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Enhancement of the Antitumor Activity of Arabinofuranosyladenine by 2′-Deoxycoformycin[1]

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SUMMARY

The 6C3HED lymphosarcoma, a tumor cell line very sensitive to 9-β-D-arabinofuranosyladenine (ara-A), and 6C3HED/ara-A, a line resistant to ara-A, were studied. Both were responsive to 9-β-D-arabinofuranosylcytosine (ara-C). Two lines of cells, L1210 and L1210/ara-C, are both resistant to ara-A and have very high levels of the deaminase that inactivates ara-A. When an effective inhibitor of the deaminase, 2′-deoxycoformycin, was combined with ara-A in the treatment of mice bearing L1210 or L1210/ara-C tumors, both became responsive to ara-A. Studies are reported on the extent of effects of 2′-deoxycoformycin at several dose levels and the duration of its effects in tumor cells and normal tissues. Single doses produce essentially complete inhibition of the deaminase, and little recovery was seen before 24 hr. However, DNA synthesis in normal tissues recovered more quickly. It is suggested that ara-A and ara-C, the former as a new derivative (9-β-D-arabinofuranosyladenine 5′-phosphate) and possibly combined with 2′-deoxycoformycin, be regarded as potentially alternative drugs for the treatment of neoplasms.

INTRODUCTION

The antimetabolite, ara-C[3] has been shown to have its antitumor effects during the S phase of growing cells. When treatment is designed to take cognizance of this finding, the experimental mouse neoplasm L1210 can be cured in a large percentage of the tumor-bearing mice (10). ara-C has been found to be the most effective single agent in the treatment of acute leukemia of adults (3). Another antimetabolite, ara-a, has what appears to be the same metabolic effects (4). However, both agents are rapidly destroyed by deaminases that are specific for the agent. The distribution of these deaminases differs for each of the 2 nucleosides. The L1210 mouse neoplasm is responsive to ara-C and has little capacity for deamination of ara-C. In contrast, L1210 is unresponsive to ara-A, apparently because it has very high levels of capacity for the deamination of ara-A (1, 5). If a suitable inhibitor for the deamination of ara-A were available, the 2 agents would then provide alternative therapy with presumably no cross-resistance. Recently, such an inhibitor (11) became available for study and was identified as 2′-dCF. In combination with ara-A, it causes the L1210 and certain other mouse neoplasms to become susceptible to ara-A. Lack of cross-resistance between ara-C and ara-A was demonstrated in experimental systems.

MATERIALS AND METHODS

ara-C (NSC 63878), ara-A (NSC 404421), ara-A-F (NSC 171240), and 2′-dCF (NSC 218321) were all obtained from Drug Research and Development, National Cancer Institute, Bethesda, Md. ara-A-5′-P was synthesized from ara-A as described earlier (6). ara-A-F and ara-A-5′-P were used rather than ara-A because they are much more soluble, and ara-A-F has been shown to be equivalent to ara-A in inhibiting at least 2 experimental tumors (8). [^{3}H]ara-A was obtained from New England Nuclear, Boston, Mass., and chromatographed on thin-layer silica gel with CH_3CN:1 M NH_4OH (85:15) when necessary to achieve radiochemical purity.

Experimental tumors used in the study were: (*a*) L1210 carried in DBA/2 mice and originally obtained from Southern Research Institute, Birmingham, Ala.; (*b*) L1210/ara-C obtained from Dr. D. H. W. Ho at the M. D. Anderson Hospital, Houston, Texas, and carried in C57BL × DBA/2 F_1 mice (hereafter called $BD2F_1$), a line resistant to ara-C and lacking the kinase for phosphorylation of ara-C; (*c*) the 6C3HED lymphosarcoma carried in C3H mice and described in earlier publications (5); and (*d*) 6C3HED/ara-A, carried in C3H mice and obtained from I. Wodinsky of Arthur D. Little, Inc., Cambridge, Mass. The 6C3HED/ara-A line has been examined by Dr. T. Hauschka at Roswell Park Memorial Institute, Buffalo, N. Y., and found to have the same karyotype and host specificity as 6C3HED. Investigations have indicated that both cell lines make equal amounts of ara-A nucleotides and have low equal levels of deaminase, but that the DNA polymerase of 6C3HED/ara-A is not as sensitive to inhibition by ara-A nucleotides, while in both lines DNA synthesis is very sensitive to inhibition by ara-C (L. Brox and G. A. LePage, unpublished results).

