## Communications to the Editor

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# Antineoplastic Activity of Platinum Complexes of *trans*-(*dl*)-1,2-Cyclopentanediamine[1]

Dichloro-*trans*-(*dl*)-1,2-cyclopentanediamineplatinum(II) and its derivatives, mixed ligand complexes with oxalato, malonato, or sulfato, were synthesized and tested against Leukemia P-388. All of these complexes have high antineoplastic activity. Among them sulfato-*trans*-(*dl*)-1,2-cyclopentanediamine revealed a very high therapeutic index and is more effective than the corresponding complex of 1,2-cyclohexanediamine.

**Keywords**——antineoplastic activity; platinum complex; 1,2-cyclopentanediamine; 1,2-cyclohexanediamine; mixed ligand complexes

Tobe *et al.*[2] reported the synthesis of platinum complexes of cycloalkylamine having a $C_3$–$C_8$ side chain and tested their efficacy as antineoplastic agents. Among them, both dichlorobiscyclohexylamine Pt(II) and dichlorobiscyclopentylamine Pt(II) had remarkably high therapeutic indices against ADJ/PC6A tumor in mice, but they were insufficiently soluble in water to allow them to administer intravenously and therefore they were found not particularly suitable for clinical use. In order to find out an active complex with high therapeutic index and low nepherotoxicity, many platinum complexes have been synthesized, and platinum complexes of 1,2-cyclohexanediamine isomers (abbreviated as dach) have been found to be one of the most promising antineoplastic agents.[3–8] In this connection, platinum complexes of *trans*-(*dl*)-1,2-cyclopentanediamine (abbreviated as dacp) being analogous to those of dach, $PtCl_2$(dacp), Pt(oxalato)(dacp), Pt(malonato)(dacp), and Pt(sulfato)(dacp), were synthesized and tested against Leukemia P-388 in $CDF_1$ mice.

Table I. Antineoplastic Activities of Platinum Complexes of *trans*-(*dl*)-1,2-Cyclopentanediamine

| Compounds | Toxic dose mg/kg | Optimum dose mg/kg | Optimum dose T/C% | Minimum effective dose[a] mg/kg | Minimum effective dose[a] T/C% | TI[b] |
|---|---|---|---|---|---|---|
| $PtCl_2$ (dacp) | 50 | 25 | 235 | 1.56 | 124 | 16 |
| Pt (oxalato) (dacp) | 25 | 12.5 | 176 | 6.25 | 128 | 2 |
| Pt (malonato) (dacp) | 400 | 200 | 186 | 12.5 | 126 | 16 |
| Pt (sulfato) (dacp) | 50 | 25 | 198 | 0.39 | 125 | 64 |

Test cells; P-388, $10^6$ cell/mouse, ip-ip, $CDF_1$ mice (6 mice/group) Administered day 1 and 5
*T/C*%; the percentile of the median survival days of treated to control mice.
*a*) Lowest dose where *T/C*% exceeds 120%.
*b*) Therapeutic index (optimum dose/minimum effective dose).

1) A part of this work was presented at the 3rd International Symposium on Platinum Coordination Complexes in Cancer Chemotherapy. Dallas, Oct. 1976. R.J. Speer *et al.* reported antineoplastic activity of the same complexes against Leukemia L-1210 in the symposium.
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Table I shows that all of the dacp Pt(II) complexes have high antineoplastic activity. Change of the dichloro leaving group with oxalato, malonato, and sulfato gives important effect on their antineoplastic activity, and obviously the leaving group plays an important role in the appearance of the antineoplastic activity of these platinum complexes. Pt(malonato)(dacp) showed activity with low toxicity, but its maximum life span was obtained at a higher dosage. Its dose response curve is very similar to that of Pt(malonato)(dach). The effective dose range of Pt(oxalato)(dacp) is very narrow. Figure 1 shows the dose response curves of dichloro and sulfato platinum complexes of dacp and dach. The complexes of dacp showed apparently higher therapeutic index than those of dach. $PtCl_2$(dacp) has a therapeutic index of 16 compared to 4 for $PtCl_2$(dach), and Pt(sulfato)(dacp) has a therapeutic index of 64 compared to 8 for Pt (sulfato) (dach).

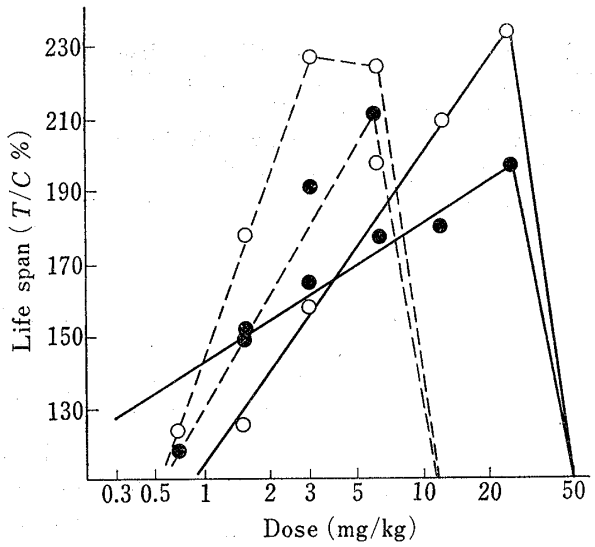


Fig. 1. Dose-Response Curves of the Platinum Complexes of dacp and dach

—○— $PtCl_2$ (dacp),
—●— Pt (sulfato) (dacp),
—○— $PtCl_2$ (dach),
—●— Pt (sulfato) (dach).

$PtCl_2$(dacp) and Pt(malonato)(dacp) complexes are slightly soluble in water, while Pt(oxalato)(dacp) and Pt(sulfato)(dacp) have excellent solubility in water, being very important from the therapeutic stand point, because the majority of platinum complexes are not very soluble in any solvents. Pt(sulfato)(dacp) is considered to be one of the most promising antineoplastic agent because of its very high therapeutic index, as well as its excellent solubility.

From these results, it may be concluded that the platinum complexes of dacp have high antineoplastic activity against Leukemia P-388 and are better than those of dach. Further detailed studies on the resolution of *trans*-(*dl*)-1,2-cyclopentanediamine, and the synthesis and antineoplastic activities of platinum complexes of their optical isomers will be reported.

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