4, 6-0-Benzylidene-D-glucopyranose (BG) in the treatment of solid malignant tumours, an extended phase I study

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Summary 4, 6-0-Benzylidene-D-glucopyranose (BG), a derivative of benzaldehyde (BA), whose anti-tumour action has often been reported, showed responses in 10 out of 24 patients (41.7%). These patients consisted of 11 cases of primary lung cancer, 4 of metastatic lung cancer, 5 of gastric cancer, and one each of cancer of the sigmoid colon, liver, pancreas and prostate. There were two complete responses (one each of ipsilateral lung metastasis from breast cancer and metastatic liver lesions due to gastric cancer). The mean total dose of BG was 392.6 g, given by intravenous infusion of 1.2 g BG in 100 ml saline twice daily. The treatment was discontinued when no response was observed after two months. Careful monitoring showed no toxic action of BG at these large doses. Complete necrotic liquefaction of tumour, without any damage to surrounding tissue, was seen in 2 of 3 cases in which histological examination was feasible. It is apparent that BG, like BA, is not a cytotoxic agent in the ordinary sense, but its mechanism of action is still unknown.

The anti-tumour effects of various aldehydes have often been reported (Osato, 1950; Conroy *et al.*, 1975; Sessa *et al.*, 1977; Derin *et al.*, 1978; Egyud & Gyorgyi, 1968). Among them, the effects of benzaldehyde (BA), originally extracted from fig fruit, on experimentally induced carcinomas (Takeuchi *et al.*, 1978; Petterson *et al.*, 1985; Soga *et al.*, 1985), on cultured cell lines (Zundel *et al.*, 1975; Miyakawa *et al.*, 1979; Watanuki & Sakaguchi, 1980; Watanuki & Sakaguchi, 1981; Isida *et al.*, 1983; Nambata *et al.*, 1982; Petterson *et al.*, 1983; Petterson *et al.*, 1983; Petterson *et al.*, 1985) and on advanced stage human carcinomas (Kochi *et al.*, 1980; Kochi *et al.*, 1985) have attracted considerable attention. Inhibition of experimental and spontaneous pulmonary metastasis in C₃H/He mice with CRT (+) cells, and dose-dependent mode of this inhibition have been reported by colleagues in other departments. (Ochiai *et al.*, 1986; Masuyama *et al.*, 1987).

Figure 1 shows the molecular structure of 4, 6-0-Benzylidene-D-glucopyranose (BG), a glucoside derivative of BA. BG is soluble enough in saline to be injected intravenously, unlike BA which has to be taken orally by the patients in the form of β -cyclo-dextrin inclusion compound. One remarkable feature common to BA and BG is the lack of toxicity, either acute or chronic. According to the past tests (Kaken in-house report, 1986), the LD₅₀ of BG in mice and rats is more than 400 mg kg⁻¹ by intravenous injection, more than 3,000 mg kg⁻¹ by oral, and more than 1,440 mg kg⁻¹ by peritoneal administration. No significant effect on Wistar rats (30 males and 30 females) was observed during, or after, a 6-month peritoneal administration of a maximum dose of 200 mg kg⁻¹ daily of BG, and similar results have been observed in beagles injected intravenously with 60 mg kg⁻¹ daily of BG for 6 months, except for a slight loss of appetite. No induction of anaphylaxis occurred due to the peritoneal injection of three doses of 30 mg BG every other day in 4 Hartley marmosets. No effect on spermatogenesis was observed by histological examination after a 6-month test (in rats and beagles), nor on reproductive functions (rats). Mutagenicity tests on *Salmonella typhimurium* strains and a strain of *Escherichia coli* were negative. BG administered to rats was distributed mainly in kidney, and 40% of the dose was excreted within 24 h; the level of hippuric acid accumulated in urine (that may suggest liberation of BA from BG) reached a maximum 3 to 6 h after administration. It is noteworthy that bone-marrow depression, gastrointestinal disturbances, and other adverse effects

Figure 1 Molecular structure of BG.

almost inherent with the currently used anti-tumour agents have never been observed for BA and BG, even when large doses were used for considerable periods.

Favourable results of a clinical trial of BG in cancers of various organs have been reported (Kochi *et al.*, 1985), including anti-tumour response in 55.3% of 65 patients, with 10.7% complete regression. The aim of the present study was to confirm the clinical efficacy of BG on various types of solid malignant carcinomas, as an extended Phase I study.

