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Dianhydrogalactitol (NSC-132313): Phase II Study in Solid Tumors

A Report of the E.O.R.T.C. Early Clinical Trial Cooperative Group*

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Abstract—*One hundred and sixty-two patients with advanced solid tumors were treated with oral dianhydrogalactitol* 30 mg/m^2 *daily for* 10 days *every* 4–6 weeks. *Dose limiting toxicity was hematopoietic. Eight objective responses were seen in* 136 *evaluable cases. Patients with gastro–intestinal cancer* (2/13 *gastric*, 1/3 *pancreatic*, 2/23 *colorectal*) *showed objective regressions lasting* 1–12+ months. *Short lasting partial remissions occurred in* 2/20 *lung epidermoid and* 1/18 *breast carcinomas. Dianhydrogalactitol has limited chemotherapeutic activity against adult solid tumors but deserves further trial in gastro-intestinal malignancies.*

INTRODUCTION

(1,2:5,6) DIANHYDROGALACTITOL (DAG) is the major conversion product of dibromodulcitol (DBD) (NSC-104800) when treated by mild alkali or human serum [1]. The dihalohexitols and their diepoxide derivatives are considered to function as bifunctional alkylating agents. DAG is active in animal tumors including P388 and L1210 leukemias, B16 melanoma, sarcoma 180 and Walker 256 carcinoma [2]. It has a higher therapeutic index than DBD against L1210 leukemia and is the most active agent against intracerebral murine ependymoblastoma [3].

^{14}C-DAG crosses the blood brain barrier and significant uptake has been found in glioma and normal brain tissue [4]. Recent phase I and II studies with DAG administered intravenously have demonstrated antitumor activity against various types of lung cancer [5, 8].

The Early Clinical Trial Group (E.C.T.G.) of the EORTC has conducted a phase II study in adult patients with solid tumors using an oral formulation. An interim progress report on 51 cases has already been presented in abstracted form elsewhere [9].

MATERIALS AND METHODS

Selection of patients

As in a previous study by E.C.T.G., priority was given to chemotherapy-resistant solid tumors for which the patient accrual was hoped to be sufficient to yield statistically relevant results i.e., epidermoid carcinomas of the head and neck and of the lung, gastrointestinal adenocarcinoma, soft tissue sarcoma, melanoma and breast cancer resistant to conventional treatment. However, patients with

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other primary tumors were added because it was felt that anecdotal information on tumor regression in rare cell types would be of interest. The criteria for inclusion were histologically confirmed diagnosis of solid tumor, measurable and evolutive disease not suitable for surgery or radiation therapy, a Karnofsky index > 40, age > 15, granulocytes > 2500/mm^3, platelets > 100,000/mm^3 and serum creatinine < 1.5 mg%. Patients with a second tumor, overt psychosis, senility, central nervous system lesions or malabsorption syndrome were excluded. Pleural effusions, bone and brain metastases were not considered measurable lesions. Patients were not eligible until 4 weeks after prior radiation or chemotherapy. The only exception was palliative radiation to a limited bone lesion outside the location of measurable tumor masses.

Treatment

DAG* was supplied as 20 mg scored tablets. All but the first 15 patients received 30 mg/m^2 in divided doses, daily for 10 days, evey 4–6 weeks.

The duration of treatment depended on response to therapy. In the absence of progression of disease or unacceptable toxicity to the patients, two or more 10 day cycles were given.

Mechanics of the study

The study was activated in July 1976 and closed in December 1977. The final analysis was made on follow-up data available as of 15 April 1978. The assessment of therapeutic results was made in accordance to standard evaluation procedures of the E.C.T.G. as outlined in a previous paper [10]. Tumor measurements, drug toxicity, weight, Karnofsky index and blood counts were recorded weekly. Serum creatinine, liver function tests and chest X-ray were obtained every 3 weeks.

Evaluation of response

The following criteria were used in assessing tumor response:

1. *Complete remission* (CR): disappearance of all symptoms and signs of the disease.

2. *Partial remission* (PR): > 50% decrease in the product of the two largest perpendicular diameters of all measurable lesions without the appearance of a new tumor. For lesions that do not lend themselves to accurate measurement the reduction should be at least 3/4 of the estimated volume.

3. *No change* (NC) is recorded, if after 9 weeks no new lesions have appeared and existing lesions have not regressed or increased in size by at least 50%.

4. *Progression* (Prog.) occurs when any lesion increase by > 50% in size or any new lesion appears regardless of what the response of the other lesions might be.

5. *Early death* (ED): death occuring within the first three weeks of treatment without evidence of severe toxicity.

6. *Toxic death* (TD): death due to drug toxicity occurring at any time during the study.

Duration of response is computed from the day when it is first documented until relapse. Only complete and partial remissions are considered as objective response to treatment.

RESULTS

Antitumor effect

One hundred and sixty-two patients entered the trial. Twenty-six (16%) cases were rejected from the final evaluation for the following reasons: ineligibility 11, protocol violation 5, lost to follow-up 4, treatment refusal 4, incomplete data 2. The distribution by primary site of the 136 evaluable cases is shown in Table 1. The accrual of 13 or more patients with epidermoid carcinoma of the head and neck, epidermoid carcinoma of the lung, stomach, colo-rectal and breast cancers makes statistical analysis relevant only for those tumor categories.

