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265 ON THE INTRA-ENVELOPE INCORPORATION OF "DENSE MATERIAL" BY IGUANA HERPES VIRUS.

R. F. Zeigel & H. F. Clark, Roswell Park Memorial Inst., Buffalo, N.Y., 14052 and Wistar Inst. Philadelphia, Pa., 19104.
(Introduced by D. F. Parsons)

An Iguana herpes virus recently characterized by Clark and Zeigel has been shown to possess dense material within the virion envelope but external to the virion capsid. By E.M. we reexamined the infective cycle in several poikilothermic cell lines hoping to establish the source of this material and the mechanism by which it is packaged. Turtle heart cell line (TH-1) was infected with iguana virus, incubated at 30° C and harvested on day 7 when C.P.E. was apparent. Observations on infected cells fixed in Dalton's chrome osmium and aqueous uranyl acetate, indicated that small (35 nm), angular intranuclear bodies were encapsidated within the virions. Patches of dense material were observed in infected cell nuclei. Virion capsids were observed in the Golgi apparatus. Virions in apposition to Golgi membranes were encased in masses of dense material similar to that observed within cell nuclei. It appeared that the dense material and viral capsids were sequestered by Golgi membranes thereby producing the viral envelope. Golgi enzymes may be incorporated within the "viral sac". Mature particles migrated to the cell periphery where they were released a la secretory granules. The implications that enveloped viruses may spuriously incorporate and transfer, "piggy-back", cell derived material will be discussed.
(Supported by USPHS Grant CA-07745).

266 EFFECT OF DOSE FRACTIONATION OF 2-FAA ON CELL SURVIVAL AND HYPERPLASTIC RESPONSE ON THE RAT LIVER.

Roy E. Albert, Lewis Bilger, and Fredric J. Burns. Institute of Environmental Medicine, New York University Medical Center, 550 First Avenue, New York, N.Y. 10016

Beginning at age 44 days, male albino Charles River rats were fed a constant diet of 2-FAA for 12 week periods as follows: (a) continuous exposure to .03% 2-FAA, (b) .06% 2-FAA, 3 weeks on, 3 weeks off (2 cycles), (c) .06% 2-FAA, 2 weeks on, 2 weeks off (3 cycles), (d) .06% 2-FAA, 1 week on, 1 week off (6 cycles). Sacrifices were done at 4, 8, and 12 weeks. The measured parameters included the persistence of hepatic H^3-DNA in rats H^3TdR-labelled as weanlings, total liver DNA, liver weight, and total cell numbers. Continuous exposure to .03% 2-FAA caused a loss of original liver cells associated with the outgrowth of parenchymal nodules but no appreciable total liver hyperplasia. Intermittent feeding reduced the amount of cell loss while causing hyperplasia. The results suggest that 2-FAA has combined hyperplastic and lethal effects, but the lethal action is more readily reversed by intermittent exposure.

267 AN EVALUATION OF 1-3-BIS(2-CHLOROETHYL)-1-NITROSOUREA (BCNU) AND IRRADIATION ALONE AND IN COMBINATION FOR THE TREATMENT OF MALIGNANT GLIOMA.

Michael D. Walker and Edmund A. Gehan for the Brain Tumor Study Group (BTSG), Bethesda, Md. 20014

A prospective, controlled and randomized study in patients harboring malignant glioma has been conducted to evaluate the efficacy of BCNU (80 mg/m^2/day for three days every 6-8 weeks), irradiation (6,000 Rads whole head in 6-8 weeks), and the combination of both as compared to a similar untreated control group. All patients received conventional neurosurgical care including tumor resection with adequate decompression and were to be randomized within three weeks of operation. Histologic diagnosis was confirmed as malignant glioma by the BTSG neuropathologic coordinator. The use of corticosteroids was controlled.

