Acknowledgment. The authors thank P. Hadházy for investigations on the isolated organ and K. Ajtay for biochemical measurements.

G. Kovács,* V. Simonidesz, I. Tömösközi
P. Körmöczy, I. Székely
Á. Papp-Behr, I. Stadler
Chinoin, Chemical and Pharmaceutical Works, Ltd.
Budapest, Hungary

L. Szekeres, Gy. Papp
Department of Pharmacology
University Medical School of Szeged
Szeged, Dóm tér 12., Hungary

Received May 14, 1981

2-β-D-Ribofuranosylthiazole-4-carboxamide, a Novel Potential Antitumor Agent for Lung Tumors and Metastases

Sir:

We are currently pursuing 2-β-D-ribofuranosylthiazole-4-carboxamide (NSC 286193, 1) as a high-priority candidate for clinical trials with potential importance for treatment of lung tumors and metastases.

Most patients with bronchogenic carcinoma benefit little from chemotherapy with currently available drugs.[1] Thus, there is a need for the identification of chemotherapeutic agents with greater activity against lung tumors. The murine Lewis lung carcinoma is one of the experimental tumors used by screening programs to identify compounds for development to clinical trial.[2] When used as an iv implant it gives rise preferentially to tumor growth in the lungs with very little involvement of other organs.[3] The ability of a tumor to form colonies in the lung following iv injection is believed to be characteristic of metastic tumors;[4] thus, the iv Lewis lung carcinoma also can be viewed as a model for metastases. We report here that 2-β-D-ribofuranosylthiazole-4-carboxamide (1)[5] has demonstrated remarkable activity against this tumor system.

Compounds prepared as part of a targeted research effort to find new antiviral agents were selected for antitumor screening on the premise that compounds known to exhibit certain kinds of biological activity (e.g., antibiotic, antiviral, antiparasitic) may have an enhanced probability of exhibiting anticancer activity. Compound 1 is an analogue of the potent antiviral agent ribavirin (2),[6-11] which has demonstrated only weak antitumor activity. In contrast, 1 exhibited poor antiviral activity[6,7] but was very effective against several murine tumors, including the Lewis lung carcinoma.

Table I. Effect of 1 on the Life Span of Mice Inoculated Intravenously with Lewis Lung Carcinoma[a]

drug	dose, mg/kg	median life span,[d,e] days post-implant	body wt change[b]	60-day survivors
		Experiment 1		
untreated controls		25.0	1.9	0/40
1	800	11.3	1.3	6/10
	400	9.5	1.2	7/10
	200	ND	1.3	10/10
	100	17	1.3	9/10
	50	ND	2.2	10/10
	25	ND	1.2	10/10
		Experiment 2		
untreated controls		18.4	1.1	0/40
1	800	8.5	−2.1	1/10
	400	ND	0.4	10/10
	200	ND	0.7	10/10
	100	46	1.3	9/10
	50	47	1.6	9/10
	25	ND	1.0	10/10
cyclophosphamide[c]	120	44.0	0.1	4/10
	90	37.5	1.3	5/10
		Experiment 3		
untreated controls		16.9	1.2	0/40
1	800	11.3	−0.8	0/10
	400	20.0	0.5	6/10
	200	16.0	0.7	8/10
	100	ND	0.9	10/10
	50	55	1.2	9/10
	25	47	1.1	7/8
cyclophosphamide[c]	300	16.3	−0.7	2/10
	150	46.0	0.3	4/10
	75	24.5	0.7	1/10
	37	20.4	1.1	0/10
		Experiment 4		
untreated controls		21.1	1.9	0/40
1	25	7	1.5	9/10
	12.5	39.5	1.9	7/10
	6.25	25.3	2.3	0/10
	3.12	22.8	1.8	0/10
	1.56	23.0	1.7	0/10
	0.78	20.0	2.0	0/10

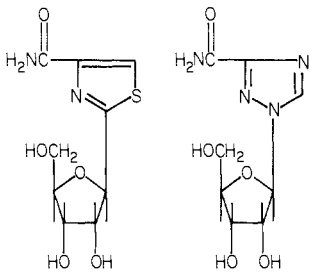
[a] Lewis lung tumor cells (10^6) were implanted iv in groups of 10 BDF_1 mice (experiment 2) or $B6C3F_1$ mice (experiments 1, 3, and 4) (40 mice in untreated control groups) 24 h before initiation of therapy. An aqueous solution of 1 was administered ip on days 1 to 9. Characteristics of the iv model have been described previously.[3] [b] Average body weight in grams on day 5 minus average body weight on day 1. [c] Positive control. Treatment on day 1 only. [d] 60-day survivors are excluded. [e] ND = no deaths.

Experiments 1, 3, and 4) (40 mice in untreated control groups) 24 h before initiation of therapy. An aqueous solution of 1 was administered ip on days 1 to 9. Characteristics of the iv model have been described previously.[3] [b] Average body weight in grams on day 5 minus average body weight on day 1. [c] Positive control. Treatment on day 1 only. [d] 60-day survivors are excluded. [e] ND = no deaths.