Eight objective responses were seen in 136 evaluable cases (6%) (Table 2). Low grade anti-tumor activity was detected in epidermoid cancer of the lung 2/20 (95% confidence limits of 0 and 21%). The clinical usefulness of those short lasting tumor responses (less than 2 months) is not evident.

In gastro-intestinal cancer 5/42 (12%) (95% confidence limits of 2 and 21%) objective regressions were recorded in the following tumor types: 2/13 gastric, 1/3 pancreatic and 2/23 colo-rectal adenocarcinomas. One patient remains in remission on treatment after more than one year (Table 2). Three additional patients showing close to 50% tumor regression were disqualified for the following reasons: early toxic death (1), appearance of brain metastases (1), lost to follow-up (1). No significant difference in

*DAG was kindly supplied by Chinoin Chemical and Pharmaceutic Works Ltd., Budapest, Hungary.

Table 1. Therapeutic response

Site	No. of pts	Response					
		CR	PR	NC	Prog.	ED	TD
Head and neck epidermoid carcinoma	13			2	7	3	1
Lung							
1. Epidermoid carcinoma	20		2	4	12	2	
2. Small anaplastic carcinoma	4				4		
3. Adenocarcinoma	4				3	1	
4. Large cell carcinoma	4				4		
5. Unspecified	1				1		
Gastro-intestinal	13	1	1	1	7		3
1. Stomach							
2. Pancreas	3	1		2			
3. Colo-rectal	23		2	2	17	1	1
4. Gall-bladder	2			1		1	
5. Oesophagus	1			1			
Breast	18		1	3	12	1	1
Sarcomas							
1. Leiomyosarcoma	2				2		
2. Osteosarcoma	1				1		
3. Liposarcoma	1				1		
4. Fibrosarcoma	1				1		
5. Pleural mesothelioma	1			1			
6. Soft tissue sarcoma	1				1		
Melanoma	7				6		1
Others							
1. Hypernephroma	5				5		
2. Bladder	2				2		
3. Uterus	3			2	1		
4. Ovary	2				1		1
5. Vagina (adenocarcinoma)	1				1		
6. Vulva	2				2		
7. Penis	1			1			
Total	136	2	6	20	91	9	8

Table 2. Duration of response

Tumor site	Response type	Duration (months)
Pancreas	C.R.	3
Gastric	C.R.	12+
G.I. colon	P.R.	11
G.I. gastric	P.R.	5½
G.I. rectum	P.R.	1
Breast	P.R.	1
Lung epidermoid	P.R.	1
Lung epidermoid	P.R.	1

response rate was seen between patients with (2/24) or without (3/18) prior chemotherapy. However the 2 CR were seen in the previously untreated group whereas 4 toxic deaths occured in previously treated patients.

No objective tumor regression was seen in melanoma (0/7) sarcoma (0/7) hypernephroma (0/5) or bladder cancer (0/2).

Toxicity

Dose limiting toxicity was hematopoietic. Eight out of one hundred and thirty-six (6%) patients died with WBC < 1500 and/or platelets < 20,000. Sepsis was documented in 1 case and bleeding in 4 cases. Prior treatment with nitrosourea or metastatic liver involvement did not appear as significant contributing factors.

Onset of toxicity was often delayed beyond day 21 with recovery by day 42. Median WBC nadir of 3500 and platelet nadir of 100,000 occurred on days 28 and 29 of the first cycle of treatment. A median hemoglobin drop of 20% of the initial value was also recorded. There was no evidence of cumulative toxicity between the first and second cycles of treatment. Moderate to severe gastrointestinal toxicity (anorexia, nausea, vomiting,

diarrhea) was seen in 24/136/ (17%). No other significant toxicity was encountered.

DISCUSSION

The most interesting aspect of this phase II study using an oral formulation of DAG was the anti-tumor activity demonstrated against gastro-intestinal malignancies. The 12% response rate is similar to that of nitrosoureas. The quality and duration of some responses suggest that DAG may be an useful agent especially in stomach and pancreatic cancers. Previous reports on phase I and II studies using i.v. DAG included very few G.I. cancers treated with adequate doses and therefore give no information about its activity in those diseases.

The previously reported low grade activity in epidermoid lung cancer is also observed in this study. The poor quality and limited duration of the two partial remissions obtained constrast sharply with those seen in the G.I. tumors.

Except for a PR of short duration documented in a patient with metastatic breast cancer presenting as an adenocarcinoma of unknown primary, no other tumor regression occurred in 17 patients with breast cancer pretreated with chemotherapy including alkylating agents. Similarly no anti-tumor activity was observed in any of the patients with other neoplastic diseases. DAG appears thus to be a chemotherapy agent with limited therapeutic activity against adult solid tumors with the possible exception of gastro-intestinal malignancies, where it deserves further trials.

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