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Phase I clinical trial of ethyl 6-deoxy-3,5-di-*O*-methyl 6-(3 methyl-3-nitrosoureido)-alpha-D-glucofuranoside (CGP 6809)

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Summary. A phase I study of single i. v. doses of a new sugar containing nitrosourea 6-deoxy-3,5 di-O-methyl 6-(3 methyl-3-nitrosoureido)-alpha-D-glucofuranoside (CGP 6809, EDMN) has been carried out in 47 patients with advanced solid tumors. Nine dose levels between 200 and 4500 mg/m^2 were examined. Nausea and vomiting were seen in most patients but were controlled with antiemetics. Myelosuppression was minimal. The dose-limiting toxicity was hepatotoxicity, occurring early (peak at days 2–4) and resolving rapidly. No cumulative toxicity was seen with an every 6 weeks schedule. Other toxicities were abdominal pain, diarrhea, arm pain, restlessness, and headache. Pharmacokinetic studies in 20 patients using an HPLC assay and in 5 patients using [^{14}C]EDMN showed a short half-life, rapid plasma clearance, rapid metabolism, and minimal excretion of unchanged drug. There was one partial response in a patient with colon carcinoma. The recommended dose for phase II studies is 3750 mg/m^2 every 6 weeks.

Introduction

Ethyl 6-deoxy-3,5 di-*O*-methyl-6-(3 methyl-3-nitrosoureido)-alpha-D-glucofuranoside (EDMN; CGP 6809; Fig. 1) is a new water-soluble nitrosourea developed by CIBA-GEIGY Ltd., Basel, Switzerland, which has shown activity against a variety of experimental solid tumors. It inhibited human melanoma WM-47, implanted in nude mice, by 95% and human bronchogenic carcinoma MBA-9812 by 77%. It was also active against the Harding Passey melanoma and the B-16 melanoma (79% and 66% inhibition, respectively) [7]. It is not teratogenic or diabetogenic and is mutogenic only at very high concentrations [1, 7]. In toxicology studies, the dose-limiting toxicity was myelosuppression, particularly thrombocytopenia if the drug was given as a single dose or daily for 5 days by slow infusion. When it was given by rapid i. v. injection neurotoxicity was dose-limiting. After administration daily for 10 days or daily for 20 days in the dog, hepatotoxicity appeared to be the predominant abnormality. In the dog the lowest dose to induce lethality was 8000 mg/m^2: in mice the LD_{10} was 2250 mg/m^2 [6].

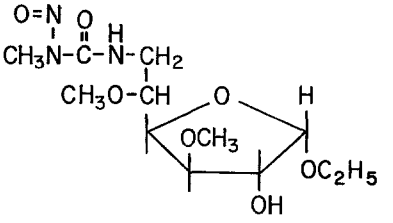

Fig. 1. Etyhl-6-deoxy-3,5-di-*O*-methyl-6-(3 3-nitrosoureido)-α-D-glucofuranoside (CGP 6809)

Pharmacokinetic studies in the rat showed that the t½ is short (12.5 min). The renal excretion of unchanged drug is less than 1% of the dose and the drug is rapidly transformed to metabolites that are excreted in the urine and feces [3]. On the basis of its wide spectrum of antitumor activity, lack of diabetogenic or mutagenic potential, combined with water solubility, EDMN was advanced to phase I clinical trial. The drug was studied as an investigational new drug (IND) passed for testing by the FDA, using a protocol approved by the IRB of this Institute. A preliminary report of this study has been presented [5].

Methods

Patients with advanced cancer not amenable to other treatments, or for whom other treatments had proven ineffective, were entered on the study, after giving written informed consent to the study and after the experimental nature of the treatment, the possible hazards, the alternatives and the freedom to withdraw at any time from the study had been carefully explained to them, both orally and in writing. The requirements for entry into the study were an expected survival of at least 2 months' duration, a performance status of 0–3 (ECOG), at least a 2-week interval since the last dose of potentially myelosuppressive therapy (6 weeks for a nitrosourea and mitomycin C) and recovery from reversible toxicity, a 3 week interval since any surgery except for minor procedures, and the absence of acute intercurrent complications or pregnancy. The minimal hematologic parameters required were a white blood cell count of at least 4000/mm^3 and a platelet count of at least 100000/mm^3. The minimum biochemical parameters required were an SGOT of less than 100 IU/l and a serum creatinine of 1.5 mg/dl or less. Patients were not allowed to have radiation, except small port radiation, during the

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course of the study. Before treatment and following each course of treatment a complete blood count (CBC) and platelet count were carried out weekly and serum Na^+, K^+, Ca^{2+} and PO_4^{3-}, creatinine, uric acid, total protein, albumin, bilirubin, alkaline phosphatase, LDH, SGOT, and BUN were measured on day 2, day 3, and then weekly. The drug was supplied by the Pharmaceutical Research Department of CIBA-GEIGY Ltd (Basel, Switzerland) in ampules containing 500 or 1500 mg. It was reconstituted in 5% dextrose in water and given i. v. initially as a 1-h infusion.