DBA/2 and C3H mice used were 3- to 5-month-old females supplied by our central breeding facility from genetically controlled breeders obtained from The Jackson Laboratory, Bar Harbor, Maine, and the National Cancer Institute, Bethesda, Md., respectively. $BD2F_1$ mice were females 8 to 10 weeks old obtained either from our central breeding facility

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[3] The abbreviations used are: ara-C, 9-β-D-arabinofuranosylcytosine; ara-A, 9-β-D-arabinofuranosyladenine; ara-A-5′-P, 9-β-D-arabinofuranosyladenine 5′-phosphate; ara-A-F, 9-β-D-arabinofuranosyladenine 5′-formate; 2′-dCF, 2′-deoxycoformycin.

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or from Sprague-Dawley, Inc., Madison, Wis. The mice from both sources gave equivalent results.

Therapy tests were conducted on groups of 6 to 8 mice as specified. Solutions of ara-A-F and ara-A-5′-P were freshly made in 0.9% NaCl solution and administered i.p., 0.25 ml/mouse. 2′-Deoxycoformycin solutions were made in 0.9% NaCl solution and kept at −20° until needed for injection, then given i.p. at 0.20 ml/mouse.

Deaminase assays were conducted with homogenates made in a VirTis 23 homogenizer and added to 1.0-ml reaction mixtures containing 0.05 M Tris-phosphate buffer, pH 7.4, and 1×10^{-3} M [^{3}H]ara-A. Incubations were for 0, 15, and 30 min and results were calculated from incubations with a tissue level giving a linear rate. Reaction mixtures were deproteinized with perchloric acid, neutralized with KOH, and aliquots were chromatographed on Whatman No. 3MM paper sheets developed with ethyl acetate:isopropyl alcohol:H_2O (650:225:125, v/v). Papers were developed overnight and solvent run off the end to obtain good separation of ara-H product from ara-A. ara-A runs ahead of ara-H. ara-H spots were eluted and eluates were counted in a scintillation counting system. Results were computed as μmoles deaminated per hr per g, wet weight.

RESULTS

As indicated in Table 1, concentrations of 2′-dCF adequate to inhibit deamination of ara-A by intact L1210 cells *in vitro* became effective within 10 min. The 50% inhibitory level under these conditions was in the vicinity of 1×10^{-6} M. Inhibition was proportional to the amount of tissue, indicating a "titration" of the deaminase. Toxicity testing was conducted with normal $BD2F_1$ female mice, 18 to 20 g. Although a single dose of 10 mg/kg was tolerated with little weight loss or other observable effect, doses of 0.5 mg/kg or greater given 2 times daily for 6 days resulted in profound weight loss and death of most mice so treated. However, daily treatment at 0.5 mg/kg for 6 days was tolerated without appreciable weight loss (<10%).

Female $BD2F_1$ mice were given i.p. injections with 2′-dCF at doses of 0.25, 0.50, and 1.0 mg/kg, and groups of 3 mice were sacrificed at intervals thereafter. Tissues were homogenized and assayed for capacity to deaminate [^{3}H]ara-A. Mice bearing 4-day L1210 ascites growth were also dosed in this manner, and the L1210 cells from these mice were used at intervals thereafter to assay for deaminase activity. The results are presented in Table 2. A single dose of 2′-dCF at 0.25 to 1.0 mg/kg almost immediately inhibited the deaminase capacity in L1210 cells and this had recovered to only 15% of control by 24 hr. Thus, a single dose would suffice to protect ara-A from deamination during a 24-hr period of therapy. Not surprising was an approximately equal inhibition of deaminase capacity in a series of normal tissues. Since the most obvious metabolic effect of ara-A on cell metabolism thus far is (as triphosphate) the inhibition of DNA synthesis (both ara-A-F and ara-A-5′-P are rapidly converted to ara-A, and then to 9-β-D-arabinofuranosyladenine 5′-triphosphate), it was interesting to study this effect after treatment with ara-A derivatives, with and without 2′-dCF pretreatment. Some data are presented in Table 3. Here it can be seen that recovery of DNA synthesis, as monitored by [^{3}H]TdR incorporation *in vivo* was slower when ara-A-F was administered after pretreatment with 2′-dCF. However, the normal tissues were recovering, in terms of this parameter, much more rapidly than was the deaminase level monitored in Table 2.

