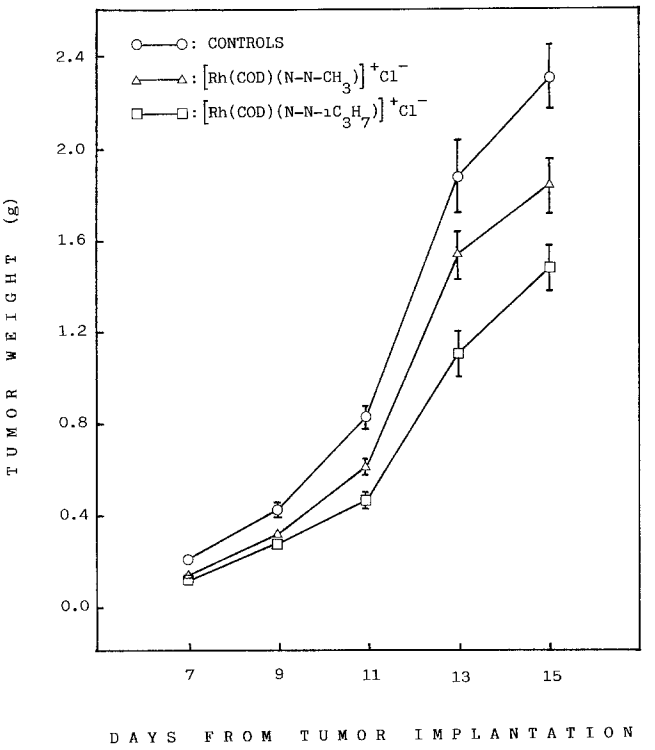

Fig. 1. Effects of $[Rh(COD)(N\text{-}N\text{-}CH_3)]^+Cl^-$ and $[Rh(COD)(N\text{-}N\text{-}iC_3H_7)]^+Cl^-$ on the growth of primary tumor in mice bearing MCa mammary carcinoma. Groups of 20 CBA mice, inoculated i.m. with MCa mammary carcinoma on day 0, were given the rhodium(I) complexes i.p. daily on days 1–12. Each mean value for the treated groups is statistically different from the corresponding mean value for the group of controls; statistically significant differences between the treated groups were observed from day 11 onward (computerized Student-Newman-Keuls test [15], $P < 0.05$)

Table 1. Effects of surgical removal of the primary tumor on the antimetastatic activity of [Rh(COD) (N-N-CH_3)]$^+Cl^-$ and [Rh(COD) (N-N-iC_3H_7)]$^+Cl^-$ in mice bearing MCa mammary carcinoma

Treatment	Surgery[a]	Spontaneous lung metastases				Animals free of large metastases[b]
		Total number	%Var	Weight (mg)	%Var	
Controls	−	16.4±1.9	−	61.6±10.8	−	3/10
[Rh(COD) (N-N-CH_3)]$^+Cl^-$	−	7.8±0.9*	−52	23.1± 5.1*	−63	7/10
[Rh(COD) (N-N-iC_3H_7)]$^+Cl^-$	−	9.9±1.0*	−40	36.1± 5.8*	−41	6/9
Controls	+	25.8±4.1	−	127.6±40.6	−	0/10
[Rh(COD) (N-N-CH_3)]$^+Cl^-$	+	32.9±3.7	+27	110.4±19.7	−13	0/8
[Rh(COD) (N-N-iC_3H_7)]$^+Cl^-$	+	31.0±6.9	+20	128.3±46.4	=	0/7

Groups of 10 CBA mice, inoculated i.m. with 10^6 MCa mammary carcinoma cells on day 0, were treated i.p. daily on days 1–12; sacrifice and lung examination for metastasis formation were carried out on day 21. Statistical analysis vs controls: computerized Student-Newman-Keuls test [15]

* $P < 0.05$

[a] Primary tumor surgically removed 24 h after the last drug administration

[b] Animals with metastases measuring >2 mm in diameter

%Var percentage of variation compared with the relevant untreated controls

Table 2. Effects of [Rh(COD) (N-N-CH_3)]$^+Cl^-$ and [Rh(COD) (N-N-iC_3H_7)]$^+Cl^-$ on lung metastasis residua after surgical removal of the primary tumor in mice bearing MCa mammary carcinoma

Compound	Number		Weight (mg)	
	median	(range)	median	(range)
Controls	25	(15–47)	86	(13–437)
[Rh(COD) (N-N-CH_3)]$^+Cl^-$	15	(1–44)	38	(5–264)
[Rh(COD) (N-N-iC_3H_7)]$^+Cl^-$	11*	(5–30)	33	(2–226)

Groups of 10 CBA mice, inoculated i.m. with 10^6 MCa mammary carcinoma cells on day 0 and undergoing surgical amputation of the primary tumor on day 13, were treated i.p. daily on days 1–12 after surgery. Sacrifice and lung examination for metastases were carried out 24 h after the last day of treatment. Statistical analysis vs controls: computerized Mann-Whitney U-test [15]

* $P < 0.05$

with the previously reported effects of tumor manipulation on metastasis promotion [1, 7] and is supported by the increased number of metastases in control mice compared with the control group, which did not undergo surgical intervention (average number of metastases per animal, 25.8 vs 16.4, respectively).

