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Copyright Statement

Phase I Study of 5-Azacytidine (NSC-102816) [1,2,3,4]

A. J. Weiss, J. E. Stambaugh, M. J. Mastrangelo, J. F. Lauclus,[5] and R. E. Bellet [6]

SUMMARY

Thirty patients with various solid tumors were treated with 5-azacytidine. Total doses ranged from 1.0 to 24.0 mg/kg and were given over a minimal period of 8 days. The major toxic effect was hematologic with significant leukopenia and thrombocytopenia usually occurring 20–30 days after the start of therapy, especially at higher dose levels. The marrow depression lasted 1–5 weeks and was fully reversible. Nausea and mild diarrhea were common following injection of the drug. Serum glutamic oxaloacetic transaminase levels rose in several patients. No other evidence of hepatic toxicity was seen. Objective remissions were noted in seven of 11 patients with cancer of the breast, two of five with melanoma, and two of six with cancer of the colon.

[Cancer Chemother Rep 56:413–419, 1972]

5-Azacytidine is an analog of cytidine in which nitrogen is substituted for the carbon in the 5 position of the pyrimidine ring. It was first synthesized by Pískala and Šorm in 1964. It is produced microbiologically by a species of Streptoverticillium, *S. Ladakanus*. It is a white crystalline material which is quite soluble in water and various organic solvents. Its formula is $C_8H_{12}N_4O_5$ (1,2).

Studies with the compound reveal it to be active against several animal neoplasms, including the L1210 tumor (3,4). It was relatively inactive, however, against the Walker 256 tumor. The compound was incorporated into plant and bacterial RNA and DNA and inhibited nucleic acid and protein synthesis (5,6). It is effective in causing chromosomal abnormalities in plants (7). Apparently, several patients have been treated in Europe; however, no published data on the results of the Czechoslovakian clinical studies have been available to date.

In animal experiments the efficacy of the drug as an antitumor agent was highly schedule-dependent, the most effective schedule being a daily dose given over 10 days.[7] The maximum tolerated dose in the most sensitive animal, the beagle, was 0.55 mg/kg/day given over a 5-day period.[7] Since data from animal studies seemed to indicate that a 10-day schedule would be proper for initial clinical use, patients in our study received beginning total daily doses of 0.03 mg/kg for 10 days.

MATERIALS AND METHODS

The drug was supplied in 50-mg vials. When the drug is to be administered, it is dissolved

[1] Received Nov 17, 1971; revised Mar 17, 1972; accepted May 3, 1972.

[2] Supported by grant CA–06071 and contract NIH–70–2136 from Chemotherapy, National Cancer Institute (NCI), National Institutes of Health, Public Health Service.

[3] 5-Azacytidine: *s*-triazin-2(1*H*)-one, 4-amino-1-β-D-ribofuranosyl-. Supplied by the Cancer Therapy Evaluation Branch, Chemotherapy, NCI.

[4] Performed as a phase I study for the Central Oncology Group (Dr. Robert O. Johnson, University of Wisconsin, Chairman).

[5] Supported by Public Health Service Research Fellowship No. 1F03-CA-52030–01 from the Department of Health, Education, and Welfare.

[6] Department of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pa.

[7] Clinical brochure: 5-azacytidine (NSC-102816), Oct 1970, 25 pp. Prepared by the NCI, Bethesda, Md.

in an appropriate volume of distilled water and then given immediately. In this study, when the drug was given intravenously (iv), it was given as rapidly as possible. Two patients were treated at each dose level. A modified Fibonacci scheme was used to determine dose increments. After toxicity occurred, dose increments were limited to 10% of the previous dose. To be eligible for the study, patients were required to have a white blood cell count (wbc) of 5000 cells/mm³ or greater and a platelet count of 140,000 cells/mm³ or greater. The blood urea nitrogen (BUN) value had to be less than 12 mg/100 ml and the bilirubin value less than 1.2 mg/100 ml. Further contraindications for therapy included radiation to the pelvis, chemotherapy in the 4-week interval prior to therapy, prior adrenalectomy or hypophysectomy, or life expectancy of less than 3 months. Complete blood cell counts and platelet counts were done at least twice weekly and blood chemistry tests were done once weekly.