The starting dose was 200 mg/m^2, 1/12th of the LD_{10} in mice, the most sensitive animal species. The planned dose escalation was by 100% increments until some sign of effect was seen, then by 50% increments to mildly toxic doses and 33% increments to moderately toxic doses.

EDMN in plasma and urine was assayed using a previously developed high-performance liquid chromatography method on an IBM C18 column with methanol water (50:50) as the mobile phase and UV detection at 229 nm [4]. Five patients at a dose of 3750 mg/m^2 received 250 μCi of EDMN labeled in the carbonyl carbon in their drug infusate. Plasma concentrations were fit to a one- or two-compartment model using the program BMDPAR on a Univac 90/80 computer [2].

Results

The 47 patients entered into the study received a total of 75 complete and 1 incomplete courses, each course consisting of a single infusion. Doses of 200, 400, 600, 900, 1350, 2000, 3000, and 4500 mg/m^2 were initially evaluated. The dose of 3000 mg/m^2 showed no substantial toxicity. A dose of 4500 mg/m^2 showed early hepatotoxicity in some patients treated. An intermediate dose of 3750 mg/m^2 was therefore evaluated. This also showed hepatotoxicity in some patients. Further patients were therefore added at 3000 mg/m^2, to complete the study. The patients entered, with their ages, diagnoses, prior therapy, and doses given, are listed in Table 1.

Nausea and vomiting were almost universal at doses higher than 400 mg/m^2. It was mild to moderate at doses up to 3000 mg/m^2 and moderate to marked at higher doses (> 3000 mg/m^2). Pretreatment and treatment after the drug dosage, with antiemetic combinations, greatly ameliorated this side effect. Three instances of borderline leukopenia were seen in 2 patients, a WBC of 3600/mm^3 after each of 2 doses of 900 mg/m^2, in patient 14 (on day 10 in each case) and a WBC of 3700/mm^3 in patient 47 on day 6 after a dose of 3000 mg/m^2. Leukocytosis on day 2 was a feature of treatment with higher doses of the drug. Three cases of platelet count < 100000/mm^3 (one each at 2000, 3000, and 4500 mg/m^2) were observed. The counts were respectively 47, 27, and 43×10^3. In two of these patients there was evidence for disseminated intravascular coagulopathy, although, in both cases, thrombocytopenia occurred at about the time it would be expected for myelosuppression from a nitrosourea.

Hepatotoxicity was the dose-limiting toxicity. It occurred early, usually being maximal on days 3–5 and resolving rapidly. At doses of 200–2000 mg/m^2, 24 patients received 33 courses. There were 6 with abnormal liver chemistries, 5 with SGOT > 100 IU/l, and 4 with serum bilirubin higher than 2 mg/dl; 3 of these patients had documented liver metastases and 2 others had colorectal carcinoma. It was concluded that, in these cases, the abnormalities were most probably due to underlying disease, particularly as it was not dose-related. Dose-related hepatotoxicity became apparent at doses of 3000 mg/m^2 or higher, being more marked at 3750 and 4500 mg/m^2 (Table 2). In a few patients studied at the highest doses

Table 1. Patients entered on study

Pt no.	Age	PS	Sex	Diagnosis	Prior therapy	Dose (mg/m^2)
1	68	2	F	Adeno ca, breast; squamous cell ca, left tonsillar area	RT, Nolvadex	200
2	51	3	M	Renal cell ca	Megace, immunotherapy CGP 15720A	200
3	63	0	M	Renal cell ca	RT	200 600
4	51	3	F	Adeno ca, cecum with liver mets	5-FU	200
5	29	2	F	Synovial cell ca, left knee	RT, ADR, DTIC, VCR, CTX	400
6	68	1	M	Well-diff. adeno ca, sigmoid colon, with liver mets	5-FU/CF, hydroxyurea	400
7	60	2	F	Breast ca, adeno ca, colon	RT, CTX, MTX, 5-FU, sodium cyanate	400
8	20	3	F	Adeno ca, colon	RT, 5-FU/CF	400
9	72	2	M	Well-diff adeno ca, colon, with lung, liver, soft, tissue mets	5-FU/CF, sodium cyanate	400
10	51	3	M	Squamous cell ca, lung	BLEO, DDP, VBL, MIT C	600
11	62	1	M	Adeno ca, sigmoid colon, with liver mets	5-FU/CF	600 1350
12	30	1	M	Malignant schwannoma, lung mets	CTX, VCR, ADR, DTIC, DDP, MTX	600
13	60	0	F	Leiomyosarcoma, uterus with lung mets	VCR, ACT D, DDP, MTX	600 1350