Analysis is based upon survival, although evaluation of multiple parameters including recurrence is being undertaken. Preliminary analysis of the 180 patients randomized to the four arms of this study indicates divergence of the survival curves. Median survival times from randomization are: Control - 17 wks; BCNU - 20 wks; Irradiation - 28 wks [vs Control $p < .01$] and BCNU plus Irradiation - 41 wks [$p < .01$]. Analysis of survival compared to age, sex, and location, time to recurrence, and duration of symptoms prior to treatment will be presented.

N.B. - CCNU is easier to use. see attached article. MMK

268 INFLUENCE OF TUMOR CELL IRRADIATION AND SPECIFIC SERUM FACTOR(S) ON LYMPHOCYTE BLASTOGENIC RESPONSES TO SOLID TUMORS.

G. Mavligit, E. Hersh and C. McBride. The Univ. of Texas M. D. Anderson Hosp. & Tumor Inst. at Houston, Houston, Texas 77025. (Introduced by J. P. Whitecar).

Cell-mediated immunity can be detected by lymphocyte (L) blastogenesis (B). To identify immunity to human solid tumors, autochthonous (auto) and allogeneic (allo) washed L from 30 patients and 30 normal donors were stimulated by irradiated (IR) and non-IR tumor cells (TC) in auto or allo sera. Single cell suspensions were prepared from fresh tumor biopsies, by mincing and sieving. 10^6 L were stimulated with 10^4-2 X 10^6 TC. After 7 days of incubation, B was measured by H^3-thymidine incorporation. All appropriate controls were subtracted and the stimulation index (SI) was calculated. Positive blastogenic response (SI $\geq$ 2.0) was detected in 87% (27/30) of the patients (median SI=9.0). The response to non-IR TC was greater than that to IR-TC (81%, SI=7.7 vs. 56%, SI=2.0, P=0.05) in the 16 patients so studied. Inhibitory effect on B was observed in 32% (9/28) of patients' sera. In 18% (5/28) it was tumor specific as reflected by unaltered mixed L reactions and the responses to phytohemagglutinin. Conversely, in 36% (10/28) the response to TC was significantly better in patients' sera, and tumor specific in 14% (4/28). Thus, non-IR TC stimulate more B than IR-TC. Patients' sera may be either inhibitory or facilitatory of the blastogenic response to TC.

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Clinical Studies with 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (NSC 79037)[1]

Heine H. Hansen, Oleg S. Selawry, Franco M. Muggia, and Michael D. Walker

National Cancer Institute-Veterans Administration Medical Oncology Service, Medicine Branch, National Cancer Institute, NIH, Bethesda, Maryland 20014, and Department of Medicine, Veterans Administration Hospital, Washington, D. C. 20422 [H. H. H., O. S. S., F. M. M.]; and Section of Neurological Surgery, Baltimore Cancer Research Center, USPHS Hospital, Baltimore, Maryland 21211 [M. D. W.]

SUMMARY

The clinical tolerance to 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea was explored in patients with advanced cancer. This compound is related to 1,3-bis(2-chloroethyl)-1-nitrosourea, an agent of recognized antineoplastic effectiveness, but has only one chloroethyl group, is more lipid soluble, and is at least as active or more active against mouse Leukemia 1210. A single p.o. dose of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea was given because of the superiority of widely spaced doses against Leukemia 1210 and the expected delayed hematological toxicity. The starting dose of 15 mg/sq m body surface area corresponded to one-third of the minimal toxic dose in the most sensitive animal species in preclinical studies. Large initial increments of drug dose at presumably nontoxic levels were followed by progressively smaller dose increments to the range of moderate, reversible toxicity. Forty patients with cancer received 82 treatments. Reproducible subtoxic decrease of thrombocytes occurred at the third dose step (50 mg/sq m); decrease of leukocytes occurred at the fifth dose step (100 mg/sq m). Dose-limiting toxicity resulting in delayed thrombocytopenia and leukopenia within 4 and 6 weeks, respectively, was reached at 130 mg/sq m. This dose was well tolerated in 6 patients when given at intervals of 6 weeks. Objective responses at toxic doses were seen in 2 of 5 patients with evaluable bronchogenic carcinoma and in both patients with malignant lymphoma. Marked neurological improvement was noted in all 3 patients with glioblastoma multiforme.

