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Absence of Delayed Lethality in Mice Treated with Aclacinomycin A

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Summary. *Two compounds that bind to or intercalate with DNA (DNA binders), e.g., adriamycin and 'dihydroxyanthracenedione', 9,10-anthracenedione, 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)-amino]-ethyl]amino]-, dihydrochloride salt, consistently caused delayed lethality (20–200 days after treatment) if administered intraperitoneally (IP). Both of these agents contain para-hydroxyl groups in the ring adjacent to the quinone ring. Certain analogs of these compounds (aclacinomycin A and 'anthracenedione acetate', 9,10-anthracenedione, 1,4-bis[[2-[(2-hydroxy-ethyl)amino]ethyl]amino]-, diacetate (salt), which do not contain para-hydroxyl groups, did not cause delayed deaths when injected IP. The only difference in the molecular structure (other than the nature of their amine salts) between dihydroxyanthracenedione and anthracenedione acetate lies in the para-hydroxyl groups in the ring adjacent to the quinone ring. Another compound that binds to DNA, m-AMSA, which has neither the quinone function nor the para-hydroxyl groups, did not cause delayed deaths after IP administration.*

Introduction

In normal, non-tumor-bearing mice, lethal toxicity that is delayed 20–200 days after treatment with anticancer drugs is a relatively rare phenomenon, often restricted to only a few selected agents (T. H. Corbett and D. P. Griswold Jr., unpublished data), e.g., mitomycin C and nitrosoureas, and often confined to a particular route of administration, e.g., IP administration of VM-26 (NSC 122819) [1] or adriamycin (ADR, NSC 123127) [2].

In addition to ADR, we have observed that dihydroxyanthracenedione (DiOHA, NSC 301739), 9,10-anthracenedione, 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]-, dihydrochloride salt, another agent that binds to or intercalates with DNA (DNA binder), also consistently displayed this phenomenon if administered IP. Further, we have observed that selected analogs of ADR or DiOHA are nearly devoid of this activity. The structure-activity relationships of this delayed death phenomenon are presented.

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Materials and Methods

Comparisons of antitumor activity of chemotherapeutic agents and their analogs are historically made at approximately equitoxic dosage levels. In these comparison studies, the upper dosage levels are selected to be frankly toxic ($\geq LD_{20}$). The highest nontoxic level for each agent (LD_{10} or less) is then selected for evaluation of tumor cell kill. Normal, non-tumor-bearing mice are often included at each drug level used in chemotherapy trials, to clearly separate toxic effects of the drugs from the debilitating effects of the tumor. The results reported in this paper were observed in these non-tumor-bearing toxicity control mice. CDF1 (BALB/c × DBA/2), BDF1 (C57BL/6 × DBA/2), and B6C3F1 (C57BL/6 × C3H) mice were supplied through the Division of Cancer Treatment, Drug Evaluation Branch (DCT, DEB), National Cancer Institute (NCI). The body weight range for all the mice within a given experiment was 18–22 g at the start of therapy. The mice were supplied with food (Wayne-Lab Blox F-6 containing 6% fat) and water ad libitum.

ADR and anthracenedione acetate (AA, NSC 287513, 9,10-anthracenedione, 1,4-bis[[2-[(2-hydroxyethyl)amino]ethyl]-amino]-, diacetate salt) were prepared in sterile, physiologic saline, while aclacinomycin A (NSC 208734) was prepared in distilled water for experiment 1712Cl and in physiologic saline in experiment 1713Dl. DiOHA was prepared in distilled water for all tests. m-AMSA (NSC 249992, methanesulfon-m-anisidide, 4'-(9-acridinylamino)-, monohydrochloride) was prepared in physiologic saline containing 0.05% Tween 80. All solutions were injected IP at 0.5 ml/mouse, subcutaneously (SC) at 0.1 ml/mouse, and intravenously (IV) at 0.2 ml/mouse. Dosages (mg/kg) were based on the mean body weights of each group. Schedules used were optimum for the test tumors being treated. All antitumor agents were supplied by DCT, DEB, NCI.

