A NEW ANTITUMOR ANTIBIOTIC, KIDAMYCIN

II. EXPERIMENTAL TREATMENT OF CANCER WITH KIDAMYCIN

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The antitumor effects of kidamycin were studied on experimental animal tumors. On EHRLICH ascites carcinoma, kidamycin was remarkably effective but the effect on leukemia SN-36 was not excellent. A slight efficacy of kidamycin on leukemia L1210 was observed. On Sarcoma-180, a good and characteristic result was obtained at a dose of 7 mg/kg, and 4 of 10 treated mice survived without tumors. Kidamycin was also effective on NF-sarcoma and YOSHIDA sarcoma.

Kidamycin[1] is one of the antibacterial and antitumor antibiotics produced by *S. phaeoverticillatus* var. *takatsukiensis*[1]. The antibiotic has antibacterial activity upon Gram-positive bacteria as previously reported[1] and also shows antitumor activity on some experimental animal tumors.

This report deals with the studies on experimental treatments of animal tumors with kidamycin.

Materials and Methods

Materials: Kidamycin free base (pure crystals) was dissolved in citrate-phosphate buffer solution (pH 3.6) directly before its use.

Experimental tumors: EHRLICH ascites carcinoma, mouse leukemia SN-36, Sarcoma-180 (solid type), NF-sarcoma[2] (NAKAHARA and FUKUOKA's sarcoma), leukemia L1210, and YOSHIDA sarcoma were tested in the present experiments.

Animals: Male *dd* strain mice weighing 20 ± 1 g for EHRLICH ascites carcinoma, mouse leukemia SN-36, Sarcoma-180 (solid type) and NF-sarcoma, CDF_1 strain mice weighing 20 ± 1 g for leukemia L1210, and male Donryu strain rats weighing 150 ± 10 g for YOSHIDA sarcoma were used.

Methods: With EHRLICH ascites carcinoma and leukemia SN-36, male *dd* mice were inoculated intraperitoneally with 1×10^7 cells of the tumors respectively. Fourty-eight hours after the implantation of each tumor cells, solutions containing various doses of the antibiotic were administered once intraperitoneally. Twenty-four hours after the implantation of 1×10^5 cells of leukemia L1210, each solution was administered intraperitoneally once a day for 8 consecutive days or every two days dividing into 3 times. With Sarcoma-180 (solid type) and NF-sarcoma, male *dd* mice were implanted with a slice of the tumor (2 mm cubics) in an axillary cavity with a trocar, respectively. Twenty-four hours after the implantation of the tumors, each solution containing various doses of the antibiotic was injected intravenously at 0.2 ml/mouse once a day for 7 or 5 consecutive days. Donryu strain rats were inoculated intraperitoneally with 1×10^6 cells of YOSHIDA sarcoma.

Daily intraperitoneal therapy of 18 mg/kg or 9 mg/kg was administered in total amount dividing in 4 or 8 times. In every experiment, untreated control animals were administered with citrate-phosphate buffer solution (pH 3.6).

Results

1. The Effects of Kidamycin on EHRLICH Ascites Carcinoma and Leukemia SN-36

Results obtained when single intraperitoneal therapy of $LD_{50}\times3\sim LD_{50}\times1/16$ doses were administered are shown in Tables 1 and 2.

Kidamycin exhibited remarkable life-prolongation effects on EHRLICH ascites tumor bearing mice, and some of them survived over 50 days without tumors as shown in Table 1. On the other hand, the antibiotic did not exhibit good effects on leukemia SN-36 (Table 2).

Table 1. Effect on EHRLICH ascites carcinoma*

Dose mg/kg	Survived days of mice										Average days	T/C×100 (%)
54.0	6	6	7	7	7	7	8	8	8	8	7.2	42.4
36.0	7	7	8	8	8	8	8	9	34	○	>14.7	> 86.5
27.0	6	7	7	8	8	8	9	10	14	41	11.8	69.4
18.0	6	6	7	7	8	8	9	13	○	○	>16.4	> 96.5
12.0	6	6	8	22	32	42	42	32	○	○	>29.0	>170.6
9.0	8	14	18	30	32	45	○	○	○	○	>34.7	>204.1
4.5	40	42	45	45	○	○	○	○	○	○	>47.2	>277.6
2.25	20	27	29	38	40	○	○	○	○	○	>40.4	>237.7
1.12	16	17	20	21	22	28	46	○	○	○	>32.0	>188.2
Control	13	14	15	16	16	20	20	20	15	21	17.0	100.0