Patients and methods

A total of 24 patients with advanced stage carcinomas were included in the present trial. The diagnoses of all cases were confirmed by histological assessment from operation or biopsy. They consisted of 11 cases of primary lung cancer, 4 with metastatic lung cancer, 5 patients with gastric cancer, and one patient each with cancer of the sigmoid colon, liver, pancreas and prostate. The characteristics of the 20 male and 4 female cases are summarised in Table I. The average age of this group was 63.6 years, ranging from 11 to 86-years-old. The performance status of the patients was evaluated before and after the treatment.

BG was a gift from Kaken Pharmaceutical Co. (Tokyo, Japan), in vials each containing 1.2 g lyophilised BG (98% 4,6-0-benzylidene glucopyranose). Doses of 1.2 g BG dissolved in 100 ml saline (pH 4.5–6.5) were infused intravenously every morning and evening during the treatment period. This dose, suggested by the manufacturer's research group, was regarded as being considerably within the safety limit, in view of the virtual lack of any toxicity suggested by animal tests, but signs of any side effects were carefully

Table I Patient characteristics

Evaluable number	24
Sex	
Male	20
Female	4
Age	
Range	11-86
Mean	63.6
Sites of tumour	
Lung	11
Metastatic lung	4
Stomach	5
Sigmoid colon	1
Liver	1
Pancreas	1
Prostate	1
Performance status*	
0	5
1	1
2	3
3	10
4	5

*pretreatment

monitored according to the WHO guidelines for toxicity. The treatment was continued for two months, and was terminated if no response was observed. The treatment was applied with patients' consent after they were informed of the nature of the trial. X-ray and endoscopic examinations were conducted every month and computed tomography was carried out when necessary for the assessment of the effect of treatment. Complete blood counts, total protein, albumin, SGOT, SGPT, LDH, alkaline phosphatase, CPK, blood urea nitrogen, creatinine, and uric acid and urinalysis were performed every two weeks for the first month of treatment, followed by monthly monitoring of the status of the patients. Body weight and symptoms were also evaluated to appraise the efficacy of therapy.

Results

Among the 24 patients treated, a complete response (CR) according to the WHO criteria was noted in two cases; one male patient with synchronous ipsilateral pleura, diaphragm

Table II List of patients in this series

No.	Patient	Sex	Age	Primary organ	Histology	Metastatic site (s)	Performance status			Total doses of BG (mg)	Response	Responding site (s)	survival time (m)
							before	after	Prior therapy				
1	M.S	M	69	lung	s.c.c. ¹	(-)	3	1	(-)	216,000	PR		7 alive ⁹
2	A.M	M	50	"	ad.sq.c. ²	spinal cord adrenal gland liver	4	4	lobectomy	254,400	PR	spinal cord liver	6 death ⁴
3	K.S	M	73	"	s.c.c.	(-)	2	0	thoracotomy	160,800	PR		10 alive
4	N.K	M	86	"	ad.c. ³	(-)	3	1	(-)	138,400	MR		9 alive
5	O.J	M	66	"	ad.c	(-)	0	0	(-)	50,400	NC		4 alive ⁹
6	I.Y	F	71	"	ad.c	brain	3	1	brain tumour extirpation	60,000	PD	necrosis of lung tumour	3 alive ⁵
7	H.K	F	46	"	carcinoid	(-)	0	0	(-)	122,400	MR		2 alive ⁵
8	K.M	M	69	"	ad.c	(-)	4	1	(-)	722,400	PR		29 alive
9	A.T	M	68	"	s.c.c.	brain	2	4	(-)	118,800	PD		7 death
10	U.S	M	42	"	ad.c	(-)	3	0	(-)	662,400	PR		17 alive
11	N.T	M	68	"	s.c.c.	kidney	1	3	lobectomy	122,000	PD		4 death
12	K.T	M	70	breast	inf.duct.c. ⁶	ipsilateral lung and pleura	3	0	(-)	662,400	CR		11 alive
13	K.I	M	65	kidney	clear c.c. ⁷	lung	4	1	nephrectomy	182,200	PR	metastatic lesion	10 alive
14	T.H	F	11	femur	osteosarcoma	bilateral lung	0	0	amputation	63,600	PD		5 death
15	M.Y	M	52	femur	chondrosarcoma	bilateral lung	0	0	amputation	22,800	PD		3 alive ⁹
16	N.K	M	51	stomach	ad.c	multiple lung etc	4	4	total gastrectomy	60,000	PD		1 death
17	K.A	F	59	"	"	local recurrence, liver, peritonitis carcinomatosa	4	4	gastrectomy	86,400	PD	necrosis of lung and liver lesions	3 death ⁴
18	T.S	M	74	"	"	multiple liver	3	1	gastrectomy	748,800	CR	liver metastases	20 alive
19	W.A	M	70	"	"	multiple liver	3	1	(-)	657,600	PR	liver	21 alive
20	H.S	M	68	"	"	multiple liver	3	1	(-)	358,800	NC		16 death
21	T.K	M	76	sigmoid	"	bilateral liver	0	0	(-)	67,200	PD		4 death
22	I.T	M	78	liver	hepatoma	(-)	2	1	(-)	301,200	PR		10 death ⁸
23	T.T	M	65	pancreas	ad.c	single liver	3	1	(-)	252,400	MR		27 death
24	T.T	M	80	prostate	"	multiple bones, lung	3	2	(-)	415,200	MR		18 alive