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Results

Lethal toxicity delayed 20–200 days after IP administration of ADR has frequently been observed in these laboratories and elsewhere [2]. This has been largely ignored since we have failed to observe the same phenomenon following drug administration by the SC or IV route (Tables 1 and 2). We have recently noted that an analog of ADR (aclacinomycin A) did not display this phenomenon when injected IP (Fig. 1). Very similar results were obtained in a confirmatory experiment (Fig. 2). Acute deaths due to leukopenia, thrombocytopenia, or gastrointestinal toxicity almost always occur less than 20 days after the last day of treatment with antitumor agents (T. H. Corbett and D. P. Griswold Jr., unpublished data). Deaths after this time were considered to be delayed (Figs. 1 and 2). It should be noted that the delayed deaths caused by ADR were clearly dose-dependent (Figs. 1 and 2).

Our interest in this delayed death phenomenon was further aroused when examination of historical data from anthracenedione analog comparison studies revealed that one of these analogs (DiOHA or mitoxantrone), which is in clinical trial in the USA, also caused delayed deaths when administered IP, whereas another analog (AA), in clinical use in Europe, appeared to be nearly devoid of this property (Fig. 3). Confirmatory experiments with this new class of DNA binders substantiated the reproducibility of these observations (Figs. 4 and 5). As observed with ADR, the delayed deaths caused by DiOHA were dose-dependent.

The lack of significant numbers of delayed deaths by ADR, DiOHA, AA or aclacinomycin A administered by other routes (SC or IV) is clear from the data presented in Tables 1–5.

The only difference in chemical structure for the anthracenedione analogs (other than the nature of the amine salts, i.e., HCl vs AcOH) is the presence of the 1,4-para hydroxyl groups in DiOHA in the ring adjacent to the quinone ring (Fig. 6). An examination of the structure of ADR also reveals the presence of para-hydroxyl groups in a ring adjacent to the

Table 1. Lack of significant numbers of delayed deaths with adriamycin administered SC in normal, non-tumor-bearing mice

Mouse strain	Adriamycin dosage (mg/kg/dose)	Schedule SC	Observation period after 1st treatment (days)	No. of mice surviving at termination of expt	No. of acute deaths (within 20 days post last Rx)	No. of delayed deaths	Days of delayed deaths (post last Rx)
BDF1	19.0	q7dx3	131	4/10	5/10	1/10	112
BDF1	12.0	q7dx3	131	9/10	1/10	0/10	–
BDF1	7.3	q7dx3	131	10/10	0/10	0/10	–
BDF1	4.5	q7dx3	131	10/10	0/10	0/10	–
CDF1	19.0	q7dx3	104	3/10	7/10	0/10	–
CDF1	11.8	q7dx3	104	9/9	0/9	0/9	–
CDF1	7.3	q7dx3	104	9/10	0/10	1/10	29
CDF1	4.5	q7dx3	104	10/10	0/10	0/10	–
BDF1	19.0	q7dx3	145	4/10	5/10	1/10	91
BDF1	12.0	q7dx3	145	8/10	0/10	2/10	87,96
BDF1	7.3	q7dx3	145	10/10	0/10	0/10	–
BDF1	4.5	q7dx3	145	10/10	0/10	0/10	–
CDF1	19.0	q7dx4	85	0/10	10/10	0/10	–
CDF1	11.5	q7dx4	85	5/10	3/10	2/10	36,44
CDF1	7.0	q7dx4	85	9/10	1/10	0/10	–
CDF1	4.5	q7dx4	85	10/10	0/10	0/10	–
BDF1	19.0	q7dx2	95	6/10	4/10	0/10	–
BDF1	12.0	q7dx2	95	10/10	0/10	0/10	–
BDF1	7.3	q7dx2	95	10/10	0/10	0/10	–
BDF1	4.5	q7dx2	95	10/10	0/10	0/10	–
BDF1	3.4	Daily x9	89	5/10	5/10	0/10	–
BDF1	2.1	Daily x9	89	10/10	0/10	0/10	–
BDF1	1.3	Daily x9	89	10/10	0/10	0/10	–
BDF1	0.8	Daily x9	89	10/10	0/10	0/10	–
BDF1	0.49	Daily x9	89	10/10	0/10	0/10	–

quinone ring, whereas aclacinomycin A has only a single hydroxyl group in either ring adjacent to the quinone ring (Fig. 7).