* Single ip. administration, LD_{50}(ip.)=18 mg/kg
○: Survived over 50 days

Table 2. Effect on leukemia SN-36*

Dose mg/kg	Survived days of mice										Average days	T/C×100 (%)
54.0	6	6	6	6	6	6	6	6	6	11	6.5	57.0
36.0	6	6	6	6	6	6	6	10	11	13	7.6	66.7
27.0	6	6	6	6	6	6	6	7	7	11	6.7	58.8
18.0	6	6	6	6	6	7	7	7	11	11	7.3	64.0
12.0	7	7	7	7	7	8	8	8	9	9	7.7	67.5
9.0	9	9	11	13	16	18	18	22	22	23	16.1	141.2
4.5	11	13	13	14	15	15	17	17	28	○	>19.3	>169.3
2.25	11	14	15	15	15	21	22	22	22	28	18.5	162.3
1.12	10	13	13	13	15	15	17	○	○	○	>24.6	>215.8
Control	8	8	11	11	11	11	13	13	13	15	11.4	100.0

* Single ip. administration
○: Survived over 50 days

2. The Effects of Kidamycin on Leukemia L1210

In daily intraperitoneal therapy for 8 days, kidamycin was not effective at total doses of 18 mg/kg (LD_{50} value), 13.5 mg/kg and 9 mg/kg respectively (Table 3). A slight efficacy was observed at a total dose of 15 mg/kg when it was administered every two days in three divided doses as shown in Table 4.

Table 3. Effect on leukemia L1210 (1)*

Total dose mg/kg	Survived days of mice										Average days	T/C×100 (%)
18.0	8	9	9	9	9	9	9	9	9	9	8.9	111.2
13.5	10	9	9	9	9	9	9	9	9	9	9.1	113.8
9.0	8	8	9	9	9	9	9	9	9	9	8.8	110.0
Control	7	7	8	8	8	8	8	8	9	9	8.0	100.0

* Intraperitoneal administration for 8 consecutive days

Table 4. Effect on leukemia L1210 (2)*

Total dose mg/kg	Survived days of mice										Average days	T/C×100 (%)
15.0	9	9	10	10	10	11	11	11	11	12	10.4	130.0
Control	7	7	8	8	8	8	8	8	9	9	8.0	100.0

* Every two days administration (3 times)

3. The Effects of Kidamycin on Sarcoma-180

Kidamycin was administered intravenously at a daily dose of 2 mg/kg or 1 mg/kg for 7 consecutive days respectively. In the case of daily injections of 2 mg/kg, a somewhat toxic reaction was observed (Fig. 1).

However, in daily therapy of 1 mg/kg, a remarkable antitumor effect was observed and 4 of 10 treated mice survived more than 40 days without tumors as shown in Fig. 2.

Fig. 1. Effect on Sarcoma-180 (solid).
Daily intravenous administration of 2 mg/kg for 7 consecutive days.
†: died

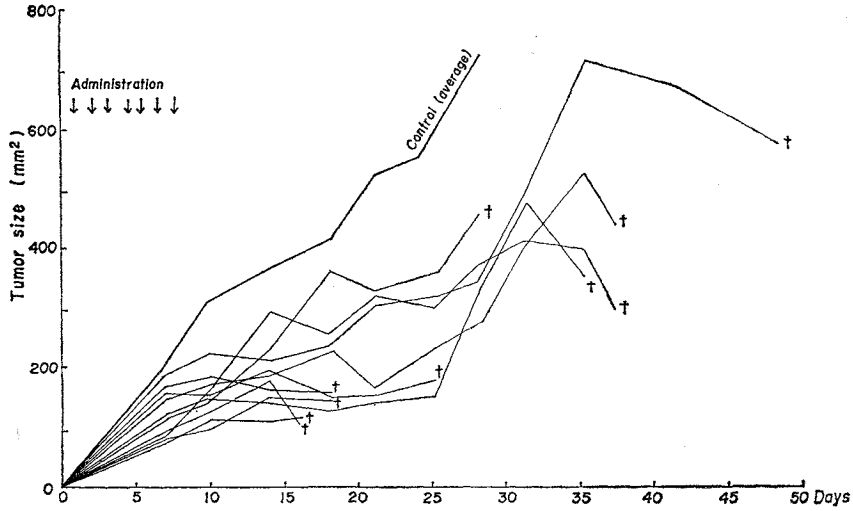
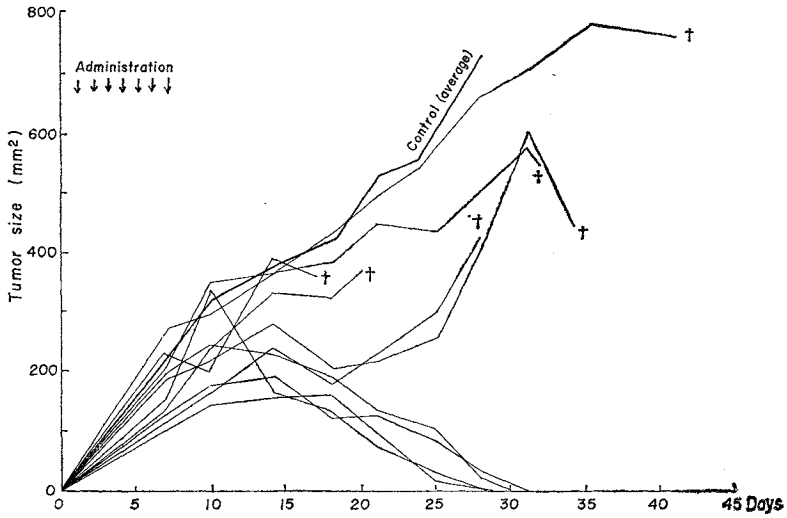


