Clinical Evaluation of Total-Body Hyperthermia Combined With Anticancer Chemotherapy for Far-Advanced Miscellaneous Cancer in Japan

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One hundred sixty-eight patients with miscellaneous far-advanced cancer received a total of 444 extracorporeally induced total-body hyperthermia (TBHT) treatments in seven Japanese hospitals. Overall, a regression of malignancy was observed in 39 of 132 evaluable patients (29.5%) and the most favorable results were obtained for patients with lung cancer. Irrespective of whether the tumors were primary or secondary lesions or recurrences, favorable results were obtained in patients whose tumors were in the lung, liver, lymph nodes, and soft tissue. No relationship was found between an objective response to TBHT and histologic types of the tumors. There was no clear relationship between an objective tumor response and the nature of the simultaneous chemotherapy during hyperthermia. Antitumor effects were not evaluable in 36 patients (21.4%). Of these 36 patients, 33 died before evaluation could be made; 24 died of various complications and 9 died of cachexia without complication. The mortality increased in proportion to the reduction of the performance status of patients before TBHT. These results indicate that TBHT should be used as therapy for patients whose tumors are in the lung, liver, lymph node, and soft tissue and then only on patients in generally good condition.

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ALTHOUGH THE MECHANISM underlying the antitumor effects of hyperthermia on heat-sensitive malignant cells remains obscure, it is now generally accepted that the heat induced must be at least 41.5°C to achieve cancer regression.[1,2] Clinical hyperthermic treatment can be applied as either local or total-body hyperthermia (TBHT). Although local hyperthermia involves minor invasion to patients, it is difficult to apply the optimal temperature to extensive tumors by this technique. We have reported[3] the effectiveness of TBHT using an extracorporeal circuit[4] in 17 patients with far-advanced gastrointestinal cancer. We now evaluate 168 patients with far-advanced miscellaneous cancer, including these 17 patients who received TBHT. We describe the therapeutic results of TBHT treatment and some problems that occurred.

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Patients and Methods

Patients

A total of 444 TBHT treatments were administered to 168 patients with far-advanced miscellaneous cancers in seven Japanese hospitals between April 1980 and May 1985. Of these patients, 148 (88.1%) had had unsuccessful chemotherapy and/or radiation therapy. As shown in Table 1, 56 of these patients (33.3%) had primary tumors and 112 (66.7%) had secondary metastatic or recurrent tumors after surgical resection of the primary tumor. The patients' characteristics (sex, age, performance status by Karnofsky's classification[5]) are shown in Table 2. The majority of patients was in generally poor condition and 55 patients (32.7%) had been receiving continuous intravenous hyperalimentation because of poor nutritional status at the time of initiation of TBHT treatment.

Extracorporeally Induced TBHT

Under general anesthesia by controlled respiration *via* an endotracheal tube, TBHT was induced using an ex-

TABLE 1. Number of Patients Treated With Total-Body Hyperthermia

Malignancies	Primary cases	Secondary cases	Total (%)
Gastric cancer	12	32	44 (26.1)
Large bowel cancer	3	28	31 (18.5)
Lung cancer	17	9	26 (15.5)
Breast cancer	1	13	14 (8.3)
Pancreatic cancer	5	2	7 (4.2)
Renal cancer		5	5 (3.0)
Malignant melanoma	1	4	5 (3.0)
Liver cancer	5		5 (3.0)
Uterine cancer	2	2	4 (2.4)
Malignant lymphoma		3	3 (1.8)
Pharyngeal cancer	2	1	3 (1.8)
Testicular cancer	1	2	3 (1.8)
Esophageal cancer	1	1	2 (1.2)
Bladder cancer	1	1	2 (1.2)
Ovarian cancer		2	2 (1.2)
Thyroid cancer	1	1	2 (1.2)
Choledochal cancer	1	1	2 (1.2)
Osteosarcoma		2	2 (1.2)
Others*	3	3	6 (3.6)

* Prostatic, parotid, and origin-unclear metastatic cancer, neuroblastoma, colon sarcoma, and mediastinal tumor: 1 case each.

tracorporeal circuit (ECC) that incorporated a heat exchanger, according to the method of Parks *et al.*[4] The patient's temperature was monitored continuously by thermister probes in the esophagus and rectum. The inguinal arterial and venous (A-V) shunts were connected to the limbs of the ECC. The arterial limb of the ECC was led through a roller pump set to maintain the flow through the ECC at 1000 to 1500 ml/minute. The initial temperature of the heat exchanger was set between 46°C and 48°C; the temperature of the blood was between 44°C and 45°C.