Lastly, m-AMSA, another DNA binder that has neither the quinone group nor para-hydroxyl groups but is an 'azaanthracene', did not cause the delayed death phenomenon following IP treatment (Table 6).

The cause of the delayed deaths following IP drug administration was presumed to be a sterile chemical peritonitis, since no specific organ damage could be histologically identified and because the

Table 2. Lack of significant numbers of delayed deaths with adriamycin administered IV in normal, non-tumor-bearing mice

Mouse strain	Adriamycin dosage (mg/kg/dose)	Schedule IV	Observation period after 1st treatment (days)	No. of mice surviving at termination of expt	No. of acute deaths (within 20 days post last Rx)	No. of delayed deaths	Days of delayed deaths (post last Rx)
B6C3F1	16.0	q12dx2	99	8/10	1/10	1/10	48
B6C3F1	11.0	q12dx2	99	9/10	1/10	0/10	–
B6C3F1	7.5	q12dx2	99	10/10	0/10	0/10	–
B6C3F1	5.1	q12dx2	99	10/10	0/10	0/10	–
B6C3F1	8.0	q7dx3	240	7/10	3/10	0/10	–
B6C3F1	5.0	q7dx3	240	8/10	0/10	2/10	42,105
B6C3F1	8.0	q7dx3	236	9/10	1/10	0/10	–
B6C3F1	5.0	q7dx3	236	9/10	0/10	1/10	187
B6C3F1	7.4	q7dx3	101	2/10	7/10	1/10	74
B6C3F1	4.7	q7dx3	101	9/10	1/10	0/10	–
B6C3F1	2.9	q7dx3	101	7/9	1/9	1/9	60
B6C3F1	14.0	q7dx2	97	0/10	10/10	0/10	–
B6C3F1	8.7	q7dx2	97	2/10	8/10	0/10	–
B6C3F1	5.4	q7dx2	97	9/10	0/10	1/10	25
B6C3F1	3.3	q7dx2	97	10/10	0/10	0/10	–
B6C3F1	2.1	q7dx2	97	10/10	0/10	0/10	–
B6C3F1	8.3	q4dx5	79	1/5	4/5	0/5	–
B6C3F1	5.2	q4dx5	79	5/5	0/5	0/5	–
B6C3F1	3.2	q4dx5	79	5/5	0/5	0/5	–
BDF1	14.0	q7dx4	115	0/10	9/10	1/10	35
BDF1	8.7	q7dx4	115	10/10	0/10	0/10	–
BDF1	5.4	q7dx4	115	9/9	0/9	0/9	–
BDF1	3.3	q7dx4	115	9/9	0/9	0/9	–
CDF1	19.0	q7dx2	117	1/10	7/10	2/10	66,95
CDF1	12.0	q7dx2	117	5/10	3/10	2/10	87,94
CDF1	7.3	q7dx2	117	9/10	0/10	1/10	54
CDF1	4.5	q7dx2	117	10/10	0/10	0/10	–
BDF1	4.1	q2dx9	90	3/10	7/10	0/10	–
BDF1	2.6	q2dx9	90	9/10	1/10	0/10	–
BDF1	1.6	q2dx9	90	10/10	0/10	0/10	–
BDF1	1.0	q2dx9	90	10/10	0/10	0/10	–
B6C3F1	8.6	q2dx7	139	1/10	9/10	0/10	–
B6C3F1	5.5	q2dx7	139	6/10	4/10	0/10	–
B6C3F1	3.5	q2dx7	139	10/10	0/10	0/10	–
B6C3F1	8.6	q2dx7	135	5/9	4/9	0/9	–
B6C3F1	5.5	q2dx7	135	9/10	1/10	0/10	–
B6C3F1	3.5	q2dx7	135	10/10	0/10	0/10	–
B6C3F1	10.0	q7dx3	199	1/13	12/13	0/13	–
B6C3F1	6.6	q7dx3	199	6/11	5/11	0/11	–
B6C3F1	4.4	q7dx3	199	10/10	0/10	0/10	–
B6C3F1	2.9	q7dx3	199	11/12	0/12	1/12	35