A series of experiments were performed to test the effects of ara-A-F, ara-A-5′-P, and 2′-dCF in the therapy of 4 tumor cell lines. These data are presented in Table 4. The 6C3HED lymphosarcoma in C3H mice has a low capacity for deamination of ara-A and is very sensitive to treatment with ara-A. Mice inoculated with 5×10^6 cells and treated only 4 times were tumor free at 50 days. The 6C3HED/ara-A line was resistant to this therapy, but was not cross-resistant to ara-C. In Experiment 3 and others, it is evident that 2′-dCF alone has no influence on host survival. It also makes evident the fact that ara-A-F alone is relatively ineffective against L1210, even on this every-3-hr schedule directed at S-phase cells, as designed by previous workers for ara-C treatment (10).

Table 1

In vitro inhibition of the deamination of [^{3}H]ara-A in L1210 cells by 2′-dCF

L1210 cells were washed from the peritoneal cavities of $BD2F_1$ mice inoculated i.p. with 5×10^5 cells 5 days earlier and centrifuged 2 min at 1470 × *g*. The packed cells were suspended in Robinson's medium (9) at pH 7.4 in 10-ml Erlenmyer flasks at a final volume of 2.0 ml, and gassed with 95% O_2:5% CO_2. 2′-dCF was added last with the flasks in ice; then incubations were conducted in a shaker waterbath at 37°. Analyses for deamination of [^{3}H]ara-A were conducted as described earlier. Results are averages of analyses on 2 flasks.

L1210 cells added (mg wet wt)	Incubation (min)	Concentration of 2′-dCF (μg/ml)	Deamination (μmole)
25	10	0	0.25
25	20	0	0.46
50	10	1.0	0.07
50	20	1.0	0.07
50	20	0.1	0.40
50	20	0.2	0.29
50	20	0.4[a]	0.17
100	20	0.4	0.31
200	20	0.4	0.39

[a] Approximately 1.5×10^{-6} M 2′-dCF.

Table 2

Duration of inhibition by 2′-dCF of ara-A deamination in L1210 cells and normal tissues

$BD2F_1$ mice were given i.p. injections of the indicated dose of 2′-dCF, and groups of 3 mice were sacrificed at intervals. Organs were removed, homogenized, and assayed for capacity to deaminate [^{3}H]ara-A. For L1210 cells, mice bearing 4-day i.p. growth after an inoculation with 2×10^6 cells were used. Values given are percentage of control and represent averages of analyses on 3 mice.

Tissue	2′-dCF dose (mg/kg)	% of control at following time intervals after 2′-dCF injection						
		0.25 hr	1 hr	3 hr	6 hr	24 hr	48 hr	72 hr
L1210	0.25	0		1		15		
L1210	0.50	0		>1	3	14		
L1210	1.00	0		>1	3	15		
Thymus	0.50		0	3	8	21	55	97
Thymus	1.00		0	1	2	4		
Spleen	0.25	1	4	26	19			
Spleen	0.50		1		9	17	25	43
Spleen	1.00		>1	>1	3	10		
Bone marrow	0.50		5		26	23	92	65
Bone marrow	1.00	2	1	1	1	7		
Liver	0.50		1	3	7	7	13	29
Liver	1.00		3	8	10			
Kidney	0.50		1	9	6	10	17	21
Kidney	1.00		1	5	5	4		

Table 3

Recovery of DNA synthesis in normal tissues after treatment with ara-A-F and 2′-dCF

$BD2F_1$ female mice were treated i.p. with 2′-dCF at 0.5 mg/kg. After 15 min, ara-A-F was injected i.p. at 55 mg/kg. At intervals thereafter [^{3}H]TdR was injected, 20 μCi/mouse, 30 min were allowed for incorporation, and tissues were processed to obtain DNA for counting and measurement, as described earlier (7). Results are averages of analyses on tissues from 3 mice.

Treatment	[^{3}H]TdR incorporation in DNA (cpm/mg DNA)			
	Bone marrow	Thymus	Spleen	L1210 cells
Control (no ara-A, no 2′-dCF)	58,000	9,770	68,700	38,500
1 hr after ara-A only	63,100	5,000	24,900	21,000
3 hr after ara-A only	60,700	8,900	52,200	39,500
1 hr after ara-A in mice pretreated with 2′-dCF	21,200	2,500	24,700	2,400
3 hr after ara-A in mice pretreated with 2′-dCF	42,600	4,100	20,400	1,950
24 hr after ara-A only				27,900
24 hr after ara-A in mice pretreated with 2′-dCF				17,000

However, when ara-A deamination was inhibited by 2′-dCF pretreatment, a considerably improved therapeutic effect was observed. In Experiment 4, it is evident that the L1210/ara-C line is not cross-resistant to ara-A-F. In Experiment 5, it is indicated that ara-A-F and ara-A-5′-P are of equivalent effect in this mouse system. Both would be rapidly converted to ara-A in the mouse. Since *in vitro* tests of ara-A toxicity in L1210 cells have been shown to be dependent on dose and time of exposure (2), the every-3-hr treatment was extended in Experiment 6. The same total dose given as 8, 10, or 12 doses spread over 24, 30, or 36 hr had essentially the same therapeutic affect. Since cross-resistance between ara-C and ara-A was not observed, Experiment 7 was performed to determine whether alternate courses of ara-A and ara-C therapy would be superior in cell kill to double courses of the single agents. No superiority was obtained with the alternate course of 2 drugs in this test system.