When the patient's rectal temperature reached 41.5°C, the temperature of the heat exchanger was reduced to between 44°C and 45°C: the blood flow was decreased to 500 to 600 ml/minute; and the rectal temperature was maintained between 41.5°C and 42°C for 2 to 7 hours, depending on patient's condition. We hoped to administer this TBHT treatment at least four times to each patient at intervals of 7 to 20 days, according to the patient's general condition. However, because they represented poor risks, some of patients received TBHT only once. Almost all the patients received some type of chemotherapeutic treatment, dependent on the regimen of each hospital, during the course of hyperthermic treatments.

TABLE 2. Characteristics of All Patients Treated With Total-body Hyperthermia

Sex	
Male	109 (64.9%)
Female	59 (35.1%)
Age (yr)	
-29	8 (4.8%)
30-49	56 (33.3%)
50-69	94 (55.9%)
70-	10 (6.0%)
Performance status (Karnofsky scale)	
100%-71%	30 (17.9%)
70%-51%	39 (23.2%)
50%-31%	50 (29.8%)
30%-20%	49 (29.2%)
Previous treatment	
C + R	43 (25.6%)
C	100 (59.5%)
R	5 (3.0%)
None	20 (11.9%)

C: chemotherapy; R: radiotherapy.

Definition of Response

Response was evaluated as follows: complete response (CR); complete regression of all recognizable disease for at least 4 weeks; partial response (PR); 50% to 99% decrease in the sum of the products of the two longest dimensions of all lesions for at least 4 weeks; minor response (MR); 25% to 49% regression in these parameters for at least 4 weeks; no change (NC); less than 25% decrease or increase in these parameters; and progressive disease (PD), greater than 25% increase in the parameters or the appearance of new lesions. The assessment was made collectively by palpation, computerized axial tomography, gallium scintigram and x-ray. Although 14 of 21 patients, whose dominant metastatic disease was located in the peritoneum (peritoneal dissemination), had measurable lesions by palpation, computerized axial tomography and gallim scintigram, seven had no measurable lesion. They were excluded from evaluation of the objective response.

Results

A total of 444 hyperthermic treatments were administered to 168 patients; the mean number of treatments was 2.64 (range, 1–8) and the mean maintenance time of temperature (41.5–42°C; rectal temperature) was 11.4 hours (range, 2–44 hours) per patient.

Antitumor Effects

As shown in Table 3, we could not evaluate any antitumor effects in 36 of 168 patients (21.4%). Three of 36 patients had no measurable disease and 33 had died before the evaluation was made. Twenty-four of 33 patients died of complications that resulted from TBHT. Another cause of death was rapid deterioration in general condition (cachexia) after the first treatment; nine patients died before an evaluation could be made, without any evidence of

TABLE 3. Nonevaluable Patients

Performance status Karnofsky scale (no. of treated patients)	No. of nonevaluable patients	Causes		
		Death due to treatment complications	Death due to cachexia after the first treatment	No evaluable or measurable lesions
100%–71% (30)	5 (16.7%)	2		3
70%–51% (39)	3 (7.7%)	3		
50%–31% (50)	8 (16.0%)	8		
30%–20% (49)	20 (40.8%)	11	9	
Total (168)	36 (21.4%)	24 (14.3%)	9 (5.4%)	3 (1.8%)

obvious complications. The incidence of these deaths from TBHT treatment increased with reduced pretreatment performance status (Table 3).

As shown in Table 4, the antitumor effects of TBHT on malignancy were evaluated in 132 patients. Overall, a regression of malignancy was found in 39 of 132 patients (29.5%). There were 2 (1.5%) CRs, 30 (22.7%) PRs, and 7 (5.3%) MRs. The most favorable result was obtained in patients with lung cancer.

Table 5 shows the anticancer effects of TBHT analyzed with respect to the site where the major malignant lesions exist, irrespective of whether these are primary or secondary lesions. A positive response to TBHT was observed in tumors situated in the lung, liver, lymph nodes, and soft tissue, but there was a poor response by tumors in the peritoneum (peritoneal dissemination), bone, stomach, pancreas, and large bowel. As shown in Table 6 there were no differences in the responses of tumors categorized by their histologic patterns.