INTRODUCTION

Nitrosoureas comprise a unique group of antineoplastic agents because of their fast antitumor action but delayed dose-limiting hematological toxicity. In addition, the nitrosoureas are lipid soluble and penetrate the blood-brain barrier. This is reflected in the response of meningeal leukemia in the mouse and in man to systemic use of these agents (2).

The first such agent to receive extensive clinical evaluation was BCNU[2] (Chart 1). BCNU was found to be effective against malignant lymphoma; certain solid tumors such as Ewing's sarcoma, neuroblastoma, bronchogenic carcinoma (3, 6); and acute leukemia in children, including leukemic meningopathy (6). Of special interest was the response of patients with Hodgkin's disease who had been resistant to conventional alkylating agents (7, 14). Other nitrosoureas have been synthesized in the search for clinically more effective analogs (15). One such compound is CCNU (Chart 1). It is at least as active as or more active than BCNU against Leukemia 1210 implanted i.p. or intracerebrally in mice (2). Because one of the chloroethyl groups in BCNU is replaced by a cyclohexyl group, CCNU cannot be considered a conventional bifunctional alkylating agent. The cyclohexyl group also results in higher lipid solubility, which might increase passage across the blood-brain barrier. In addition, it facilitates radioactive labeling identification in pharmacological studies (10, 11). Toxicological studies with CCNU in dogs and monkeys showed that CCNU produced toxicity to the liver, gastrointestinal tract, bone marrow, lymphoid tissue, and kidneys (2). Delayed hepatotoxicity and renal toxicity were the principal dose-limiting factors in dogs; they occurred as late as 1 month after medication. Dose schedule studies in mice with Leukemia 1210 also suggested that widely spaced doses of CCNU were superior to daily administration and that there was no advantage in weekly dosage instead of a single dose (2). On the basis of these preclinical data with CCNU and clinical experience with BCNU, it was decided to explore human tolerance to CCNU with single doses in patients with advanced cancer. The purpose was to determine a safe maximum tolerated single dose of CCNU, to explore tolerance to repeated doses of CCNU, and to make preliminary observations on possible therapeutic effects.

MATERIALS AND METHODS

CCNU was supplied in capsules of 10, 20, and 40 mg containing lactose and magnesium stearate as bulk and was stored at −10° until use to prevent decomposition. The dosage was calculated in mg/sq m body surface area to the nearest 10 mg and was given p.o. on an empty stomach. Only patients with microscopically confirmed diagnosis of cancer not amenable to conventional therapy were treated. Adequate bone marrow function, defined as a white blood count of more than 5,000 cells/cu mm and a platelet count of more than 200,000/cu mm, and normal liver and renal functions were all necessary for inclusion in the study. Measurable tumor

[1] Presented in part at the 61st Annual Meeting of the American Association for Cancer Research, Philadelphia, Pa., March 1970.

[2] The abbreviations used are: BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea; CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea.

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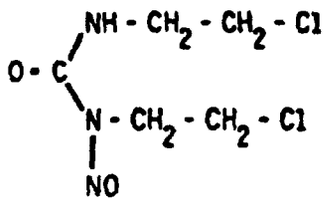

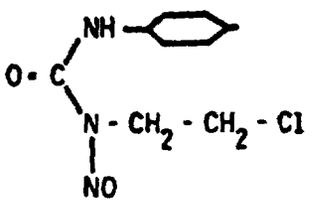

Chart 1. Molecular structure of BCNU (*top*) and CCNU (*bottom*).

masses were not a prerequisite because the study was designed primarily for determination of host tolerance and drug safety; however, serial measurements of accessible tumor lesions were obtained wherever possible. Responses were determined by averaging the product of the diameters of measurable lesions. A response was considered complete when there was a total disappearance of all measurable lesions and partial where there was a decrease of more than 50% in tumor size in the absence of new or increasing lesions elsewhere. Because of difficulties in objective measurements in patients with primary brain tumors, functional improvement for periods of 2 months or longer was considered a partial response. Definition of improvement was based on serial neurological examinations with special attention to performance status. In no instances were glucocorticoids or radiotherapy administered concomitantly with the institution of CCNU.

