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Clinical Studies with Tubercidin Administered by Direct Intravenous Injection[1, 2]

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SUMMARY

Tubercidin (NSC 56408), a cytotoxic antibiotic, was used in the treatment of 93 patients with various types of advanced neoplastic disease in a Phase I study to determine human toxicity. Significant toxicity was limited to the observation of nephrotoxicity in 18 cases and local irritation of veins in 12. Tumor response was suggested in only 3 cases, all of which were cases of primary carcinoma of the pancreas.

INTRODUCTION

Tubercidin (NSC 56408; 6-amino-9-D-ribofuranosyl-7-deazapurine) is a potent, cytotoxic antibiotic which inhibits macromolecule synthesis and reproduction of mammalian cells *in vitro* and growth of certain experimental tumors *in vivo* (1, 3). It was selected for clinical trial based on (*a*) its unique nucleoside structure, (*b*) type of biochemical activity, (*c*) inhibitory action of growing mammalian cells, and (*d*) antitumor activities in animals.

The purpose of this study was to determine the toxicity of tubercidin for human beings. On the basis of animal data (1) we anticipated that human toxicity might include abnormal glucose tolerance, hepatotoxicity, and nephrotoxicity.

MATERIALS AND METHODS

All patients selected for study were 15 years old or older and had histologically proved malignant disease other than of the hematopoietic system (Table 1). Previous chemotherapy, irradiation, or extensive surgical treatment had to have been completed 4 weeks or more before the patient entered this study. Patients who had had extensive irradiation, particularly to the pelvis, or chemotherapy resulting in significant marrow depression were not selected because of the possibility of premature toxicity. Patients having extensive liver involvement with increased values for serum alkaline phosphatase, serum bilirubin, and serum glutamine-oxalacetic transaminase were excluded, as were those having severe renal involvement. Patients entering the study were estimated to have a life expectancy of more than 60 days. A performance status of 50 or more on the Karnofsky scale (2) was required.

Table 1

Sites of primary tumors

Site	Cases
Lung	14
Kidney	10
Bone and connective tissue (sarcoma)	10
Colon or rectum	10
Breast	9
Head and neck	8
Pancreas	6
Skin (melanoma)	6
Ovary	5
Cervix	2
Stomach	2
Other	9
Unknown	2
Total	93

Dry tubercidin was dissolved in sterile 0.9% NaCl solution (20 mg in 20 ml) just before administration. Intravenous injections were given daily, ideally for 10 consecutive days, in each course of treatment. The initial dose was 0.025 mg/kg/day based on ideal or actual weight, whichever was less. Telephone conferences were held by the participating investigators at 2- to 3-week intervals, and when significant toxicity was not observed the dose was increased by gradual increments to 0.3 mg/kg/day. The number of therapeutic trials at each dosage level is shown in Table 2.

RESULTS

Of the 93 patients treated, 8 received 2 courses of therapy, 2 received 3 courses, and 1 received 7 courses. Altogether 111 therapeutic courses were given.

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[2] Tubercidin was supplied by the Cancer Chemotherapy National Service Center, National Cancer Institute.

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Table 2

Courses of treatment with various doses of tubercidin: 93 patients

With few exceptions, treatment at a given dose was continued for 10 days.

Dose (mg/kg/day)	Courses of treatment
0.025	6
0.035	2
0.045	1
0.050	2
0.065	1
0.075	2
0.100	8
0.120	2
0.125	4
0.150	13
0.175	4
0.200	42
0.225	4
0.250	15
0.275	3
0.300	2
Total	111

Table 3

Clinical abnormalities after treatment

System	Degree of abnormality	
	Mild or moderate	Severe
Renal	11	7
Venous (thrombosis)	7	5
Gastrointestinal	10	0
Hematopoietic	6	0
Hepatic	2	0

Before therapy was instituted the following laboratory procedures were carried out in each case: fasting blood sugar and 2-hr postprandial blood sugar, blood urea nitrogen or nonprotein nitrogen, serum alkaline phosphatase, serum glutamic-oxalacetic transaminase, serum bilirubin, urinalysis, blood leukocyte and platelet count, and blood hemoglobin. These studies were repeated twice weekly during therapy and for 1 week thereafter. Subsequently, they were repeated at least once weekly for 4 weeks or until the values began to return to normal, whichever was later. If a specific laboratory study seemed to be changing abnormally, more frequent examinations were carried out.

Observations were recorded of the physical effects on all systems but especially of changes relative to the gastrointestinal, dermal, renal, endocrine, and nervous systems. Weight and physical performance were checked weekly. Wherever possible, tumor measurements also were made weekly; however, this was a Phase I study, and objective measurements were not required for admission to this study.

Toxicity. Clinical abnormalities found after treatment are indicated in Table 3. Despite its inclusion in the table, hepatic toxicity was not clearly established. Two patients were found to have slight elevation of values for alkaline phosphatase and serum glutamic-oxalacetic transaminase without alteration of those for sulfobromophthalein retention or serum bilirubin.