Patients undergoing TBHT were simultaneously receiving a variety of chemotherapeutic drugs, the exact nature of the regimen being determined by each hospital. There was no clear relationship between an objective tumor response and the nature of the simultaneous chemotherapy as shown in Table 7. A slight favorable response to TBHT was observed when cis-diamminedichloroplatinum (II) (CDDP) (30–60 mg/m^2 per treatment) was administered alone or as the main drug in multiple combination chemotherapy than when Adriamycin (doxorubicin) and/or mitomycin C were employed. Although it was a small number of patients, one of two patients who received carbazilquinone or bleomycin

TABLE 4. Effects of Total-Body Hyperthermia on Malignancy

Malignancies	No. of evaluable patients	Antitumor effects (%)				
		CR	PR	MR	NC	PD
Gastric cancer	30		5 (16.7)		15 (50.0)	10 (33.3)
Large bowel cancer	29		5 (17.2)	1 (3.4)	13 (44.8)	10 (34.5)
Lung cancer	22	1 (4.5)	7 (31.9)	2 (9.1)	7 (31.8)	5 (22.7)
Breast cancer	10		2 (20.0)	2 (20.0)	6 (60.0)	
Pancreatic cancer	6				5 (83.3)	1 (16.7)
Renal cancer	4		1 (25.0)		1 (25.0)	2 (50.0)
Malignant melanoma	4		1 (25.0)		2 (50.0)	1 (25.0)
Liver cancer	3		2 (66.7)		1 (33.3)	
Uterine cancer	4			1 (25.0)	3 (75.0)	
Malignant lymphoma	2	1 (50.0)	1 (50.0)			
Pharyngeal cancer	2				1 (50.0)	1 (50.0)
Testicular cancer	2		2 (100.0)			
Esophageal cancer	1		1 (100.0)			
Bladder cancer	1			1 (100.0)		
Ovarian cancer	2				1 (50.0)	1 (50.0)
Thyroid cancer	1		1 (100.0)			
Choledochal cancer	2				1 (50.0)	1 (50.0)
Osteosarcoma	2		1 (50.0)		1 (50.0)	
Others*	5		1 (20.0)		1 (20.0)	3 (60.0)
Total	132	2 (1.5)	30 (22.7)	7 (5.3)	58 (43.9)	35 (26.5)
			39 (29.5)			

CR: complete response; PR: partial response; MR: minor response; NC: no change; PD: progressive disease.

* See Table 1.

TABLE 5. Antitumor Effects Analyzed by Site of Malignancy

Cancer site	No. of evaluable patients	Antitumor effects (%)			
		CR	PR	MR	NC, PD
Lung	41	1 (2.4)	12 (29.3)	1 (2.4)	27 (65.9)
Liver	21		8 (38.1)	1 (4.8)	12 (57.1)
Lymph nodes	15	1 (6.7)	3 (20.0)	2 (13.3)	9 (60.0)
Soft tissue	14		4 (28.6)	3 (21.4)	7 (50.0)
Peritoneum	14		1 (7.1)		13 (92.9)
Bone	9		1 (11.1)		8 (88.9)
Stomach	8		1 (12.5)		7 (87.5)
Pancreas	6				6 (100.0)
Large bowel	4				4 (100.0)

showed PR. Furthermore, we were unable to elucidate the effect of the timing of the administration of the drugs on the antitumor response. When TBHT was performed without combined chemotherapy, no PR was obtained, and MR was found in only two of six patients.

In all our patients there was a relationship between the response of the tumors and the pretreatment performance status of the patient. An objective response was found in only 3 of 29 evaluable patients (10.3%) whose pretreatment performance status (Karnofsky's criteria) had been less than 30%. On the other hand, an objective response was obtained in 36 of 103 evaluable patients (35.0%) whose performance was 31% or more. The number of hyperthermic treatments also was closely related to the patients' pretreatment performance status. Ninety patients received one or two TBHT treatments and 78 patients received TBHT more than three times. An objective response was observed in 13 of 55 evaluable patients (23.6%) who received one or two treatments and 26 of 77 evaluable patients (33.8%) who received more than three treatments.