Minimal serial observations included weekly physical examination and determination of body weight, hematocrit, white blood cell count, and differential, reticulocyte, and platelet counts. Liver function tests included serum alkaline phosphatase, serum glutamic oxalacetic transaminase, serum glutamic pyruvate transaminase, prothrombin time, serum albumin, and total protein. Renal studies consisted of serum creatinine, blood urea nitrogen, and urinalysis. Single doses of CCNU were administered, followed by an observation period of 2 months in order to allow observations of delayed toxicity and recovery. The initial dose of CCNU was 15 mg/sq m. Thereafter, with escalation in decreasing steps, doses of 30, 50, 75, 100, and 130 mg/sq m were explored. Patients were entered initially at spaced intervals of at least 2 weeks to reduce the risk of unpredictable toxicity. Simultaneous entry of patients was permitted as moderate, reversible toxicity was recognized. Three patients were entered per dose step of nontoxic doses. This number was doubled as toxicity was noted in order to explore individual variability of drug tolerance. Once a safe maximum tolerated single dose of CCNU was established and the pattern of toxicity was defined, tolerance to repeated doses given every 8 weeks and every 6 weeks was explored.

RESULTS

Of 40 patients entered, 32 were evaluated for toxicity. Eight patients died too soon to demonstrate drug toxicity. There were no drug-related deaths. The drug toxicity encountered is detailed below.

Acute Toxicity. Administration of CCNU frequently resulted in nausea and vomiting occurring 3 to 6 hr after drug ingestion, which was often followed by 2 to 3 days of anorexia. These symptoms were observed sporadically at a dose of 30 mg/sq m and consistently at a dose of 130 mg/sq m (Table 1). When repeated doses were given, prior administration of antiemetics and sedatives diminished and sometimes prevented these side effects. One patient described shortness of breath and swelling of the face 4 hr after intake of 100 mg/sq m of CCNU, but no abnormalities were noted on physical examination or on the chest X-ray.

Delayed Toxicity. Suppression of thrombocytes and leukocytes was the most consistent dose-limiting side effect of CCNU. A decrease of platelets was already noticeable at 50 mg/sq m (Chart 2), while a fall in leukocytes was not demonstrated before a dose level of 100 mg/sq m was reached (Chart 3). The thrombocytopenia appeared earlier, was of shorter duration, and subsided earlier than the leukopenia (Tables 2 and 3). No consistent change was noted in the hematocrit or reticulocyte count. Platelet transfusions were given on 1 occasion to 1 patient with bronchogenic carcinoma because of hemoptysis in the presence of a platelet count of 46,000/cu mm. Bone marrow examinations in 6 patients performed at the time of maximal toxicity showed a quantitative reduction in the precursors of the formed elements of the blood with a more pronounced effect on the megakaryocytes and myeloid series than on the erythroid series. Qualitative studies of the bone marrow smears showed no changes in the morphology of the hematopoietic cells.

Hepatic and Renal Toxicity. In contrast to the toxicological animal data, there was no consistent hepatic or renal dysfunction during or after treatment with CCNU. Only 1 patient at 50 mg/sq m experienced a transient, reversible increase of serum glutamic oxalacetic transaminase and serum glutamic pyruvate transaminase without change in other tests from 2 to 4 weeks after treatment with return to normal levels after 14 days. During the same period, this patient also received chlorpromazine.