Previously reported data showed that [Rh(COD) (N-N-CH_3)]$^+Cl^-$ is ineffective when tested for direct activity on lung metastases, suggesting that the participation of modifications occurring in the primary tumor was responsible for the reduction in the formation of spontaneous metastases in the treated groups. Data shown in Table 2 fit with this observation but indicate that the use of the isopropyl derivative after the surgical excision of the primary tumor reduced the formation of lung metastases. Despite a rather high variability within the groups, the median number of metastases in the group treated with [Rh(COD)(N-N-iC_3H_7)]$^+Cl^-$ was statistically different from that obtained in the control group.

The effects of [Rh(COD)(N-N-CH_3)]$^+Cl^-$ and [Rh(COD)(N-N-iC_3H_7)]$^+Cl^-$ on artificial metastases induced by i.v. inoculation of MCa mammary carcinoma cells are indicated in Table 3. [Rh(COD)(N-N-CH_3)]$^+Cl^-$ was completely inactive, regardless of the amount of tumor inoculum given. On the contrary, [Rh(COD)(N-N-iC_3H_7)]$^+Cl^-$ significantly reduced the number and weight of artificial lung metastases of MCa mammary carcinoma, the reduction being of the same magnitude as that observed in the growth of spontaneous lung metastases. In a similar study conducted in mice bearing Lewis lung carcinoma, [Rh(COD)(N-N-iC_3H_7)]$^+Cl^-$ given at the same dose and treatment schedule showed no activity even using rather low amounts of tumor cell inocula (10^4 tumor cells/mouse). These data show a different efficacy for [Rh(COD)(N-N-iC_3H_7)]$^+Cl^-$ against metastasis formation, depending on the tumor model used, and indicate that Lewis lung carcinoma metastases are more refractory to drug treatment than those of MCa mammary carcinoma.

These data (a) confirm the antineoplastic activity of the pyridinal-methyl derivative previously studied in another solid metastasizing tumor, the Lewis lung carcinoma [12], (b) indicate a dissociation of the effects on the primary tumor from those on lung metastasis formation and survival, and (c) suggest that the antimetastatic activity of the methyl derivative is qualitatively different from that of the isopropyl analog.

Taken together, the results of the present study show that [Rh(COD)(N-N-iC_3H_7)]$^+Cl^-$ inhibits the growth of MCa mammary carcinoma at any site of tumor growth (i.e., at the primary and metastatic levels). The antitumor action of [Rh(COD)(N-N-CH_3)]$^+Cl^-$ does not seem to be related to a direct cytotoxicity to tumor cells in the lung

Table 3. Effects of [Rh(COD) (N–N–CH_3)]$^+Cl^-$ and [Rh(COD) (N–N–iC_3H_7)]$^+Cl^-$ on lung metastases artificially induced by i.v. inoculation of MCa mammary carcinoma cells

Tumor inoculum size (cells/mouse)	Compound	Artificial lung metastases[a]			
		Total number	%Var	Weight (mg)	%Var
2.5x10^5	Controls	41.9±3.9	–	258±32	–
	[Rh(COD) (N–N–CH_3)]$^+Cl^-$	35.0±6.4	−16	208±38	−19
	[Rh(COD) (N–N–iC_3H_7)]$^+Cl^-$	28.0±2.4*	−33	143±19*	−44
2.5x10^4	Controls	18.1±1.0	–	110±20	–
	[Rh(COD) (N–N–CH_3)]$^+Cl^-$	16.1±2.1	−11	90±18	−17
	[Rh(COD) (N–N–iC_3H_7)]$^+Cl^-$	11.1±0.9**	−39	60±10*	−45

Groups of 10 CBA mice, implanted i.v. with MCa mammary carcinoma cells on day 0, were treated i.p. daily on days 1–12. Statistical analysis vs controls: computerized Student-Newman-Keuls test [15]
* $P<0.05$, ** $P<0.01$
[a] Determined at sacrifice on day 14 after tumor implantation
%Var percentage of variation compared with the relevant untreated controls

Table 4. Effects of in vivo treatment of MCa mammary carcinoma with [Rh(COD) (N–N–CH_3)]$^+Cl^-$ or [Rh(COD) (N–N–iC_3H_7)]$^+Cl^-$ on tumor viability and metastasizing ability in intact or immunosuppressed hosts