The criteria for objective remissions were those of the Central Oncology Group, that is, a 50% or greater reduction in the area of the tumors being measured as approximated by a 50% reduction in the product of the major diameter of the tumor and its perpendicular. The regression must have lasted for a minimal period of 4 weeks with no new lesions appearing during this time. All lesions were measured weekly.

RESULTS

Tables 1 and 2 present a summary of the drug toxicity observed in the 30 patients treated. As can be seen, mild hematologic depression was noted at total doses of 12–16 mg/kg, and rather severe hematologic depression was noted in most patients receiving total doses of more than 16 mg/kg. The diarrhea noted was transient, occurring 2–3 hours after each injection; it was not disabling. In this series, we did not see stomatitis and dermatitis was rare. Hepatic function changes are found in animals treated with 5-azacytidine. Several of our patients had reversible rises in serum glutamic oxaloacetic transaminase (SGOT) levels, but no other hepatic abnormalties were noted. Although the hematologic depression was at times quite severe, serious infection occurred in only one patient and no patients died from this complication. Nausea almost invariably occurred after drug administration.

TABLE 1.—Hematologic toxicity

Patient No.	Sex	Dose[a]	Leukopenia			Thrombocytopenia		
			Nadir count (× 10³ cells/mm³)	Day nadir occurred	Day count normal	Nadir count (× 10³ cells/mm³)	Day nadir occurred	Day count normal
1	F	0.55 mg/kg, OD × 10	3.8	12	18	116	14	18
2	F	0.5 mg/kg, OD × 15	3.8	36	40	118	25	29
3	M	0.75 mg/kg, OD × 11	None	—	—	118	14	17
4	F	1.1 mg/kg, OD × 10	None	—	—	112	23	30
5	M	1.2 mg/kg, OD × 10	3.55	22	33	116	19	22
6	F	1.4 mg/kg, OD × 10	3.9	27	30	None	—	—
7	F	1.0 mg/kg, OD × 15	3.5	18	23	112	10	55
8	F	1.0 mg/kg, OD × 15	0.85	28	56	98	31	48
9	F	1.0 mg/kg, OD × 15	3.1	29	45	42	32	62

TABLE 1.—Hematologic toxicity—Continued

Patient No.	Sex	Dose*	Leukopenia			Thrombocytopenia		
			Nadir count (× 10^3 cells/mm^3)	Day nadir occurred	Day count normal	Nadir count (× 10^3 cells/mm^3)	Day nadir occurred	Day count normal
10	F	1.0 mg/kg, OD × 15	1.9	29	51	84	26	48
11	F	1.6 mg/kg, OD × 10	2.6	11	60	66	22	32
12	M	1.6 mg/kg, OD × 10	2.2	20	65	74	20	70
13	F	1.6 mg/kg, OD × 10	2.4	22	28	104	18	25
14	F	1.8 mg/kg, OD × 10	1.8	27	40	98	30	43
15	F	1.8 mg/kg, OD × 10	1.1	31	45	106	5	26
16	M	1.8 mg/kg, OD × 10	3.5	17	21	96	24	31
17	M	2.0 mg/kg, OD × 10	4.3	18	20	73	20	Died Day 20
18	M	2.0 mg/kg, OD × 10	0.5	18	Abnormal until Day 48	None	—	Died Day 48
19	F	2.0 mg/kg, OD × 10	None	—	—	88	49	56
20	F	2.0 mg/kg, OD × 10	1.2	22	42	48	28	42
21	F	2.0 mg/kg, OD × 10	0.95	23	72	46	20	55
22	F	2.0 mg/kg, OD × 10	2.9	32	37	90	11	77
23	F	2.0 mg/kg, OD × 10	3.3	23	68	96	54	86
24	M	2.0 mg/kg, OD × 10	1.0	28	50	52	31	53
25	M	2.2 mg/kg, OD × 10	0.9	29	39	32	17	27
26	F	2.2 mg/kg, OD × 10	0.25	23	57	38	23	54
27	F	2.4 mg/kg, OD × 10	1.0	26	50	116	26	28

*OD = daily dose.