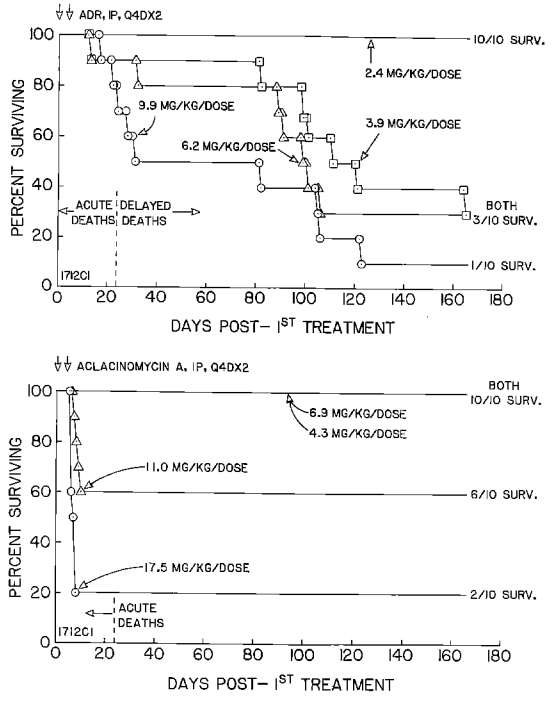

Fig. 1. IP treatment of normal, nontumor B6C3F1 female mice with adriamycin or aclacinomycin A. The upper dosage levels were chosen to induce 20% or more acute deaths (leukopenia). The mice were randomized prior to drug administration. *Arrows* indicate time and duration of treatment

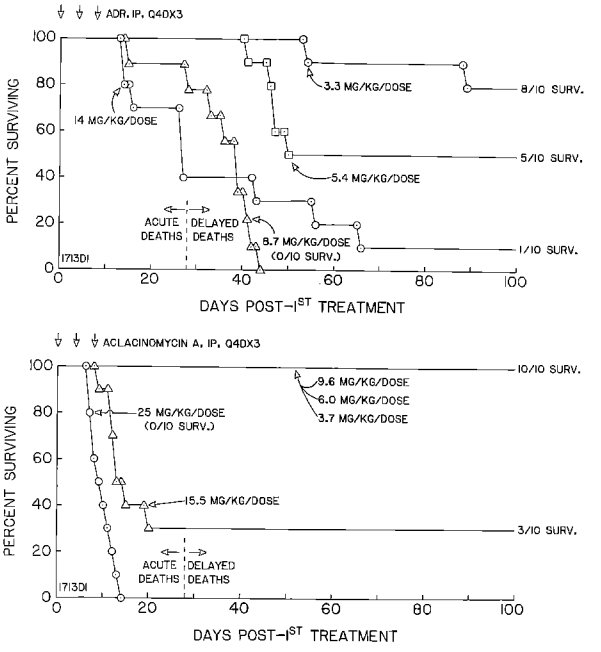

Fig. 2. IP treatment of normal B6C3F1 male mice with adriamycin or aclacinomycin A. The mice were randomized prior to drug administration