1. s.c.c: squamous cell carcinoma, 2. ad.sq.c: adenosquamous cell carcinoma, 3. ad.c: adenocarcinoma, 4. autopsy, 5. operation, 6. inf. duct C: infiltrating ductal carcinoma, 7. clear c.c: clear cell carcinoma, 8. myocardial infarction, 9. change to other therapy, (Dept. of Surg., Toyama Med. & Pharm., Univ., July, 1987).

and lung metastases due to breast cancer, and a patient with metastatic liver lesions due to gastric cancer. A partial response (PR) was noted in 8 of the 24 patients, while MR was seen in 4 patients, yielding an overall response rate of 58.3%. An anti-tumour response rate of 41.6% is obtained if only CR and PR are considered. Ten of the 24 patients showed no response (NC) to therapy, or had progressive disease (Table II). At the start of treatment, the majority (18 of 24) of the patients had a performance status of grade 2 or worse. As shown in Table III, marked improvement of performance status was noted in patients who showed an objective therapeutic response (CR and PR), and improvement in performance status was also noted among those patients with MR or NC response. The mean survival time of the total cases at completion of the trial was 10.3 months. The 2 patients who had a CR anti-tumour response are still alive 11 and 20 months after the treatment (Figures 2 and 3).

Therapeutic assessment by histologic study was possible in three of the 24 cases, apart from appraisal of the size of the tumours by clinical methods. Of these three cases, two were evaluated by postmortem studies, and one was studied by examination of surgical specimens obtained through operation following BG treatment. Characteristic tissue response to BG, i.e., massive necrosis of the tumour tissue, was found but no apparent damage was found in the surrounding normal tissue.

No haematological, liver, renal or cardiac toxicity was attributable to treatment, and no nausea, vomiting or other adverse reactions were noted.

Discussion

Among 24 patients response was seen in 10, with 2 CR. These results were comparable to those of Kochi *et al.* (1985), and support the view that BG can be clinically useful for the treatment of tumours. One of the interesting features revealed in this study is the apparent lack of accompanying toxicity of BG, at least with the size of dose used, which is exceptional for anti-tumour agents and widens the future potential use of this drug. Another is the specific necrotic liquefaction of the tumour cells by this treatment, without any damage to surrounding normal cells seen in two cases in which histological assessment was feasible. This feature, which might have also been present in the other cases, may be a characteristic of BG.

Watanuki *et al.* (1980, 1981) noted that benzaldehyde selectively inhibited the uptake of nutrients into SV-40 transformed cell lines, but not their normal counterparts. These findings were also confirmed by other investigators (Takeuchi *et al.*, 1978; Ishida *et al.*, 1983). The mechanism of the anti-tumour action of BG is still unclear, except that it might

be related to that of BA and is probably entirely different from those of most anti-tumour agents, as suggested by the observed tumour cell-specific necrosis. It is not even clear if BG is actually a prodrug of BA, though this is suggested by the increase in urine hippuric acid level.

Figure 2 Plan PA views of the metastatic lesions of the left pleura (●), lung (→), diaphragm (↗) and pericardium (>) before the treatment with BG.

Figure 3 After a total of 662.4 g of BG has been administered, a complete disappearance of all the tumours were observed.

Table III Improvement in performance status noted in patients treated with BG

Therapeutic response	Performance status		Number of cases(s)
	Pretreatment	after	
CR	3	0	1
	3	1	1
	4	1	2
PR	3	1	2
	3	0	1
	2	1	1
	2	0	1
MR	3	1	2
	3	2	1
NC	3	1	1

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