Hematopoietic toxicity of a mild degree was observed in 6 cases. Leukopenia, range 2900 to 4500 leukocytes/cu mm, was observed transiently in these cases. Neither thrombocytopenia nor anemia was found.

Ten patients evidenced gastrointestinal toxicity manifested by anorexia, nausea, and vomiting. In all instances adequate control was provided by conventional antiemetic therapy, and the symptoms usually disappeared within 24 to 48 hr after therapy was discontinued.

Unquestionably, tubercidin is an irritating substance. Several instances were reported in which accidental extravasation occurred with resultant inflammation and ulceration. Venous thromboses proximal to sites of injection were observed in 12 cases. In 5 such cases venous thrombosis was prominent enough to interfere seriously with subsequent administration of the drug.

The most distressing problem encountered was that of renal toxicity, manifested mainly by proteinuria, azotemia, or both. These findings are summarized in Table 4. Proteinuria was a more common finding than was azotemia. Return to pretreatment levels was not always observed. Renal toxicity seldom occurred when patients received less than 0.2 mg/kg/day tubercidin. Renal toxicity was evident in the case of 2 patients receiving second courses of therapy 1 month after their initial courses, but renal toxicity was found neither in 2 patients receiving 3 therapeutic courses nor in the single patient who received 7 courses. Toxicity resulted in 4 of 10 cases of renal carcinoma in which nephrectomy had been done for removal of the primary tumor. Although several deaths occurred after tubercidin therapy, in no instance was there clear-cut evidence of the deaths being drug related.

Tumor Response. As already emphasized, this was a Phase I study, and tumor response was of secondary interest. However, attempts were made to evaluate any possible antitumor effect wherever measurable lesions existed. In only 3 instances was there a suggestion that this drug exerted a favorable effect on the tumor being treated. Interestingly, particularly with respect to correlating preclinical data and the potential effect of the drug on pancreatic tissue, all 3 were cases of primary pancreatic carcinoma of the islet cell type. One of the patients reported substantial subjective improvement, but no change was observed in his measurable tumor or in biochemical values. A second course of therapy was given without apparent benefit, and the patient subsequently died. Another patient evidenced moderate reduction in size of an intraabdominal mass after treatment and experienced corresponding subjective improvement. He received 3 courses of treatment with tubercidin, but his veins became so thrombosed that he declined further treatment because of the difficulties encountered in finding patent veins. A third patient experienced both subjective and objective improvement after tubercidin therapy. He seeming-

Table 4

Summary of cases in which treatment with tubercidin resulted in nephrotoxicity

Case	Age (yr)	Site of primary tumor	Treatment		Evidence of toxicity				Comment
					Urine		BUN (mg/100 ml)		
			Dose (mg/kg)	Days	Microscopic abnormality, grade[a]	Proteinuria, grade[a]	Before treatment	After treatment	
1	50	Lung	0.035	10	1	1	6	156	Died within 3 wk of treatment but death thought to be drug related
2	61	Cervix	0.175	10	0	1	15	72	
3	77	Thyroid	0.175	10	1	1	23	44	
4	49	Kidney	0.200	10	0	2	N[b]	N	Proteinuria without azotemia
5	23	? (Fibro-sarcoma)	0.200	10	0	0	23 (urea)	56 (urea)	
			0.300[c]	10	0	3	N	N	Urea unchanged
6	57	Kidney	0.200	10	0	2	21 (urea)	44 (urea)	
			0.300[c]	10	1	4	N	N	Urea showed no significant change
7	58	Kidney	0.200	8			17	105 (later 32)	
8	44	Unknown	0.200	10	2	4	12	42	
9	52	Rectum	0.200	10	0	4	N	N	BUN unchanged
10	56	Pancreas	0.200	10	0	4	N	N	BUN unchanged
11	58	Kidney	0.200	10	0	4	12	94 (later normal)	
12	54	Lung	0.200	10	1	4	23	64	
13	49	Bladder	0.225	9	1	1	42 (ureau)	408 (urea)	Increase in value of urea not considered entirely drug related
14	22	Skin (melanoma)	0.250	10	1	4	N	N	BUN unchanged
15	69	Ovary	0.250	10	0	4	16	104	
16	62	Breast	0.275	10	0	1	12	26	
17	64	Lung	0.275	10	1	4	17	105	
18	70	Rectum	0.275	8	0	0	21	300	

[a] Basis 0 to 4.
[b] N, normal range for laboratory; for blood urea nitrogen (BUN) (several laboratories), approximately 9 to 10 mg/100 ml; for urea (one laboratory), 10 to 40 mg/100 ml.
[c] Second course given after interval of 1 mo.

ly had reduction in size of an intraabdominal mass after the initial course of therapy. Consequently, he has received a total of 7 courses. His veins proximal to sites of injection have become badly thrombosed making further therapy at such sites impractical. At present, his tumor remains in regression.

DISCUSSION

Tubercidin is an interesting antibiotic with possible antitumor properties, particularly against islet cell pancreatic carcinoma. Since nephrotoxicity and local irritation of veins limit the usefulness of this drug, further study might be encouraged in an effort to circumvent these factors through other dosage schedules or methods of administration.

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