Experience with Repeated Doses. After a single dose of 130 mg/sq m was established as a safe maximal tolerated dose, repeated doses of CCNU were given every 8 weeks without prohibitive cumulative toxicity. The dose interval was therefore shortened to 6 weeks, with repeated dosage prior to full recovery of the delayed hematological toxicity. Nine patients were exposed to 2 to 4 doses of CCNU at 130 mg/sq m p.o. every 8 weeks, while dose scheduling every 6 weeks was explored in 6 patients. In either schedule, repeated doses caused no change of the median nadir of hematological toxicity (Tables 3 and 4), although the duration of

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Table 1
Toxicity following single p.o. dose of CCNU at increasing dose levels

Dose (mg/sq m)	No. of patients	No. with vomiting	No. with thrombocytopenia (cu mm)			No. with leukopenia (cu mm)		
			<200,000	<100,000	<30,000	<5000	<3500	<2000
15	3	0	0	0	0	0	0	0
30	7	1	3	1	0	0	0	0
50	7	1	2	0	0	0	0	0
75	6	1	4	1	0	3	0	0
100	6	2	5	1	0	4	1	0
130	15	11	15	11	3	12	7	1

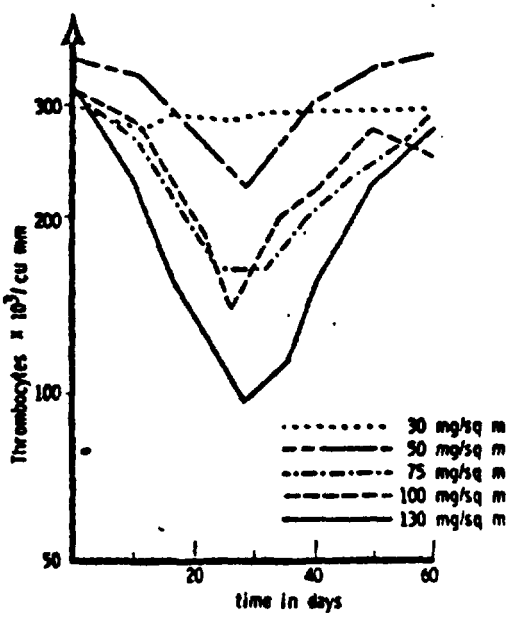

Chart 2. Median values of thrombocytes following single p.o. doses of CCNU at increasing dose levels.

thrombocytopenia was slightly increased. Hence, the compound can be administered every 6 weeks without development of prohibitive cumulative toxicity. Furthermore, the presence of residual leukopenia or thrombocytopenia at the time of dose administration does not preclude the expected return of counts to normal over the ensuing 2 to 3 weeks. No hepatic or renal dysfunction occurred during repeat treatment with CCNU.

Antitumor Effect. Twenty-three patients received a drug dose of either 100 or 130 mg/sq m of CCNU. Eleven of the 23 patients had measurable disease. This group was considered evaluable with regard to the antitumor effect of CCNU. There were 2 complete and 5 partial responses (Table 4). Of special interest was the functional improvement obtained in all 3 patients with glioblastoma multiforme. The latter patients were all hemiplegic and bedridden and in one instance comatose at the time of treatment. They all improved to the point where they were able to walk without assistance, permitting outpatient follow-up for the subsequent treatments. In one case, decrease in the size of tumor was demonstrated by serial brain scans with ^{95}Tc. Similar responses have recently been reported in a number of patients with primary brain tumors treated with BCNU (17, 18).

DISCUSSION

The mechanism of action of the nitrosoureas has not been clearly defined. Alkylation has been suggested as the major mode of action mainly because of the chemical structure of BCNU and its demonstrable activity against both dividing and nondividing L1210 cells in culture (12). However, a hamster plasmacytoma with acquired resistance to cyclophosphamide was sensitive to nitrosoureas (15), and clinical observations have shown that resistance to classical alkylating agents did not correlate with resistance to BCNU in Hodgkin's disease (7, 14). These findings suggest possible actions other than alkylation. In contrast to BCNU, CCNU has only 1 chloroethyl group, so that the cytotoxic action of CCNU is unlikely to rest with this single group *per se*. Other possible active groups must be explored among the degradation products of the nitrosoureas in aqueous media, as postulated for BCNU (9). The intermediates produced by the cleavage of the bond between the nitrosated nitrogen and the carbonyl carbon give