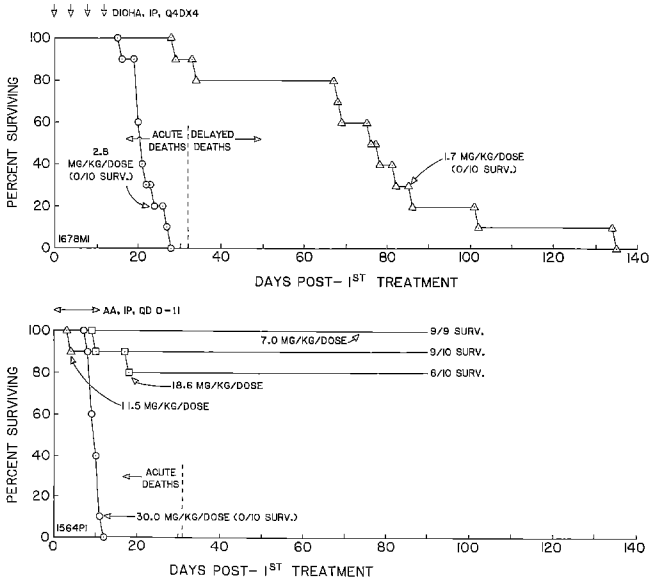

Fig. 3. IP treatment of normal mice with anthracenedione acetate (AA), BDF1 female mice, or dihydroxyanthracenedione (DiOHA), CDF1 male mice (two separate experiments). The upper dosage levels were chosen to induce 20% or more acute deaths (leukopenia)

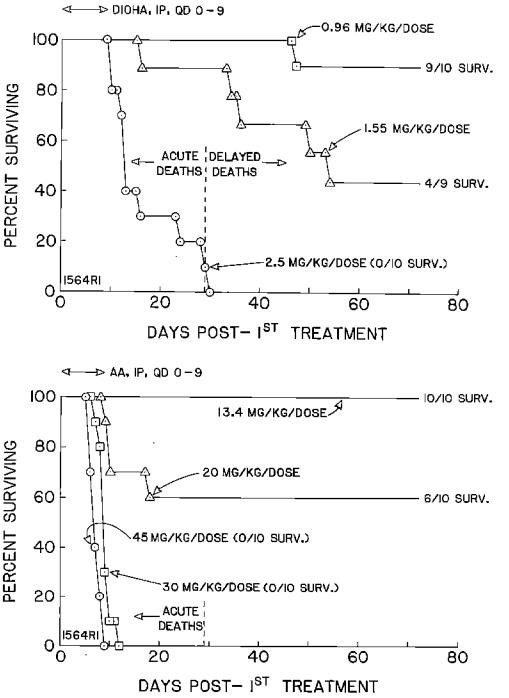

Fig. 4. IP treatment of normal BDF1 female mice with anthracenedione acetate or dihydroxyanthracenedione. The mice were randomized prior to drug administration

Table 3. Lack of significant numbers of delayed deaths with dihydroxyanthracenedione (DiOHA) administered IV or SC in normal, non-tumor-bearing mice

