Antitumor Activity of Benzaldehyde[1]

Mutsuyuki Kochi,[2,*] Setsuo Takeuchi,[3] Takeo Mizutani,[3] Ko Mochizuki,[2] Yoshiaki Matsumoto,[2] and Yoshiharu Saito[2,4]

SUMMARY

Ninety patients with inoperable carcinoma in the terminal stages and 12 patients in serious condition with other tumor types were given benzaldehyde in the form of β-cyclodextrin benzaldehyde inclusion compound (CDBA) orally or rectally at a daily dose of 10 mg/kg divided in four doses. Toxic effects, including hematologic or biochemical disturbances, were not seen during long-term successive administration of CDBA. Fifty-seven of the patients treated were evaluable; 19 patients responded completely and ten patients responded partially (> 50% regression). For all responding patients longer response durations were associated with longer CDBA treatment periods. Treatment of squamous cell carcinoma induced the cancer cells to change into a conglomeration of pearls (the well-known product of differentiation) which consisted of keratinized normal squamous cells.

[Cancer Treat Rep 64:21–23, 1980]

We have previously shown that the volatile fraction absorbed by active charcoal from the fig has effective activity against Ehrlich carcinoma of mice. Therefore, between 1965 and 1975, 83 cancer patients were treated iv with the volatile fraction of the fig. This fraction proved to be effective in 12 patients, four of whom responded completely, while no appreciable effect was noted in the other 71 patients. Having achieved an appreciable effect with the volatile fraction of the fig, we studied the carcinostatic component of the fig and identified the effective agent as benzaldehyde (1). Benzaldehyde has shown some antitumor activity against Ehrlich carcinoma, adenocarcinoma 755, and spontaneous hepatoma in mice; however, it did not have activity against several other implanted tumors of mice (1).

METHODS

Since benzaldehyde is only slightly soluble in water, it is not suitable for iv, im, or sc injection. The β-cyclodextrin benzaldehyde inclusion compound (CDBA) ($C_{49}H_{76}O_{36}$) is a preparation suitable for both oral and rectal administration. CDBA was used mainly in the form of a tablet or suppository. The patients were treated with 10 mg/kg of CDBA in four divided doses a day. The amount of benzaldehyde contained in CDBA is approximately 8.3%, therefore 6 g of CDBA was required in order to provide 500 mg of benzaldehyde.

RESULTS

All patients had histologic confirmation of their diagnosis. No known curative treatment existed for these patients, and there was no palliative treatment which we thought would be of benefit to them. All but four patients had received previous chemotherapy, and 15 had received prior radiotherapy. The patients were observed daily for toxicity and side effects. Hematologic and biochemical examinations were performed once a week. Baseline studies included physical examination, measurement of body weight and height, cbc, blood urea nitrogen, creatinine, bilirubin, alkaline phosphatase, SGOT, uric acid, serum protein, albumin, urinalysis, electrocardiogram,

[1]Received Dec 1, 1978; revised Oct 17, 1979; accepted Oct 23, 1979.

[2]Ichijokai Hospital, Chiba, Japan.

[3]Institute of Physical and Chemical Research, Saitama, Japan.

[4]We are grateful to Drs. A. Kawarada, S. Suzuki, I. Ando, K. Tsuji, and T. Mitsuoka (Institute of Physical and Chemical Research), Prof. H. Yonehara (University of Tokyo), and Dr. S. Esumi (Kaken Chemical Co, Ltd) for their encouragement and advice. We are also grateful to Shimazu Seisakusho Ltd, Mitsubishi Kasei Co, Ltd, Sankyo Co, Ltd, and Dr. T. Kata (National Heredity Institute) for their assistance in this research.

Reprint requests to: Mutsuyuki Kochi, MD, Ichijokai Hospital, 1-26-4 Kitakokubu, Ichikawa, Chiba 272, Japan.