An analysis of the tumor response with respect to the presence or absence of previous treatment before TBHT (Table 2) shows that 148 patients had received chemotherapy, chemotherapy combined with radiotherapy or radiotherapy alone. In these patients an objective response was obtained in 32 of 115 evaluable patients (27.8%). Whereas, in 20 patients who had received no previous treatment, an objective response was observed in 7 of 17 evaluable patients (41.2%). One-year survival rates for patients with tumor regression (CR, PR, MR), NC, and with PD were 36.4%, 17.3%, and 0%, respectively.

Complications

Table 8 shows complications due to TBHT. The incidence of complications and the mortality increased in proportion to the reduction of the performance status of patients before TBHT. Six patients died of lung complications (lung edema in four and pneumonia in two) and six died of hepatic insufficiency. All six patients who died of hepatic insufficiency had manifested obstructive jaundice before TBHT. Five patients died of bleeding from cancer (gastric cancer in two cases; lung cancer, breast cancer, and liver cancer in one case each) and three patients died of massive bleeding from other sites (intratracheal, intra-abdominal, and superior mesenteric aneurysmal bleeding in one case each). Two patients died of cardiovascular shock, and one each died of renal insufficiency and femoral wound infection (sepsis). None of the patients with manifested neurotoxicity died.

TABLE 6. Histologic Pattern and Antitumor Effects

Histologic pattern	No. of evaluable patients	Antitumor effects (%)			
		CR	PR	MR	NC, PD
Epithelial tumor					
Adenocarcinoma	94	1 (1.1)	16 (17.0)	6 (6.4)	71 (75.5)
Squamous cell carc	11		3 (27.3)		8 (72.7)
Small cell carc	3		2 (66.7)		1 (33.3)
Hepatocellular carc	3		2 (66.7)		1 (33.3)
Clear cell carc	4		1 (25.0)		3 (75.0)
Germinal cell carc	2		2 (100.0)		
Subtotal	117	1 (0.9)	26 (22.2)	6 (5.1)	84 (71.8)
Nonepithelial tumor					
Malignant melanoma	4		1 (25.0)		3 (75.0)
Leiomyosarcoma	2				2 (100.0)
Osteogenic osteosarcoma	2		1 (50.0)		1 (50.0)
Malignant lymphoma	2	1 (50.0)	1 (50.0)		
Liposarcoma	1				1 (100.0)
Neuroblastoma	1				1 (100.0)
Subtotal	12	1 (8.3)	3 (25.0)		8 (66.7)
Unknown	3		1 (33.3)	1 (33.3)	1 (33.3)

CR: complete response; PR: partial response; MR: minor response; NC: no change; PD: progressive disease; carc: carcinoma.

TABLE 7. Combined Anticancer Chemotherapy and Antitumor Effects

Drugs	No. of evaluable patients	Antitumor effects (%)			
		CR	PR	MR	NC, PD
CDDP	63	1 (1.6)	17 (27.0)	4 (6.3)	41 (65.1)
Adriamycin (doxorubicin)	32	1 (3.1)	6 (18.8)		25 (78.1)
Mitomycin C	23		5 (21.7)	1 (4.3)	17 (73.9)
ACNU	4				4 (100.0)
Carbazilquinone	2		1 (50.0)		1 (50.0)
Bleomycin	2		1 (50.0)		1 (50.0)
None	6			2 (33.3)	4 (66.7)

CDDP: cis-diamminedichloroplatinum (II); ACNU: nimustin hydrochloride; CR: complete response; PR: partial response; MR: minor response; NC: no change; PD: progressive disease.

Discussion

Recent progress in experimental studies on hyperthermia and improvements in the heating method have led to the introduction of hyperthermic therapy. Since far-advanced cancer shows extended infiltration into neighboring organs and/or metastasis to other organs, induction of TBHT appears to be a reasonable treatment. We evaluated the results of TBHT performed in 168 patients with far-advanced cancer in seven Japanese hospitals.

Although several methods[4,6–8] for the induction of TBHT have been reported, in this series all patients were treated by the method of Parks *et al.*[4] which employs an ECC that incorporates a heat exchanger. This method facilitates the rapid heat induction and provides accurate temperature control.

In our study of the antitumor effects of TBHT, we found an overall response rate (CR, PR, MR) of 29.5% from a total of 132 evaluable patients (Table 4). Although this response rate is far from satisfactory, if we consider that almost all patients in this series had been unsuccessfully treated by other methods and were in the terminal stage of their disease, this result is encouraging as a multimodal cancer treatment.