Mouse strain	DiOHA dosage (mg/kg/dose)	Schedule IV	Observation period after 1st treatment (days)	No. of mice surviving at termination of expt	No. of acute deaths (within 20 days post last Rx)	No. of delayed deaths	Days of delayed deaths (post last Rx)
CDF1	2.5	q2dx6	90	3/9	6/9	0/9	–
CDF1	1.2	q2dx6	90	8/10	2/10	0/10	–
CDF1	0.6	q2dx6	90	10/10	0/10	0/10	–
CDF1	2.5	q2dx6	86	4/10	4/10	2/10	24, 37
CDF1	1.2	q2dx6	86	7/10	0/10	3/10	31, 49, 54
CDF1	0.6	q2dx6	86	10/10	0/10	0/10	–
BDF1	3.2	q2dx5, days 1 & 19	126	0/10	10/10	0/10	–
BDF1	2.1		126	5/10	3/10	2/10	30, 47
BDF1	1.3		126	3/10	3/10	4/10	26, 27, 36, 59
BDF1	0.85		126	9/9	0/9	0/9	–
CDF1	2.8	q2dx7	81	0/10	10/10	0/10	–
CDF1	1.7	q2dx7	81	1/10	9/10	0/10	–
CDF1	1.1	q2dx7	81	10/10	0/10	0/10	–
CDF1	0.67	q2dx7	81	10/10	0/10	0/10	–
CDF1	6.5	q4dx3	142	0/10	9/10	1/10	126
CDF1	4.0	q4dx3	142	7/10	2/10	1/10	25
CDF1	2.5	q4dx3	142	8/10	1/10	1/10	53
CDF1	1.5	q4dx3	142	6/10	0/10	4/10	24, 35, 44, 47
CDF1	4.3	q4dx5	105	0/7	7/7	0/7	–
CDF1	2.7	q4dx5	105	2/7	5/7	0/7	–
CDF1	1.7	q4dx5	105	7/7	0/7	0/7	–
CDF1	1.06	q4dx5	105	0/5	5/5	0/5	–
CDF1	7.2	q8dx3	105	2/7	4/7	1/7	86
CDF1	4.5	q8dx3	105	3/7	4/7	0/7	–
CDF1	2.8	q8dx3	105	4/7	3/7	0/7	–
CDF1	1.8	q8dx3	105	7/7	0/7	0/7	–
CDF1	3.2	q2dx6	106	0/10	10/10	0/10	–
CDF1	2.1	q2dx6	106	8/10	2/10	0/10	–
CDF1	1.4	q2dx6	106	9/10	0/10	1/10	67
CDF1	1.0	q2dx6	106	10/10	0/10	0/10	–
CDF1	3.2	q2dx4	129	2/10	8/10	0/10	–
CDF1	2.1	q2dx4	129	10/11	0/11	1/11	118
CDF1	1.4	q2dx4	129	10/10	0/10	0/10	–
CDF1	1.0	q2dx4	129	12/12	0/12	0/12	–
BDF1	3.9	Daily x9[a]	89	0/10	10/10	0/10	–
BDF1	2.4	Daily x9	89	3/9	6/9	0/9	–
BDF1	1.5	Daily x9	89	10/10	0/10	0/10	–
BDF1	0.93	Daily x9	89	10/10	0/10	0/10	–
BDF1	0.57	Daily x9	89	9/10	1/10	0/10	–
B6C3F1	13.0	q6dx3[a]	138	2/10	8/10	0/10	–
B6C3F1	8.0	q6dx3	138	9/10	1/10	0/10	–
B6C3F1	4.8	q6dx3	138	9/10	0/10	1/10	23
B6C3F1	3.9	Daily x12[a]	77	0/10	10/10	0/10	–
B6C3F1	2.4	Daily x12	77	0/10	10/10	0/10	–
B6C3F1	1.5	Daily x12	77	5/10	5/10	0/10	–
B6C3F1	0.93	Daily x12	77	10/10	0/10	0/10	–
B6C3F1	0.57	Daily x12	77	10/10	0/10	0/10	–
B6C3F1	2.0	q2dx7	129	0/10	10/10	0/10	–
B6C3F1	1.4	q2dx7	129	8/10	1/10	1/10	52
B6C3F1	0.9	q2dx7	129	10/10	0/10	0/10	–
B6C3F1	0.6	q2dx7	129	10/10	0/10	0/10	–

[a] Drug administered SC

Table 4. Lack of significant numbers of delayed deaths with anthracenedione acetate (AA) administered IV or SC in normal, non-tumor-bearing mice

Mouse strain	AA dosage (mg/kg/dose)	Schedule IV	Observation period after 1st treatment (days)	No. of mice surviving at termination of expt	No. of acute deaths (within 20 days post last Rx)	No. of delayed deaths	Days of delayed deaths (post last Rx)
CDF1	30.0	q2dx10	92	1/9	8/9	0/9	–
CDF1	20.0	q2dx10	92	3/10	6/10	1/10	29
CDF1	13.3	q2dx10	92	9/10	1/10	0/10	–
CDF1	8.8	q2dx10	92	10/10	0/10	0/10	–
BDF1	30.0	q2dx8	126	8/10	2/10	0/10	–
BDF1	20.0	q2dx8	126	10/10	0/10	0/10	–
BDF1	13.3	q2dx8	126	10/10	0/10	0/10	–
BDF1	8.8	q2dx8	126	10/10	0/10	0/10	–
BDF1	30.0	q2dx9	90	2/9	7/9	0/9	–
BDF1	20.0	q2dx9	90	3/10	7/10	0/10	–
BDF1	13.0	q2dx9	90	10/10	0/10	0/10	–
BDF1	8.6	q2dx9	90	10/10	0/10	0/10	–
BDF1	71.0	Daily x9[a]	89	0/10	10/10	0/10	–
BDF1	44.0	Daily x9	89	2/10	8/10	0/10	–
BDF1	27.0	Daily x9	89	8/10	2/10	0/10	–
BDF1	16.6	Daily x9	89	10/10	0/10	0/10	–
BDF1	10.0	Daily x9	89	10/10	0/10	0/10	–
B6C3F1	71.0	Daily x12[a]	77	0/10	10/10	0/10	–
B6C3F1	44.0	Daily x12	77	0/10	9/10	1/10	21
B6C3F1	27.0	Daily x12	77	8/10	2/10	0/10	–
B6C3F1	16.6	Daily x12	77	10/10	0/10	0/10	–
B6C3F1	10.0	Daily x12	77	10/10	0/10	0/10	–