Table 3 presents the initial remissions seen in this series and the relationship of dose to remission. Because parallel pharmacologic studies were being conducted (8), the patients selected for this study fell into relatively limited patterns of disease. Almost all patients treated who had either breast cancer or melanoma had soft tissue disease as their primary manifestation of cancer. In the group of patients with breast cancer, most had either chest wall recurrences or unresectable tumors involving the breast, while most of the patients with melanoma had multiple, subcutaneous, metastatic disease. In either group, lesions were measurable. All objective remissions were partial; no complete remissions were seen.

TABLE 2.—Non-hematologic toxicity*

Patient No.	Sex	Dose†	Degree of—				Rise in SGOT value (units)	
			Nausea	Diarrhea	Stomatitis	Dermatitis	From	To
28	F	0.55 mg/kg, OD × 10	0	0	0	0		
1	F	0.55 mg/kg, OD × 10	3	2	1	0		
2	F	0.5 mg/kg, OD × 15	2	1	1	0	73.5	174
3	M	0.75 mg/kg, OD × 11	0	0	0	0		
4	F	1.1 mg/kg, OD × 10	2	1	0	0		
5	M	1.2 mg/kg, OD × 10	1	1	0	0	14.0	30.0
29	F	1.2 mg/kg, OD × 10	0	0	0	0		
30	F	1.2 mg/kg, OD × 11	0	0	0	0		
6	F	1.4 mg/kg, OD × 10	0	0	0	0		
7	F	1.0 mg/kg, OD × 15	2	0	0	0	16	40.0
8	F	1.0 mg/kg, OD × 15	3	1	0	0	40	168
9	F	1.0 mg/kg, OD × 15	2	1	0	0	26.5	86.5
10	F	1.0 mg/kg, OD × 15	2	2	1	1		
11	F	1.6 mg/kg, OD × 10	2	0	0	0		
12	M	1.6 mg/kg, OD × 10	1	1	0	0		
13	F	1.6 mg/kg, OD × 10	1	2	0	0		
14	F	1.8 mg/kg, OD × 10	2	1	0	0	20	95.0
15	F	1.8 mg/kg, OD × 10	1	0	0	0		
16	M	1.8 mg/kg, OD × 10	1	1	0	0		
17	M	2.0 mg/kg, OD × 10	2	0	0	0		
18	M	2.0 mg/kg, OD × 10	3	2	1	0	47.5	142
19	F	2.0 mg/kg, OD × 10	1	1	0	0		
20	F	2.0 mg/kg, OD × 10	2	1	1	1		
21	F	2.0 mg/kg, OD × 10	2	1	0	0	75	144
22	F	2.0 mg/kg, OD × 10	3	1	1	0	26.5	96.0
23	F	2.0 mg/kg, OD × 10	2	1	0	0		
24	M	2.0 mg/kg, OD × 10	2	1	0	0	12.5	29.5
25	M	2.2 mg/kg, OD × 10	2	2	0	0		
26	F	2.2 mg/kg, OD × 10	2	2	0	0		
27	F	2.4 mg/kg, OD × 10	2	1	0	0		

*0 = No toxicity; 1 = mild toxicity; 2 = moderate toxicity; 3 = incapacitating toxicity.
†OD = daily dose.

The data suggest that 5-azacytidine may be useful in the treatment of the soft tissue metastatic disease of breast cancer and malignant melanoma. One significant remission and one borderline remission were seen in patients with cancer of the colon.

Several of the patients with breast cancer who had objective remissions had received prior therapy with 5-fluorouracil (5-FU) or cytosine arabinoside or both and were resistant to both.[8] Thus, there did not appear to be any cross resistance to 5-azacytidine in patients treated unsuccessfully with other available antipyrimidines.

The length of the remission obtained is not

[8] 5-Fluorouracil: NSC-19893.
Cytosine arabinoside: NSC-63878; cytosine, 1-β-D-arabinofuranosyl-, monohydrochloride.

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