DISCUSSION

ara-C is established as an effective agent in the treatment of the acute leukemias of adults. Its efficacy may depend upon tumor levels of phosphorylating and deaminating capacity. This would also be likely for ara-A, where the deaminase and phosphorylating enzymes are different from those for ara-C. The 2 agents appear to have very similar or identical metabolic effects (4). It would be logical then to regard

Table 4

Treatment of tumor-bearing mice with ara-A, 2′-dCF, and ara-C

L1210 and L1210/ara-C were transplanted in $BD2F_1$ female mice, i.p., 1×10^5 cells/mouse. 6C3HED and 6C3HED/ara-A were transplanted in C3H female mice, 5×10^6 cells/mouse. Where groups of more than 8 mice are listed, experiments conducted in identical manner have been pooled. The day of tumor transplantation is designated Day 0. 2′-dCF was given only once daily prior to the 1st ara-A therapy in L1210 experiments.

Experiment	No. of mice	Tumor	Treatment	Average survival (days)	T:C[a]	Maximum wt. loss (%)
1	14	6C3HED	Controls, 0.9% NaCl solution.	12.5 ± 1.7[b]	100	
	14	6C3HED	ara-A-F, 0.20 mmole/kg 2 times daily, Days 1 and 2.	50[c]	400+	6
	14	6C3HED	ara-A-5′-P, 0.20 mmole/kg 2 times daily, Days 1 and 2.	40.6 ± 3.0	325	7
	14	6C3HED	ara-C, 0.08 mmole/kg 2 times daily, Days 1 and 2.	50[c]	400+	9
2	14	6C3HED/ara-A	Controls, 0.9% NaCl solution.	11.5 ± 1.1	100	
	14	6C3HED/ara-A	ara-A-F, 0.20 mmole/kg 2 times daily, Days 1 and 2.	10.9 ± 1.0	95	5
	14	6C3HED/ara-A	ara-A-5′-P, 0.20 mmole/kg 2 times daily, Days 1 and 2.	11.0 ± 1.2	96	3
	14	6C3HED/ara-A	ara-C, 0.08 mmole/kg 2 times daily, Days 1 and 2.	35.0 ± 5	280	7
3[d]	6	L1210	Control, 0.9% NaCl solution every 3 hr, Days 1, 4, and 7.	7.3 ± 0.5	100	
	6	L1210	2′-dCF, 0.5 mg/kg once, Days 1, 4, and 7.	7.5 ± 0.7	103	
	6	L1210	ara-A-F, 0.13 mmole/kg every 3 hr, 8 doses/day, Days 1, 4, and 7.	8.7 ± 1.0	119	
	6	L1210	ara-A-F, 0.19 mmole/kg every 3 hr, 8 doses/day, Days 1, 4, and 7.	9.1 ± 0.8	125	
	6	L1210	2′-dCF, 0.5 mg/kg + ara-A-F, 0.13 mmole/kg every 3 hr, 8 doses/day, Days 1, 4, and 7.	12.3 ± 0.8	168	
	6	L1210	2′-dCF, 0.5 mg/kg + ara-A-F, 0.19 mmole/kg every 3 hr, 8 doses/day, Days 1, 4, and 7.	16.1 ± 1.1	221	
4[d]	12	L1210/ara-C	Control, 0.9% NaCl solution every 3 hr, Days 1, 4, and 7.	8.9 ± 0.5	100	
	12	L1210/ara-C	ara-C, 20 mg/kg, every 3 hr, 8 doses/day, Days 1, 4, and 7.	9.0 ± 0.5	101	
	12	L1210/ara-C	2′-dCF, 0.5 mg/kg, Days 1, 4, and 7.	9.0 ± 0.5	101	
	12	L1210/ara-C	ara-A-F, 0.19 mmole/kg every 3 hr, 8 doses/day, Days 1, 4, and 7.	9.5 ± 0.6	107	
	12	L1210/ara-C	2′-dCF, 0.5 mg/kg, ara-A-F, 0.19 mmole/kg every 3 hr, 8 doses/day, Days 1, 4, and 7.	15.5 ± 1.1	174	
5	12	L1210	Controls, 0.9% NaCl solution every 3 hr, 8 doses/day, 1 and 4	8.5 ± 0.5	100	
	12	L1210	2′-dCF, 0.5 mg/kg, Days 1 and 4.	8.5 ± 0.5	100	
	12	L1210	2′-dCF, 0.5 mg/kg, ara-A-F 0.19 mmole/kg, every 3 hr, 8 doses/day Days 1 and 4.	17.8 ± 1.2	209	
	12	L1210	2′-dCF, 0.5 mg/kg, ara-A-5′-P, 0.19 mmole/kg every 3 hr, 8 doses/day, Days 1 and 4.	18.1 ± 1.4	213	
6	8	L1210	Controls, 0.9% NaCl solution, every 3 hr, 8 doses/day, Days 1 and 4.	8.5 ± 0.5	100	−16
	8	L1210	2′-dCF, 0.5 mg/kg, Days 1 and 4.	8.5 ± 0.5	100	−18
	8	L1210	2′-dCF, 0.5 mg/kg, ara-A-5′-P, 0.19 mmole/kg every 3 hr, 8 doses/day, Days 1 and 4.	19.1 ± 0.4	225	−8
	8	L1210	2′-dCF, 0.5 mg/kg, ara-A-5′-P, 0.15 mmole/kg every 3 hr, 10 doses/day, Days 1 and 4.	20.2 ± 0.3	238	−12
	8	L1210	2′-dCF, 0.5 mg/kg, ara-A-5′-P, 0.125 mmole/kg every 3 hr, 12 doses/day, Days 1 and 4.	19.0 ± 1.0	224	−12