[a] Drug administered SC

Table 5. Lack of significant numbers of delayed deaths with aclacinomycin A administered IV in normal, non-tumor-bearing mice

Mouse strain	Aclacinomycin A dosage (mg/kg/dose)	Schedule IV	Observation period after 1st treatment (days)	No. of mice surviving at termination of expt	No. of acute deaths (within 20 days post last Rx)	No. of delayed deaths	Days of delayed deaths (post last Rx)
B6C3F1	32.0	q7dx2	97	0/5	5/5	0/5	–
B6C3F1	20.0	q7dx2	97	1/5	4/5	0/5	–
B6C3F1	13.0	q7dx2	97	5/5	0/5	0/5	–
B6C3F1	8.3	q7dx2	97	5/5	0/5	0/5	–
B6C3F1	5.3	q7dx2	97	5/5	0/5	0/5	–
B6C3F1	27.8	q7dx2	71	2/10	8/10	0/10	–
B6C3F1	18.5	q7dx2	71	4/9	4/9	1/9	38
B6C3F1	12.3	q7dx2	71	5/8	1/8	2/8	38, 43
B6C3F1	8.1	q7dx2	71	9/10	0/10	1/10	61
B6C3F1	27.8	q7dx2	70	1/10	9/10	0/10	–
B6C3F1	18.5	q7dx2	70	8/10	2/10	0/10	–
B6C3F1	12.3	q7dx2	70	10/10	0/10	0/10	–
B6C3F1	8.1	q7dx2	70	9/9	0/9	0/9	–
B6C3F1	12.0	q4dx4	58	0/10	9/10	1/10	33
B6C3F1	7.4	q4dx4	58	9/10	1/10	0/10	–
B6C3F1	4.6	q4dx4	58	10/10	0/10	0/10	–
B6C3F1	12.0	q4dx4	55	0/10	10/10	0/10	–
B6C3F1	7.4	q4dx4	55	9/10	0/10	1/10	41
B6C3F1	4.6	q4dx4	55	10/10	0/10	0/10	–

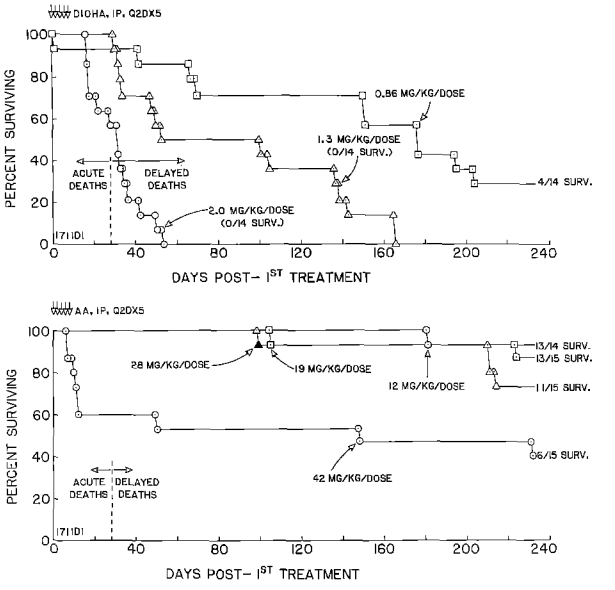

Fig. 5. IP treatment of normal CDF1 male mice with anthracenedione acetate of dihydroxyanthracenedione. The mice were randomized prior to drug administration. One animal (▲) was found at necropsy to have congenital absence of the right kidney

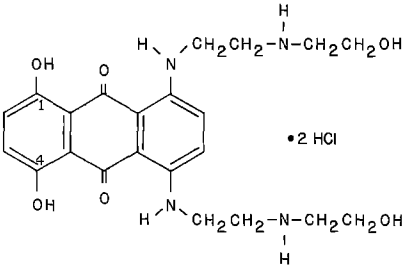

Fig. 6. Chemical structure of dihydroxyanthracenedione: 9,10-anthracenedione, 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino] ethyl]amino]-, dihydrochloride salt

phenomenon was not observed following SC administration.

