Coordination Metal Complexes of Rh(I), Ir(I) and Ru(II): Recent Advances on Antimetastatic Activity on Solid Mouse Tumors*

GIANNI SAVA, SONIA ZORZET, LAURA PERISSIN
Istituto di Farmacologia, Facoltà di Farmacia, Università degli Studi di Trieste, Italy
GIOVANNI MESTRONI, GRAZIA ZASSINOVICH and ALESSANDRA BONTEMPI
Dipartimento di Science Chimiche, Università degli Studi di Trieste, Italy

Abstract

Following pioneering observations on the mouse Ehrlich ascites carcinoma, the result of cooperation between the Institutes of Chemistry and Pharmacology of the University of Trieste, more recent studies have characterized some aspects of the antimetastatic properties of coordination metal complexes other than platinum compounds.

The compounds examined, rhodium(I) and iridium(I) derivatives of the type $[Mchel(L–L)]^{+/0}$ (chel = pyridinalimine (N–N–R), acetylacetonate; L–L = 1,5-hexadiene, 1,5-cyclooctadiene, norbornadiene), both with a square-planar structure, and an octahedral ruthenium(II) derivative $RuCl_2$(dimethylsulfoxide)$_4$ were tested using the solid metastasizing tumor of the mouse, Lewis lung carcinoma. The conclusions which can be drawn from the resulting data concern the role of the metal, of the leaving group and of the non-leaving group as well. It was found that the organometallic complexes of Rh(I) are more active than those of Ir(I); within the Rh(I) derivatives of the type $[Rh(I)COD(N–N–R)]^+Cl^-$ (R = CH_3, C_2H_5, iC_3H_7), the higher the hydrosolubility, the higher is the antitumor and particularly the antimetastatic effect; as far as the diolefinic ligands are concerned, the higher the chelating effect the higher are the antimetastatic properties of the resulting compound. Separate conclusions can be made for the Ru(II) derivative. Comparison of its antimetastatic effects with those of *cis*-dichlorodiammineplatinum(II) (cisplatin) using three solid mouse tumors, clearly shows a better therapeutic index for the former, suggesting that within this class of compounds it is conceivable to obtain derivatives with an antineoplastic activity comparable to or even higher than that of cisplatin.

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Introduction

A large series of organometallic complexes of group VIII coordination metals have been tested for their antineoplastic activity in experimental models of murine tumors. The attention of the workers in this field was mainly devoted to the examination of platinum derivatives, with the objective of developing analogs with antineoplastic characteristics better than those of cisplatin. The discovery of this compound leaves room for further research on new compounds, although, out of more than 1500 platinum derivatives studied at present, none clearly showed a therapeutic activity better than that of cisplatin.

With regard to rhodium, iridium and ruthenium complexes, it must be noted that very little work has been done to characterize their antitumor activity. Following the collection of data existing on these metals (see reviews 1 and 2), it is worth noting the findings of Bear [3, 4] on rhodium(II) carboxylates which, unlike many rhodium(III) derivatives tested [5], expressed interesting antitumor activity in both Ehrlich ascites carcinoma and L1210 lymphoid leukemia. Ruthenium derivatives showed controversial results, depending upon the tumor system used: ruthenium(II) chelates with 1,10-phenanthroline or 2,2′-bipyridine were active in Landschutz ascites cell [6] and inactive in the more invasive P388 lymphocytic leukemia [7]. The activity of ruthenium red has been shown in detail [8, 9], whereas iridium complexes, apart from some iridium(III) derivatives, have been even less investigated [1, 2].

Results and Discussion

Rhodium(I) Derivatives: Effects on the Ascitic Forms of Murine Tumors and on Leukemias

Rhodium(I) complexes of the type $[Mchel(L–L)]^{+/0}$, with square-planar geometry, have been synthesized and tested for antitumor activity in

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murine-transplantable tumors. The capacity to reduce the growth of Ehrlich ascites carcinoma has been found to vary widely between the compounds used [10–12]. A significant increase in the antitumor activity is obtained with complexes having an acetylacetonate moiety instead of groups such as piperidine, bipyridine and phenanthroline [10–12]. Yet, the presence of the diolefinic ligand 1,5-cyclooctadiene confers more favorable antitumor properties than norbornadiene: the use of the flexible 1,5-hexadiene group causes inactivation of the resulting complex [11]. These pioneering studies were also extended, for selected compounds, to the solid form of sarcoma 180 and to the lymphoid leukemia L1210 [12]. In both cases, however, few additional indications were discovered, since, in many instances, the treatment was completely ineffective.

More recently, and following the above reported observations, the antineoplastic activity of rhodium(I) thiazoles of the type $[Rh(CO)_2(L)(Cl)]$ were L is a substituted thiazole, were tested in four *in vivo* tumor systems [13, 14]. Many of these compounds were found to be active on Ehrlich ascites carcinoma, the 2-aminothiazole and 2-amino-6-bromobenzothiazole were active also on the ascitic form of sarcoma 180, whereas more malignant tumor systems such as P388 lymphocytic leukemia and L1210 lymphoid leukemia did not respond to treatment. Antileukemic activity was shown for compounds of the type [*cis,cis*-1,5-cyclooctadienerhodium(I)(N–N–R)]$^+Cl^-$, were R is CH_3, C_2H_5 and C_3H_7; the activity on P388 lymphocytic leukemia was independent of the treatment schedule used [16].