The activity of 1 against the Lewis lung carcinoma is exceptional for both its degree of activity and its range of effective doses (Table I). Following daily ip administration of an aqueous solution of 1 on days 1–9, an impressive number of 60-day survivors was observed over a wide dosage range in three experiments (Table I, experiments

(1) Wolf, J.; Livingston, R.; Perez, C. A.; Stolbach, L. L. in "Cancer Research, Impact of the Cooperative Groups"; Hoogstraten B., Ed.; Masson Publishing, New York, 1980; pp 159–179.
(2) Goldin, A.; Venditti, J. M. *Recent Results Cancer Res.* **1980**, *70*, 5–20.
(3) Ovejera, A. A.; Johnson, R. K.; Goldin, A. *Cancer Chemother. Rep.* **1975**, *5*, 111–125.
(4) Hanna, N.; Fidler, I. J. *Cancer Res.* **1981**, *41*, 438–444.
(5) Srivastava, P. C.; Pickering, M. V.; Allen, L. B., Streeter, D. G.; Campbell, M. T.; Witkowski, J. T.; Sidwell, R. W.; Robins, R. K. *J. Med. Chem.* **1977**, *20*, 256–262.
(6) Sidwell, R. W.; Huffman, J. H.; Khare, G. P.; Allen, L. B.; Witkowski, J. T.; Robins, R. K. *Science* **1972**, *177*, 705–706.
(7) Witkowski, J. T.; Robins, R. K.; Sidwell, R. W.; Simon, L. N. *J. Med. Chem.* **1972**, *15*, 1150–1154.
(8) Khwaja, T. A.; Popovic, M. R.; Witkowski, J. T.; Robins, R. K.; Halpern, R. M.; Smith, R. A. *Proc. Am. Assoc. Cancer Res.* **1972**, *13*, 91.
(9) Jolley, W. B.; Chu, W. T.; Slater, J. M.; Hinshaw, D. B.; Randhawa, A. S. *Ann. N.Y. Acad. Sci.* **1977**, *284*, 585–590.
(10) Potter, C. W.; Phair, J. P.; Vodinelich, L.; Renton, R.; Jennings, R. *Nature (London)* **1976**, *259*, 496–497.
(11) Newman, H.; Vodinelich, L.; Potter, C. W., *Eur. J. Cancer* **1977**, *13*, 821.

0022-2623/82/1825-0107$01.25/0



1 (NSC 286193) 2 (ribavirin)

1–3). The lowest dose tested in these experiments, 25 mg/kg, gave 10 of 10, 10 of 10, and 7 of 8 long-term survivors, most of which were free of tumor as determined by examination of the lungs. At 400 mg/kg, there were 7 of 10, 10 of 10, and 6 of 10 long-term survivors in experiments 1, 2, and 3, respectively. The highest dose tested, 800 mg/kg, produced 6 of 10 long-term survivors in experiment 1, but only 1 of 10 and 0 of 10 survivors in experiments 2 and 3, respectively. In the latter two experiments, the reduction in the number of 60-day survivors and the decrease in the median survival time of the dying animals compared to that of the control mice are suggestive of drug toxicity. However, all mice were alive on day 5 (deaths would be attributed to acute drug toxicity), and weight loss, also associated with drug toxicity, was not large. In a fourth experiment (Table I) in which lower dosage levels of 1 were evaluated, a dose of 12.5 mg/kg still produced 7 of 10 60-day survivors. Doses of 6.5 mg/kg and below had little effect on extending the life span of the mice.

Other examples of agents that are effective against this Lewis lung tumor are cyclophosphamide and the nitrosourea BCNU.[3] As illustrated in Table I, cyclophosphamide, used as a positive control in experiments 2 and 3, also produced 60-day survivors when administered on day 1. However, in experiment 3 where 1 produced more than 50% 60-day survivors over a 16-fold dosage range, cyclophosphamide produced 40% long-term survivors at only one dosage level. This finding supports previously published data which demonstrated that cyclophosphamide produced 40% or more 60-day survivors over an approximate twofold dosage range.[3] Also, in the same report, the dosage range of BCNU which produced 60-day survivors was shown to be approximately twofold. In fact, efficacy over the broad dosage range observed with 1 is unique in the NCI's experience with the iv Lewis lung model.

In addition, 1 was evaluated against intracerebrally implanted Lewis lung carcinoma. The objective was to determine if the high plasma concentrations of 1, potentially achievable because of the low toxicity and high aqueous solubility, would be sufficient to permit an effective dose to reach the ic-implanted tumor cells. Following daily ip administration on days 1–9, 1 was effective against the ic-implanted tumor at all dosage levels tested (25–800 mg/kg), producing increased life spans (ILS) ranging from 66 to 121% (median survival time of control mice was 9.6 days). By comparison, MeCCNU[12] administered on days 1 and 5 produced a similar response (108% ILS) but was effective only at one dosage level (30 mg/kg).[13]

The activity of 1 against ic Lewis lung is evidence that the so-called "blood–brain barrier" (BBB) is not, in this case, an insurmountable obstacle. The tumor has been too little studied to clearly define the role of the BBB, but ic tumors are often found to be refractory to agents effective against the same tumors implanted elsewhere, a fact commonly attributed to the BBB.

Excellent activity also was observed for 1 against the ip-implanted P388 and L1210 murine leukemias.[14] Increased life spans of 145% at 800 and 700 mg/kg in the P388 system and 130% at 600 mg/kg in the L1210 system were obtained following ip administration of 1 on days 1–9. The activity against these tumors was not so profound at lower doses as it was against the Lewis lung carcinoma. No long-term survivors (30-day) were observed in the L1210 leukemia system; one of six mice survived to day 30 at the highest doses in one of two P388 experiments.

(12) *trans*-1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea.
(13) From NCI's experience, MeCCNU is less effective when administered on a daily treatment schedule.
(14) Geran, R. I.; Greenburg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep., Part 3* **1972**, *3*(2), 7–9.

R. K. Robins, P. C. Srivastava
Cancer Research Center, Department of Chemistry
Brigham Young University, Provo, Utah 84602

V. L. Narayanan,* J. Plowman, K. D. Paull
Developmental Therapeutics Program
Division of Cancer Treatment, National Cancer Institute
Silver Spring, Maryland 20910

Received September 8, 1981