Discussion

Obviously, if the delayed death phenomenon observed in mice is relevant to humans, neither ADR nor DiOHA should be used IP in patients. If treatment of a peritoneal effusion (such as occurs with certain ovarian and colon tumors) is to be carried out with a DNA binder, m-AMSA, aclacinomycin A, or AA (rather than ADR or DiOHA) would be indicated for trial, based on these observations in mice.

The finding that delayed deaths can be induced by an antitumor agent administered IP is not original with the work reported herein. Avery et al. found that VM-26 caused the delayed death phenomenon when injected IP but not by other routes [1]. They

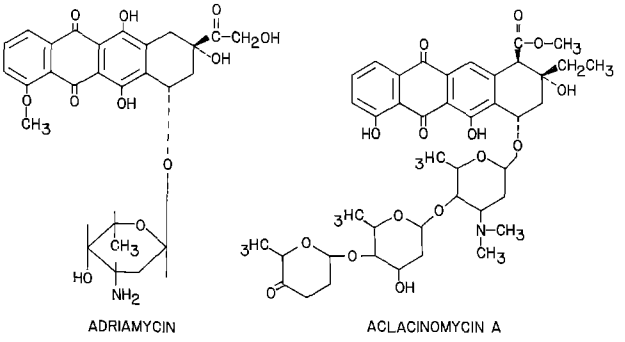

Fig. 7. Chemical structures of adriamycin and aclacinomycin A

Table 6. Absence of delayed lethal toxicity with IP administration of m-AMSA in normal, non-tumor-bearing mice

Mouse strain	m-AMSA dosage (mg/kg/dose)	Schedule IP	Observation period after 1st treatment (days)	No. of mice surviving at termination of expt	No. of acute deaths (within 20 days post last Rx)	No. of delayed deaths
CDF1	37	q2dx4	76	0/10	10/10	0/10
CDF1	23	q2dx4	76	0/10	10/10	0/10
CDF1	14	q2dx4	76	5/10	5/10	0/10
B6C3F1	40	q4dx5	95	0/5	5/5	0/5
B6C3F1	26	q4dx5	95	2/5	3/5	0/5
B6C3F1	17	q4dx5	95	5/5	0/5	0/5
B6C3F1	11	q4dx5	95	5/5	0/5	0/5
B6C3F1	7	q4dx5	95	5/5	0/5	0/5
CD8F1	100	q7dx4	89	0/6	6/6	0/6
CD8F1	75	q7dx4	89	0/6	6/6	0/6
CD8F1	50	q7dx4	89	3/6	3/6	0/6
CD8F1	25	q7dx4	89	6/6	0/6	0/6
CD8F1	12	q7dx4	89	6/6	0/6	0/6

noted 'distention of the abdomen due to ascites and megacolon' in mice treated IP with VM-26, and tentatively linked the delayed deaths to chemical peritonitis. None of the mice in our studies exhibited ascites or megacolon, and no consistent lesion could be identified by histologic examination of the various organ systems. Progressive weight loss and lethargy were the only consistent symptomatology noted.

The finding that the delayed death phenomenon was related to the presence of para-hydroxyl groups in the ring adjacent to the quinone ring for the anthracenediones and perhaps for the two anthracyclines studied is of particular interest and may provide the basis for a more rational synthesis of analogs. The possibility that the same physiologic actions (and molecular structures) that are responsible for the delayed death phenomenon are also linked to other undesirable side-effects, e.g., cardiotoxicity, awaits the acquisition and testing of a larger series of related agents and the results of clinical trials that will determine if DiOHA, AA, aclacinomycin A, m-AMSA, and other related agents cause myocardial changes similar in nature to those of ADR.

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