Rhodium(I) and Iridium(I) Derivatives: Antitumor and Antimetastatic Activity on Lewis Lung Carcinoma

Particular attention has been given in the last three years to the effects of rhodium(I) coordination complexes on the growth of Lewis lung carcinoma and its metastases in mice. This tumor system grows *in vivo* in a way similar to that of the most common human solid malignant neoplasms, and allows one to distinguish the effects on the primary site of tumor growth from those on the lung metastases which spontaneously arise during the first two weeks following s.c. or i.m. tumor implantation. The compounds tested in this tumor system were given with a treatment schedule chosen to cover the first two weeks of tumor growth and of consequent metastasis formation. Under these conditions, almost all the compounds studied were found to be active as antimetastatic agents [15, 16], although differences exist as far as the mechanism of the reduction of metastasis formation is concerned. Generally, the following considerations can be made:

(a) Substitution of the piridinalimine group with acetylacetonate increases the antineoplastic activity.

(b) The presence of the diolefinic ligand norbornadiene in place of 1,5-cyclooctadiene, contrary to what was found with Ehrlich ascites carcinoma [10, 11], does not reduce the antimetastatic activity. Within the series of dimeric compounds studied, complexes having 1,5-cyclooctadiene and norbornadiene are equally active; the substitution of these diolefins with 1,5-hexadiene totally abolishes the antimetastatic effect.

(c) In the series of compounds having leaving groups containing nitrogen ($[RhCOD(N–N–CH_3)]^+Cl^-$, $[RhCOD(N–N–C_2H_5)]^+Cl^-$ and $[RhCOD(N–N–C_3H_7)]^+Cl^-$), it can be stated that the higher the hydrosolubility of the compound used, the higher is the antimetastatic activity; a dependence of the antimetastatic activity on the electronic effect of the carbonyl function on the oxidizability of the molecule can also be operative.

(d) Compounds having leaving groups containing nitrogen show similarly pronounced effects on primary tumor and on lung metastases; the other compounds tested, and the dimeric complexes ($[RhNBDCl]_2$, $[RhCODCl]_2$ and $[RhEDCl]_2$) in particular, display negligible effects on subcutaneous tumor growth, in spite of a remarkable antimetastatic effect.

It was thus found that the mechanism of the antimetastatic action is different and, depending on the compound used, can be attributed to either cytotoxicity at the primary tumor level or to a predominant effect directed to the lung colony development. These effects can be concomitantly operative ([RhacacCOD], $[RhCOD(N–N–CH_3)]^+Cl^-$) or the antimetastatic activity can be predominant over the antitumor effect ($[RhCODCl]_2$, [RhacacNBD], $[RhNBD(N–N–CH_3)]^+Cl^-$ and $[RhNBDCl]_2$).

Iridium(I) complexes have also been studied: [IracacCOD] and $IrCODCl]_2$. They were chosen in order to compare their antitumor and antimetastatic properties with those of the rhodium(I) analogs having the same chemical structure [15]. The resulting data indicate that:

(a) The substitution of Rh with Ir confers different properties to the molecule: the acetylacetonate derivative is inactivated whereas the antimetastatic effect is increased for the 1,5-cyclooctadiene dimer $[IrCODCl]_2$.

(b) The loss of activity of [IracacCOD], as compared with [RhacacCOD], concerns only the antimetastatic effects; the activity on primary tumor growth remains equally pronounced. Similarly, the increased antimetastatic activity of $[IrCODCl]_2$ as compared with $[RhCODCl]_2$ is not paralleled by the appearance of activity on primary tumor growth, which in both cases in negligible.

cis-[RuCl$_2$(DMSO)$_4$]: Antimetastatic Activity in Solid Malignant Tumors

Among the metallo-organic complexes of group VIII transition metals, considerable attention has

been dedicated to *cis*-tetrakisdimethylsulfoxide dichlororuthenium(II). This complex has been found to have interesting antitumor properties since the initial studies on Ehrlich ascites carcinoma and on L1210 lymphoid leukemia [10]. The antitumor activity in these tumor systems, although not superior to that of cisplatin, was accompanied by less extensive histological damage to spleen and intestinal mucosa. The use of solid metastasizing tumors of the mouse, and the comparison of its antitumor activity with that of cisplatin, at equitoxic dosages, has further indicated some advantages of this molecule [15, 17]. Data obtained at present [17] indicate possible advantages of *cis*-$[RuCl_2(DMSO)_4]$ over cisplatin in the tumor systems used, particularly considering the weak toxicity for normal tissues at therapeutically active dosages.

Conclusions

Data available on the antineoplastic activity of rhodium(I) and iridium(I) derivatives, at present, are limited to a few reports, some of them involving tumor systems whose predictivity is doubtful. Nevertheless, the results obtained testing 11 derivatives on the growth of s.c. Lewis lung carcinoma and on its pulmonary metastases indicate that, within this class of compounds, different degrees of activity can be identified, giving interesting suggestions for the synthesis of new derivatives with specific antitumor or antimetastatic activity. It thus seems that the antineoplastic activity of these complexes could be increased by changing the nature of the diolefinic ligand, using analogs of the piridinal derivative, which is more polar than those presently described, and examining the role of the metal atom (substitution of Rh with Ir) in a larger series of derivatives.

The only ruthenium derivative studied was *cis*-$[RuCl_2(DMSO)_4]$. Comparison with cisplatin makes this complex particularly interesting, and suggests that probably within this class of compounds there is much room for further investigation on new derivatives. Accordingly, investigation of the differences in the mechanism of action between cisplatin and *cis*-$[RuCl_2(DMSO)_4]$ could account for the different behavior of these compounds on either tumor and/or normal host tissues.

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