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A Clinical Investigation of Total-Body Hyperthermia as Cancer Therapy[1]

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Abstract

Seventy-seven patients have been treated with total-body hyperthermia to 42°C alone or in combination with chemotherapy, radiation, or immunotherapy in a preliminary investigation of this modality. Most had advanced cancers progressing despite other antineoplastic therapy. An overall objective response rate of 43% was obtained, with an additional 15% achieving good subjective palliation. Results did not differ significantly for hyperthermia alone or combined with another modality, but the trend favored combination therapy. Mortality and morbidity were acceptable and not significantly increased by adding chemotherapy or radiation to the regimen. These results are preliminary and need confirmation by further controlled studies.

Introduction

Interest in thermotherapy for cancers began almost 100 years ago with Coley and pyrogenic vaccines (13, 19). There have been extensive *in vitro* and *in vivo* experimental data confirming the selective lethal effects of heat within the range of 41–43°C (106–110°F) on neoplastic cells while normal cells were spared (2, 11, 12, 18, 22). While the exact mechanism of thermal injury has not yet been identified, additional experimental work has shown a synergistic cytotoxic effect when heat is combined with radiation (1, 5, 6, 17, 19) and chemotherapy (4, 23, 25). Recent technological advances have allowed the clinical application of thermotherapy to human neoplasms in 3 basic forms: (*a*) local heating of an accessible neoplasm as by microwaves or ultrasound (7, 8); (*b*) regional perfusion as of a limb (3, 20, 21); or (*c*) whole-body heating by surface (9, 10, 15, 16, 24) or extracorporeal means. This report will document the results observed with one method of whole-body heating by surface conduction.

Materials and Methods

During the past 4 years, 77 patients with various primary cancers were treated by a method described previously (10). Briefly, core body temperature is elevated to 108°F (42°C) under light, general anesthesia using a modified water blanket set at 120°F (49°C) and held there for 2 or more hr. Vital signs, core temperature, electrocardiography, and urine output are carefully monitored, and fluid and electrolyte losses are replaced. Patients are recovered overnight in an intensive care unit, and biochemical and hematological parameters are monitored daily for the first few days.

All patients treated had histological confirmation of cancer, and most had advanced lesions refractory to surgery, chemotherapy, radiation therapy, or immunotherapy. Patients were evaluated with routine staging procedures to detect lesions suitable for repeated measurements to determine response to thermotherapy; however, patients were not excluded for this reason. In addition, 5 patients were treated prophylactically after curative resections of lesions with high likelihood of recurrence. The physiological status of patients was also determined with particular attention to cardiac and liver function because significant impairment of these organs is a relative contraindication to whole-body hyperthermia. In addition, patients with short expected survival are now excluded.

Hyperthermia alone was utilized in the early part of this series. Subsequently, other treatment modalities, such as chemotherapy, radiotherapy, and immunotherapy, have been combined with heat to determine if a synergistic effect could be demonstrated by a greater response rate. In addition, the question of whether such combination therapy could be tolerated or if significant toxicity would result was investigated.

Results

Data generated from the analysis of the records of 77 patients who underwent 170 separate treatments (range, 1 to 8 treatments) spending 580 hr at core body temperatures of 41.5°C (107°F) or greater form the basis for this report. Physiological and biochemical changes resulting from this method of total-body hyperthermia have been previously reported (10). Briefly, pulse rates rose while blood pressure usually varied little. Fluid replacement averaged about 840 ml/hr, whereas measured urine outputs during treatment averaged 115 ml/hr. Mild metabolic acidosis, dilutional hyponatrenia, hypokalemia, and lowered levels of calcium, magnesium, and phosphate were the main metabolic changes observed. Leukocytosis and a drop in platelet counts with transient prolongation of coagulation parameters suggestive of mild disseminated intravascular coagulation (DIC) were the hematological changes seen. Major organ damage was reflected in elevation of serum glutamic-oxaloacetic transaminase and lactate dehydrogenase indicating mild liver necrosis, although no evidence of central nervous system, renal, or pulmonary dysfunction was seen. Skeletal muscle necrosis was reflected in modest elevations of creatine phosphokinase.