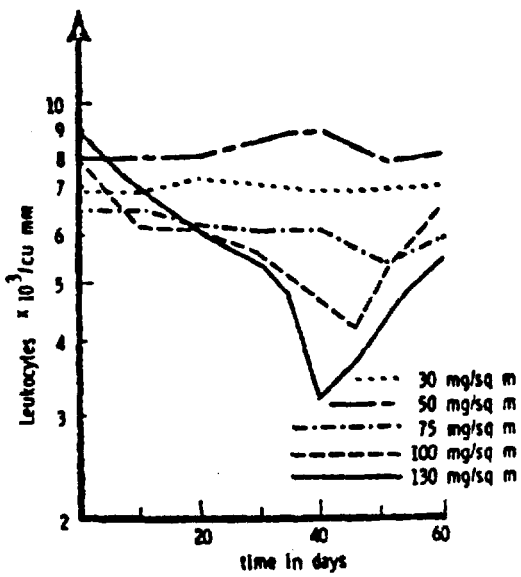

Chart 3. Median values of leukocytes following single p.o. doses of CCNU at increasing dose levels.

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Table 2
Thrombocytopenia following single and repeated doses of CCNU, 130 mg/sq m

Dose	Nadir: Median day	Nadir: Range	Nadir: Counts x 10^3 (cu mm) Median	Nadir: Counts x 10^3 (cu mm) Range	Duration <100,000 (days) Median	Duration <100,000 (days) Range
			Every 8 weeks			
1	29	18–42	87	38–140	6	0–25
2	31	22–41	94	28–175	10	0–40
3	30	22–43	72	22–140	15	0–30
			Every 6 weeks			
1	26	18–31	67	37–98	6	0–10
2	34	29–36	79	63–88	11	7–20
3	33	29–35	84	39–133	10	0–23

Table 3
Leukopenia following single and repeated doses of CCNU, 130 mg/sq m

Dose	Nadir: Median day	Nadir: Range	Nadir: Counts x 10^3 (cu mm) Median	Nadir: Counts x 10^3 (cu mm) Range	Duration <5000 (days) Median	Duration <5000 (days) Range
			Every 8 weeks			
1	42	21–65	3.8	1.2–6.5	15	0–28
2	42	22–56	4.2	2.4–6.0	16	0–40
3	46	32–56	4.2	3.8–5.0	10	0–30
			Every 6 weeks			
1	44	24–60	3.5	2.0–4.5	12	7–14
2	41	36–50	3.3	2.4–4.1	9	7–15
3	46	36–51	5.2	3.6–6.5	14	0–28

rise to the highly reactive isocyanate intermediate and an unstable diazoalkane, ethylenediazohydroxide. The latter reacts to give vinyl alcohol, which rearranges to acetaldehyde, while the isocyanate degrades further by hydrolysis to amine. This pathway indicates that diazoalkane as well as the isocyanates may be the intermediates with antitumor activity. Several of these intermediates of CCNU have been synthesized, and, when evaluated in a recent study, the antitumor activity appeared to rest with the isocyanate portion of the molecule (1). In addition to this theoretical interest, the present study indicates that CCNU can be used clinically at a starting dose of 130 mg/sq m every 6 weeks with relative safety in patients with solid tumors. The initial gastrointestinal toxicity and delayed thrombocytopenia and leukopenia are similar to the effects following BCNU, but, in contrast to BCNU, no hepatic or renal toxicity was observed. In addition, p.o. administration of CCNU appeared to give predictable effects, whereas absorption of BCNU p.o. appears to be erratic (8). The delayed bone marrow toxicity occurring after administration of these compounds is unique and currently unexplained. Recent data by Young and DeVita (19), using the ...-labeling technique with thymidine-^{3}H and -^{14}C in ... showed that the nitrosoureas result in early sustained prolongation of the DNA S phase. Similar prolongation of the S phase, affecting bone marrow cells, might precede lethal injury for several generations or, alternatively, affected stem cells might fail for some time to replenish early bone marrow progenitor cells in spite of the reduction of proliferating pool size which normally stimulates this repopulation (13).