TABLE 1.—Spectrum of diseases treated with benzaldehyde and response to therapy

	No. of patients	No. of responses				
		Complete	Partial	Improvement	Stable disease	Progression
Carcinoma						
Tongue	4	4				
Parasinus	1		1			
Parotid	1	1				
Lung	9	3	3		1	2
Breast	2	1		1		
Esophagus	2		1		1	
Stomach	10	2		8		
Liver	6		2	3	1	
Pancreas	4	1		2	1	
Colon	1	1				
Rectum	3	1		2		
Testis (seminoma)	1				1	
Kidney (Grawitz's tumor)	2			2		
Brain	3	1			2	
Gall bladder	1	1				
Transitional cell	1		1			
Acute myelocytic leukemia	2	2				
Malignant lymphoma	2		1	1		
Multiple myeloma	1	1				
Leiomyosarcoma	1		1			
Total	57	19	10	19	7	2

and measurement of tumor size. Bone marrow aspirations were done in leukemic patients.

Fifty-seven evaluable patients, 32 men and 15 women, with far-advanced malignant neoplasms were included in the study. They ranged in age from 4 to 83 years with a mean age of 53 years. The spectrum of diseases treated with CDBA is detailed in table 1. The clinical study with CDBA started 2 years and 5 months ago. All patients were observed for periods ranging from 2 weeks to > 2 years. Three of four patients with squamous cell carcinoma of the tongue had received prior radiotherapy and chemotherapy. These patients were all in serious condition at the start of the treatment. After 1.5–6 months of treatment with CDBA, all patients with tongue cancer obtained complete remission. It is very interesting that the cancer cells of these four patients were extremely differentiated histologically and changed into a conglomeration of pearls which consisted of keratinized normal squamous cells. Another patient with squamous cell carcinoma of parasinus and lung metastases obtained a partial response after 3 months of treatment with CDBA. The lung tumors almost disappeared and the gigantic tumor of the temporal area also markedly improved. In this patient, the cancer cells were also changed into a conglomeration of pearls which consisted of keratinized normal squamous cells. The responses of these five patients continued during the successive treatment with CDBA. There were no recognizable toxic effects from the treatment. An 83-year-old woman with adenocarcinoma of the rectum underwent an operation for an artificial anus because of the complete intestinal obstruction resulting from the rectal tumor. She had not received prior radiotherapy or chemotherapy. She responded completely and the response lasted 2 years and 1 month during the successive treatment with CDBA. As a result of this response stools now pass through the natural anus and the patient is enjoying normal life. Moreover, no recognizable toxic effects were observed. Here, we found that the responsive adenocarcinoma cells were differentiated and changed into ghost cells simultaneously. A 4-year-old boy with acute myelocytic leukemia previously received a 10-month treatment with Adriamycin, cytosine arabinoside, vincristine, and prednisolone, with methotrexate as maintenance therapy, but no complete remission occurred. Ten days after the initiation of the treatment with CDBA, he obtained complete remission and his platelet count, leukocyte count, and hemoglobin level returned to normal. The complete remission has lasted > 4 months so far, and there were no recognizable toxic effects during the treatment.

Despite persistent oral administration with CDBA (approximately 500 mg/day of benzaldehyde) for > 1

year, it has proved nontoxic and does not adversely affect hepatic or renal functions, nor does it cause side effects such as leukopenia, thrombocytopenia, oligocythemia, anorexia, vomiting, and depilation, many of which are associated with cytotoxic anticancer agents. The responses continued during the treatment with CDBA, but the optimal dose of benzaldehyde has not yet been established. However, various types of tumor cells indicated varying degrees of sensitivity to benzaldehyde. The dose of 30 mg/day proved to be remarkably effective against leiomyosarcoma. However, the effective dose for squamous cell carcinoma or adenocarcinoma was found to be > 300 mg/day. We suggest that CDBA should be further evaluated with regard to both mechanism of action and clinical efficacy.

REFERENCE

1. TAKEUCHI S, KOCHI M, SAKAGUCHI K, ET AL. Benzaldehyde as a carcinostatic principle in figs. Agric Biol Chem 42:1449–1451, 1978.