Table 1. Patients entered on study

Pt no.	Age	PS	Sex	Diagnosis	Prior therapy	Dose (mg/m^2)
14	69	2	M	Adeno ca, prostate	DES, DDP Estracyt, 5-FU, CTX, MTX/CF, GGP 15720A, CHIP, Anandron	900
15	62	2	M	Squamous cell ca, pyriform sinus	DDP, CHIP	900
16	63	1	F	Adeno ca, colon with lung mets	CGP15720A, 5-FU/CF, Amicar	900 2000
17	54	2	M	Adeno ca, colon	5-FU, CF	1350
18	56	2	M	Adeno ca, unknown primary with mets to liver, bone	RT, CGP 15720A	1350 2000
19	68	2	F	Adeno ca, sigmoid colon	5-FU, CF, IF	1350
20	69	3	M	Squamous cell ca, larynx	RT, DDP	1350 3000
21	43	2	M	Malignant melanoma with mets to soft tissue, lungs, brain	DTIC, ADR, BCNU, ACT D, VCR, DDP	2000
22	66	1	M	Adeno ca, cecum	RT, 5-FU, MITC	2000
23	49	3	F	Small cell ca, lung, with mets to bones	CTX, ADR, VCR, DDP, CHIP, VP-16	2000
24	57	1	M	Squamous cell ca, mouth, with mets to bones	RT, DDP, CHIP	3000
25	37	3	F	Small cell ca, lung, with subcutaneous mets	CHIP	3000
26	58	1	F	Adeno ca, R lung	CTX, ADR, MTX, procarbazine, DTIC, CHIP, VP-16	3000
27	55	1	M	Renal cell ca with bone mets	RT, DDP, VP-16	4500
28	67	2	F	Leiomyosarcoma of retroperitoneum	RT, DTIC, CTX, VCR, ADR, DDP, MTX	4500
29	53	0	M	Malignant melanoma with liver mets	BCNU, ACT D, VCR, DTIC, DDP, VP-16	4500
30	72	1	M	Adenoca, rectum, with lung mets and groin nodules	RT, 5-FU, DDP, VP-16	4500
31	55	1	M	Adeno ca, rectum	RT, 5-FU	4500
32	48	2	M	Ca thyroid	I^{131}, ADR, DDP, VP-16	4500
33	55	0	M	Renal cell ca with lung mets	IF	3750
34	60	1	M	Epidermoid ca, head and neck	RT, DDP, CHIP, VP-16	3750
35	24	2	M	Sarcoma of left retroperitoneum with lung mets	RT, CTX, VCR, DTIC, DDP	3750
36	44	1	M	Adeno ca, colon, with liver and lung mets	5-FU, MTX, DDP	3750
37	64	2	M	Adeno ca, unknown, with liver and lung mets	VP-16, DDP	3750[a]
38	46	1	M	Adeno ca, rectum	DDP, 5-FU	3750
39	60	1	M	Renal cell ca	IF	3750
40	60	0	F	Adeno ca, colon	DDP, 5-FU	3750
41	59	0	F	Adeno ca, rectum, with lung mets	5-FU	3750
42	61	0	M	Adeno ca, cecum, with liver mets	5-FU/CF	3000
43	69	3	M	Small cell ca, lung	CHIP, VP-16, DDP, 5-FU	3000
44	47	0	M	Adeno ca, colon	RT, 5-FU	3000
45	53	1	F	Adeno ca, rectum with lung mets	RT, 5-FU	3000
46	64	1	F	Adeno ca, colon	RT, 5-FU, DDP	3000
47	57	1	F	Adeno ca, pancreas	Streptozotocin, MIT C, 5-FU	3000

[a] Patient developed severe arm pain during infusion. Drug stopped when a total dose of 2890 mg/m^2 had been given