Table 4—*Continued*

Experiment	No. of mice	Tumor	Treatment	Average survival (days)	T:C[a]	Maximum wt. loss (%)
	8	L1210	2′-dCF, 0.5 mg/kg, ara-A-5′-P, 0.10 mmole/kg every 3 hr, 12 doses/day, Days 1 and 4.	13.6 ± 0.8	160	−12
7	12	L1210	Controls, 0.9% NaCl solution, every 3 hr, Days 1 and 5.	8.7 ± 0.3	100	−11
	12	L1210	2′-dCF, 0.5 mg/kg, Days 1 and 5.	8.5 ± 0.5	98	−12
	12	L1210	2′-dCF, 0.5 mg/kg, ara-A-5′-P, 0.19 mmole/kg, every 3 hr, 8 doses/day, Day 1.	11.3 ± 0.7	130	3
	12	L1210	ara-C, 15 mg/kg every 3 hr, 8 doses/day, Day 1.	12.0 ± 0.4	138	−5
	12	L1210	2′-dCF, 0.5 mg/kg, ara-A-5′-P, 0.19 mmole/kg every 3 hr, 8 doses/day, Days 1 and 5.	17.0 ± 1.0	195	9
	12	L1210	ara-C, 15 mg/kg every 3 hr, 8 doses/day, Days 1 and 5.	19.1 ± 1.1	219	10
	12	L1210	2′-dCF, 0.5 mg/kg, ara-A-5′-P, 0.19 mmole/kg every 3 hr, 8 doses/day, Day 1, ara-C, 15 mg/kg every 3 hr, 8 doses/day, Day 5.	18.7 ± 0.9	215	11
	12	L1210	ara-C, 15 mg/kg, every 3 hr, 8 doses/day, Day 1, 2′-dCF, 0.5 mg/kg, ara-A-5′-P, 0.11 mmole/kg every 3 hr, 8 doses/day, Day 5.	20.0 ± 0.7	230	9

[a] T:C, ratio of average survival time of mice implanted with drug-treated cells to average survival time of control mice.
[b] Average ± S.E.
[c] Experiment terminated at 50 days.
[d] Five × 10^5 cell inoculum/mouse.

them as alternative drugs for individual circumstances of enzyme levels providing a favorable situation for one over the other. Where cross-resistance is lacking, as illustrated in the experimental systems described herein, they could even be considered for use in combined therapy regimens. This feature was not found in our experimental example, however. Although the derivative ara-A-5′-P may make this unnecessary in humans (6), the deaminase inhibitor 2′-dCF appears likely to extend greatly the tumor spectrum of ara-A, and in an experimental example, the L1210 leukemia was able to convert an unresponsive to a responsive neoplasm within acceptable host toxicity. (Lack of host toxicity to 2′-dCF was dependent on a suitable dosage regimen.)

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