Treatment of tumor donors	Cy treatment of tumor recipients[a]	Primary tumor weight (g)		Spontaneous lung metastases			
				Total number		Weight (mg)	
		mean	(range)	mean	(range)	mean	(range)
–	–	1.6	(1.5–1.8)	13	(9–20)	85	(29–198)
[Rh(COD) (N–N–CH_3)]$^+Cl^-$	–	2.5*	(2.2–3.0)	6**	(0–11)	32***	(0– 68)
[Rh(COD) (N–N–iC_3H_7)]$^+Cl^-$	–	2.4*	(2.1–2.8)	13	(8–20)	89	(30–129)
–	+	1.1	(0.5–1.4)	10	(7–16)	60	(16–177)
[Rh(COD) (N–N–CH_3)]$^+Cl^-$	+	1.5	(1.2–2.1)	14	(5–24)	51	(12–106)
[Rh(COD) (N–N–iC_3H_7)]$^+Cl^-$	+	1.1	(0.7–1.6)	16	(10–20)	69	(37– 94)

Groups of 5 CBA female mice were implanted i.m. with 50-mm^3 fragments of MCa mammary carcinoma obtained from donors similarly implanted 13 days before, and treated i.p. daily for 12 consecutive days following tumor implantation. Primary tumor weight was estimated on day 14, and lung metastasis examination was carried out on day 21 after tumor implantation. Statistical analysis vs controls: computerized Mann-Whitney U-test [15]
* $P<0.01$, ** $P<0.055$, *** $P<0.08$
[a] 180 mg/kg cyclophosphamide given i.p. on day −1 (before tumor implantation)

Table 5. Modification of the weight of the spleen, kidney and liver in tumor-bearing hosts treated with [Rh(COD) (N–N–CH_3)]$^+Cl^-$ and [Rh(COD) (N–N–iC_3H_7)]$^+Cl^-$

Compound	Organ weight (mg) determined:					
	2 days after treatment (A)			15 days after treatment (B)		
	spleen	kidney	liver	spleen	kidney	liver
Controls	121± 7	391±19	1,406±62	121± 7	391±19	1,406±62
[Rh(COD) (N–N–CH_3)]$^+Cl^-$	157±13*	360±11	1,138±27**	166±12**	352±23	1,240±80
[Rh(COD) (N–N–iC_3H_7)]$^+Cl^-$	155±16*	357±17	1,197±39**	177± 9**	380±27	1,470±54

Groups of 10 mice, inoculated i.m. with 10^6 MCa mammary carcinoma cells on day 0 and undergoing surgical removal of the primary tumor on day 13, were treated i.p. daily on days 1–12 (*B*) or on days 14–25 (*A*). Sacrifice and determination of organ weight were carried out on day 27. Statistical analysis vs controls: computerized Student-Newman-Keuls test [15]
* $P<0.05$, ** $P<0.01$

site; this finding is in agreement with previous observations obtained in the Lewis lung system [12]. The results of the experiment illustrated in Table 4 further stress the existence of a qualitatively different mechanism of action for the two complexes on lung metastasis formation. The viability and clonogenicity of MCa mammary carcinoma cells obtained from primary tumors is significantly modified by in vivo treatment, as is indicated by the statistically significantly larger tumors obtained in intact mice inoculated i.m. with 50 mm^3 mammary carcinoma fragments prepared from mice treated in vivo. The effect on tumor malignancy, expressed by the capacity to form

spontaneous lung metastases, is of particular interest. Despite a 1.5-fold larger primary tumor, mice inoculated with MCa mammary carcinoma cells and treated with $[Rh(COD)(N\text{-}N\text{-}CH_3)]^+Cl^-$ exhibited a reduced capacity to form spontaneous lung metastases. This effect is reverted by the use of cyclophosphamide-treated (immunosuppressed) mice, suggesting the participation of drug-induced antigenic variations [10, 15] capable of eliciting host responses against the treated tumor cells.

These data, together with those previously reported in the literature, seem to suggest that the antineoplastic action of rhodium(I) organometallic complexes could differ from compound to compound, even for complexes having minor changes within their chemical structure. Of particular interest is the antimetastatic action of the $[Rh(COD)(N\text{-}N\text{-}CH_3)]^+Cl^-$ derivative. This complex appears to inhibit lung metastasis formation by intervention in the primary tumor mass via a mechanism probably unrelated to a direct cytotoxicity to tumor cells. It seems more likely that the inhibition of spontaneous lung metastases could be the result of a chemical xenogenization of metastatic tumor cell populations, principally tumor cell clones endowed with metastatic ability [9]. It could thus be expected that among the rhodium(I) complexes, compounds might exist that are capable of partial or total interaction with tumors via a mechanism of action that includes responses different from a direct cytotoxicity to tumor cells.

In agreement with these considerations, it is interesting to note that both complexes are capable of inducing a long-lasting hyperplasia of the spleen, still evident 14 days after treatment withdrawal (Table 5). Data reported in Table 5 also show the absence of an appreciable decrease in the weight of the kidneys and that liver toxicity, indicated by the statistically significant reduction in liver weight at the end of treatment, is transient, being completely reversed within 2 weeks after drug withdrawal. These latter aspects seem particularly interesting and deserve further investigation. Experiments aimed at ascertaining the role of the nonspecific host responses in the antitumor effects of rhodium(I) complexes will be undertaken to confirm this view.

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