Fig. 2. Effect on Sarcoma-180 (solid).
Daily intravenous administration of 1 mg/kg for 7 consecutive days.
†: died



4. The Effects of Kidamycin on NF-Sarcoma

Twenty-four hours after the implantation of the tumor, 2.8 mg/kg/day or 1.4 mg/kg/day of kidamycin was injected intravenously for 5 consecutive days. Ten days after the implantation of the tumor, all mice were sacrificed and each tumor was weighed to compare with that of untreated control mice. In the experiment of daily intravenous therapy of 2.8 mg/kg for 5 days the antibiotic was toxic on treated animals, but kidamycin exhibited a good antitumor effect when it was administered intravenously at a dose of 1.4 mg/kg/day for 5 consecutive days as shown in Table 5.

Table 5. Effect on NF-sarcoma*

Sample	Total dose mg/kg	Inhibitory ratio %	Antitumor index
Kidamycin	14.0 (LD_{50})	died	toxic
	7.0	55.4	++
Mitomycin C	5.0 (LD_{50})	36.4	+
	2.5	−5.5	−

* Daily iv. administration of total dose/5/day for 5 days

Table 6. Effect on YOSHIDA sarcoma

Experiment No.*	Total dose mg/kg	Survived days			T/C×100 (%)
1	18.0	8	9	9	(ave.) 8.7	138
	9.0	8	9	9	8.7	138
2	18.0	8	9	10	9.0	143
	9.0	8	8	9	8.3	131
Control		6	6	7	6.3	100

* 1: Daily ip. administration of total dose/4/day for 4 days
2: Daily ip. administration of total dose/8/day for 8 days

5. The Effects of Kidamycin on YOSHIDA Sarcoma

Twenty-four hours after the implantation of the tumor, kidamycin was administered by intraperitoneal route once a day at total doses of 18 mg/kg and 9 mg/kg in divided doses, 8 times or 4 times, respectively.

The prolongation of the life of treated animals as compared to untreated control animals was observed as shown in Table 6.

Discussion

In considering the results on EHRLICH ascites carcinoma, kidamycin was remarkably effective at doses of 2.25 mg/kg to 9.0 mg/kg, but the effects of kidamycin on leukemia SN-36 were not excellent.

A slight efficacy of kidamycin on leukemia L1210 was observed at a total dose of 15 mg/kg. On Sarcoma-180 (solid type), kidamycin was somewhat toxic at a total dose of 14 mg/kg; however, a good and characteristic result was obtained at a total dose of 7 mg/kg when it was administered intravenously. That is, during the first 2 weeks, the extent of growth of tumors in treated mice was similar to that on untreated control mice, but thereafter, the size of the tumor in treated mice began to decrease. Although all untreated control mice died within 25 days with tumors, at the 40th day after the implantation of the tumor, 4 of 10 treated mice survived without tumors.

The therapy of a total dose of 7 mg/kg was effective on NF-sarcoma, however, at a total dose of 14 mg/kg (LD_{50} value, intravenously), a toxic reaction was observed. On YOSHIDA sarcoma, kidamycin showed a slight life-prolongation at a dose of 18 mg/kg (LD_{50} value, intraperitoneally) and 9 mg/kg.

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