It is very interesting to note that, in our series, favorable antitumor effects were obtained exclusively in patients whose dominant tumors were in the lung, liver, lymph nodes, and soft tissue. Poor results were observed in pa-

TABLE 8. Complications Due to Total-Body Hyperthermia

Complication	Pretreatment performance status Karnofsky scale (no. of treated patients)				Total no. of patients
	100%–71% (30)	70%–51% (39)	50%–31% (50)	30%–20% (49)	
Pulmonary complication	2 (1)	1 (1)	3 (1)	5 (3)	11 (6)*
Hepatic insufficiency			3 (2)	5 (4)	8 (6)
Hemorrhage in cancer site					
Gastric cancer			2 (1)	1 (1)	3 (2)
Liver cancer			1 (1)		1 (1)
Lung cancer				1 (1)	1 (1)
Breast cancer		1 (1)			1 (1)
Hemorrhage in another site					
Trachea	1 (0)		1 (1)		2 (1)
Intra-abdominal				1 (1)	1 (1)
Ruptured aneurysma			1 (1)		1 (1)
Gastrointestinal		2 (0)	2 (0)	1 (0)	5 (0)
Cardiovascular shock		1 (1)	1 (1)	1 (0)	3 (2)
Renal insufficiency	1 (0)		1 (0)	2 (1)	4 (1)
Local infection (sepsis)	1 (1)		2 (0)		3 (1)
Neurotoxicity					
Foot drop	3 (0)	2 (0)	2 (0)	3 (0)	10 (0)
Hallucinations		2 (0)	3 (0)	1 (0)	6 (0)
Ataxia	2 (0)	3 (0)		1 (0)	7 (0)

* No. of deaths in parentheses.

tients with dominant tumors in the peritoneum, bone, stomach, pancreas, and large bowel (Table 5). Although we are unable to explain the reason for this difference, this result may be important and useful, hereafter, for evaluation of patients as possible candidates for treatment by TBHT.

To augment the antitumor effects of TBHT, the simultaneous use of antitumor drugs during hyperthermia is indispensable. A minor response was observed in only two of six patients when TBHT was performed without accompanying chemotherapy (Table 7). Which chemotherapeutic agent is most valid? Experimentally, both *in vitro* and *in vivo,* an augmented antitumor effect has been observed when hyperthermia has been combined with a number of chemotherapeutic agents.[9-12] Although a slight favorable response was observed when CDDP[13] was administered during hyperthermia in this series, there was no clear relationship between an objective tumor response and the nature of the simultaneous chemotherapy.

Thirty-three of 168 patients (19.6%) died of complications or of cachexia without complications after relative short periods of TBHT. Furthermore, 20 of 33 patients who died had poor performance status of less than 30%, by Karnofsky's classification,[5] before TBHT (Table 3). These results suggest that we should reconsider the bases for selection of patients for treatment with TBHT and that we should pay greater attention to the possible development of fatal complications.

Treatment by TBHT involves several unfavorable aspects, such as high cost; high incidence of fatal complications as well as nonfatal neurologic or muscle toxicity;[3,4] relatively low 1-year survival rates, even in patients with tumor regression; a decrease in host-immunocompetence;[14,15] and an increased possibility of enhanced distant metastases, as observed in an experiment[16] with an animal model. However, we can anticipate some useful antitumor effects from TBHT in hopeless patients with terminal cancer, who have received unsuccessful prior treatment, when TBHT is the multimodal cancer therapy of last resort. Further efforts are necessary to increase the safety of TBHT and to minimize complications, as well as to augment its antitumor effects. Total-body hyperthermia should not be performed on patients in poor condition and with obstructive jaundice. Full attention should be paid for an A-V shunt flow volume because an excessive flow rate causes the development of lung edema even in patients in good general condition. Total-body hyperthermia should be performed more than three times for patients whose dominant tumors are in the lung, liver, lymph nodes, and soft tissue, irrespective of whether the tumors are primary or secondary.

Ideally, in the future, the selection of patients for treatment of TBHT combined with anticancer drugs should be decided by the results of thermosensitivity and thermochemosensitivity assay, performed on the cancer cells of each patient. Such assays for sensitivity to hyperthermia have been reported already using xenografts of human tumors in nude mice[17] and by a human tumor stem cell assay.[18] Further efforts are necessary to introduce assays for sensitivity into the clinical applications of TBHT.

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