Seventy-seven patients with 78 tumors from 16 different primary sites were treated (Table 1). Most had advanced cancers with large tumor burdens progressing after previous surgery, radiation, chemotherapy, or immunotherapy. Five patients at high risk for recurrence were treated prophylactically after resection of gross disease. Most patients had a measurable lesion or biochemical marker available for objective evaluation; however, 2 with known residual tumors did not. Recently, other therapeutic modalities such as chemotherapy and

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radiation therapy were given in combination with hyperthermia to determine the tolerance, toxicity, and effectiveness of such combinations. Four patients were treated with more than one regimen. Overall, the objective response rate in the 72 evaluable patients was 43% with an additional 15% achieving good subjective palliation, mainly pain relief. Only 4 patients had a complete regression of measurable tumor; the remainder achieved partial regression. Of the 5 patients treated prophylactically, 2 have developed recurrent cancer at 1 and 2 years after treatment while the others remain free of disease from 1 to 3 years after treatment. Forty-one % failed to respond favorably to systemic thermotherapy. There was no significant difference in response rates between those receiving hyperthermia alone or those in which heat was combined with chemotherapy or radiation, but the trend favored the combination therapy groups (Table 2). More importantly, analysis of the biochemical and hematological data revealed no significant increase in toxicity in the thermochemotherapy group. The drugs investigated were 5-fluorouracil (9 mg/kg), cytoxan (200 mg/sq m), and DTIC (200 mg/sq m) in adenocarcinomas, bronchogenic carcinomas, and melanomas, respectively. The combined hyperthermia-radiation group was small (4 patients), but only one-half of the patients completed the proposed protocol, perhaps indicating the rigorousness of this combination. Patients treated with combined radiation and hyperthermia were to receive daily radiation (150 to 200 rads) and have total-body hyperthermia immediately following the midweek treatment for a minimum of 4 weeks.

Mortality and morbidity for this technique have been reported previously and will only be summarized briefly here (10). No deaths occurred during treatment; however, there were 5 deaths attributable to the procedure, most of which should be avoidable by proper patient selection and appropriate monitoring and life support measures. Complications, such as blistering of the skin, pulmonary edema, peroneal nerve palsy, and seizures occurred and are also avoidable. Other side effects or complications such as cardiac arrhythmias, circumoral herpes, fatigue, and diarrhea appear to be unavoidable sequelae of the procedure described.

Table 1

Results achieved with hyperthermia

Primary site	No.	Response		
		Objective	Subjective	None
Lung	22	6	4	8
Melanoma	13	8		5
Kidney	7	1		6
Colon	8	3	1	3
Prostate	5	2	1	2
Stomach	4	1	2	1
Soft-tissue sarcoma	4	2		2
Hematological	4	4		
Breast	2	1	1	
Pancreas	2		1	1
Osteosarcoma	2		1	1
Ovary	1			
Small intestine	1			
Thyroid	1	1		
Head and Neck	1	1		
Multiple myeloma	1	1		
Total	78	31	11	29

Table 2

Response rates of treatment with total body hyperthermia alone or in combination

	No. of patients	No. responding	% response
TBH[a] alone	42	22	52
TBH and drugs	29	17	59
TBH and X-ray	4	2	50
TBH and immunotherapy	6	4	67

[a] TBH, total-body hyperthermia.

Discussion

While many laboratory data exist to confirm the efficacy of heat in the range of 41–43°C (106–110°F) to destroy selectively cancer cells while sparing normal cells, few clinical series have tried to confirm or exploit this apparent difference in thermal sensitivity. Stehlin *et al.* (20, 21), Pettigrew *et al.* (15, 16), and others (7–9, 24) have recently used forms of thermotherapy in clinical subjects with success. The present series also demonstrates the beneficial effect of thermotherapy on subjects with advanced cancers refractory to other modalities. While the results observed were transient partial regressions of measurable tumors in most instances, there were some complete remissions usually in patients with small tumor burdens. Dramatic pain relief was also observed in several patients. The technique developed has proven to be effective in achieving the necessary core temperature of 42°C (108°F) and has shown to be safe for properly selected and monitored patients. Patients with significant cardiac or liver disease are high-risk subjects for total-body hyperthermia (10). Also the synergistic advantage demonstrated experimentally of combining radiation or chemotherapy with hyperthermia was supported by the preliminary results observed thus far without any great increase in toxicity or decrease in patient tolerance. More subjects need to be studied under the combined hyperthermia-radiation protocol to verify this combination as clinically feasible.

While the results utilizing heat as antineoplastic therapy reported thus far have been largely uncontrolled and tumor regression has usually been partial and transient, beneficial results in a significant percentage of patients are encouraging. Furthermore, most of the patients treated had solid neoplasms which are most refractory to chemotherapy and were far advanced or progressing despite previous application of the various therapeutic modalities. The most important aspect of studies completed to date has been the development of techniques to apply heat in the effective range to patients with acceptable mortality and morbidity. Further refinements in techniques of applying hyperthermia could simplify the procedure and eliminate the need for general anesthesia in most, if

not all, subjects. Preliminary work, such as that reported here, suggests the safety of combining such modalities as radiation, chemotherapy, and immunotherapy with thermotherapy to achieve enhanced cytotoxic effects. The need to confirm these preliminary data in controlled studies is obvious.

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