The objective antitumor effect in this study resulting from CCNU given to patients with lymphoma and bronchogenic carcinoma and the marked clinical improvement in patients with glioblastoma were gratifying and indicated its potential clinical usefulness. A high degree of lipid solubility and the lack of ionization in aqueous media explain the passage across the blood-brain barrier. Infusion of ethylene-^{14}C CCNU in dogs has indicated that radioactivity in the cerebrospinal fluid exceeded plasma levels 3-fold (10). Serial cerebrospinal fluid determinations in man after p.o. administration at doses varying from 30 to 100 mg/sq m showed concentrations which were about 50% of concurrent plasma ^{14}C levels (11).

A final comment should be made on the method used in this study for arriving at a safe maximum tolerated dose of CCNU. The starting dose of CCNU at 15 mg/sq m corresponded to approximately one-third of the minimal toxic

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Table 4
Diagnoses and responses

Diagnosis	Total on study	Total evaluable for response[a]	Responses		Duration of response (wk)
			Complete	Partial	
Carcinoma of lung	18				
Adenocarcinoma	5	2		1	34
Oat cell	2	2	1		26
Others	11	1			
Melanoma	4	2			
Miscellaneous	5	2			
Glioblastoma multiforme	3			3	18, 12+, 29+
Reticulum cell sarcoma	1	1		1	12
Lymphosarcoma	1	1	1		6+

[a] Patients receiving 100 or 130 mg/sq m and having measurable disease (excepting glioblastoma multiforme).

dose of the compound in preclinical trials of 40 and 39 mg/sq m for dogs and monkeys, respectively (2). The mg/sq m body surface was used as a predictive denominator for hematopoietic, hepatic, and renal toxicity (5). Thereafter, as no toxicity was detected, the dose was escalated with a modification of the Fibonacci search scheme (16). This schedule permitted large initial increments of drug dose at supposedly nontoxic levels, while the proportional increase of drug dose was smaller at higher dose levels as the range of expected toxicity was reached (Table 1). It was possible, by using this method of escalation, to detect reproducible changes of decreased leukocytes and thrombocytes within the normal range ("subtoxic change") and thus predict toxicity at the next higher dose level. As sporadic toxicity was noted, the study of additional patients made it possible to acquire information about variability of host tolerance to the agent. The above-mentioned study design is under further exploration here.

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P. O. Box 1663
Los Alamos, New Mexico 87544

IN REPLY REFER TO: ADRT

March 5, 1973

[redacted]

Dear [redacted]

The pi meson facility will not treat patients until next year. Please remember that when we do start to treat patients, it will be an experiment at first. We do not know whether the pi meson beam will be better than ordinary x-ray therapy.

It is difficult for me to give advice about a patient whom I do not know. However, I am enclosing an abstract about the use of certain chemicals after radiotherapy. This has been encouraging in some patients. Please give the letter to the child's physician at the University Clinic of Essen. If they are interested, I would suggest that they write directly to Dr. Michael D. Walker.

Sincerely,

M. Klugerman

Morton M. Klugerman, M. D.
Assistant Director for
Radiation Therapy

MMK:maf
Encls: As noted

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Los Alamos, New Mexico 87544

IN REPLY
REFER TO: ADRT

March 5, 1973

Dear Colleague:

I am enclosing a letter I received from [redacted]nd my reply. I apologize for sending the enclosed abstract but it occurred to me that this information might not be available to you. More recent reports by Dr. Michael D. Walker, as yet unpublished, are even more encouraging.

If you wish, why not write directly to him. His address is

Dr. Michael D. Walker
Baltimore Cancer Research Center
3100 Wyman Park Drive
Baltimore, Maryland 21221
Phone: (301) 338-1100

Again, may I apologize for interfering.

Sincerely,

M. Kligerman

Morton M. Kligerman, M. D.
Assistant Director for
Radiation Therapy
Professor of Radiology
University of New Mexico

MMK:maf
Encls: As noted

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Radiation Therapist
University Clinic of Essen
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Kindness of [redacted]

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