Abbreviations: RT, radiation therapy; 5-FU, 5-fluorouracil; ADR, adriamycin; DTIC, dacarbazine; VCR, vincristine; CTX, cytoxan; VBL, vinblastine; DDP, cisplatin; ACT D, actinomycin D; BLEO, bleomycin; MTX, methotrexate; BCNU, carmustine; VP-16, etoposide; CHIP, iproplatin; MIT C, mitomycin C; IF, interferon; DES, diethylstibestiol; CF, citrovorum factor; CGP15720A, 1-[2-[2-(4-pyridyl)-2-imidazoline-1-yl]-ethyl]-3-(4-carboxy-phenyl)urea

Table 2. Abnormalities in liver function following the three highest doses of EDMN

Dose mg/m²	No.[a]	SGOT (IU/l)		Serum bilirubin (mg/dl)	
		100–300	>300	2–4	>4
3000	10	2	0	0	0
3750	8	1	4	2	1
4500	6	4	1	0	1

[a] Number of patients evaluable for hepatotoxicity

with repeated administration, liver abnormalities did not increase with successive courses. Patient 30 received four courses of the drug. The highest levels of SGOT seen after the four courses were, respectively, 133, 127, 41 and 93 IU/l. Patient 39 received three courses of EDMN at a dose of 3750 mg/m², with no evidence of hepatic abnormalities. Patient 38 received two doses of 3750 mg/m². The SGOT was 113 IU/l after the first and 52 IU/l after the second dose.

Other side effects were abdominal pain (11), diarrhea (4), arm pain (2), restlessness (2), and headache (2). (Numbers in parentheses denote number of patients with the observed side effect.)

There were no fatalities or long-term sequelae of drug treatment in the present study. One patient with colon carcinoma with subcutaneous metastases had a partial response lasting 4 months.

Pharmacokinetic analyses were carried out in 20 patients at doses ranging from 200 to 3750 mg/m². The pharmacokinetics were linear over this dose range, the AUC correlating with dose with $r = 0.9699$. Plasma decay after infusion was monophasic at lower doses (up to 900 mg/m²) and generally biphasic at higher doses. The terminal phase half-life was 0.48–2.23 h, with a median of 0.93 h. The plasma clearance ranged from 12.5–66.6 l/h with a median of 31.7 l/h. The volume of distribution at steady state ranged from 17.2 to 58.9 l, with a median of 32.6 l. Five patients who received [^{14}C]EDMN showed rapid metabolism of the drug to more water-soluble chemical species which were largely recovered in the urine. Urinary excretion of unchanged drug was less than 1% of the dose.

Discussion

Preclinical toxicology of EDMN indicated a schedule-dependent pattern of toxicity. Rapid i. v. injection of the drug in dogs led to dose-limiting neurotoxicity consisting of convulsions. With slow infusion as a single dose, the limiting toxicity was myelosuppression, whereas when the drug was given daily hepatotoxicity became predominant.

The drug in this trial was given in widely spaced doses, and it was anticipated that the toxicity would be delayed myelosuppression. It is of interest that, even at the most toxic doses, definitive evidence of myelosuppression was difficult to establish. Hepatotoxicity occurred early, during a period when it could easily be overlooked, as the values usually returned to normal by day 8. However, the pattern of toxicity seen in the dog after multiple doses was early hepatotoxicity.

Of interest in the present trials is the steepness of the dose-response curve. A dose of 3000 mg/m² led to minimal toxicity. Doses of 3750 and 4500 mg/m² both produced marked hepatotoxicity in some patients. The degree of hepatotoxicity appears to have been approximately equivalent at the two doses, presumably the result of the small numbers treated. Attempts were made to correlate some pharmacokinetic parameter with the appearance of hepatotoxicity, but with the small numbers of patients available in this study, we were unable to identify any pharmacokinetic parameter which consistently correlated with the presence or absence of hepatotoxicity.

The pharmacokinetic analysis and studies with radiolabeled EDMN showed data consistent with previous findings in the rat [3] and essentially those anticipated from the fact that this is a nitrosourea. At higher doses a biphasic plasma decay after infusion was noted; at lower doses a second phase could not be identified, presumably because of the limits of detection of the assay procedure. The terminal phase half-life is short, the plasma clearance is high, and the drug is eliminated almost exclusively by metabolism. The nature of the metabolites has not yet been identified. In phase II trials, an attempt will be made to correlate pharmacokinetic parameters with toxicity or response or both.

The recommended dose for phase II trials is 3750 mg/m² given as a single i. v. infusion. However, since the major toxic manifestation is hepatotoxicity, which occurs early and resolves rapidly, a second trial using an every 2 weeks schedule is being undertaken to determine whether more drug can be delivered safely if the dosage interval is shortened.

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