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Whole-body Hyperthermia in Cancer Therapy: a Report of a Phase I–II Study*

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Abstract—*Twenty-seven patients were treated with whole-body hyperthermia alone or in combination with either chemotherapy or radiotherapy. Whole-body hyperthermia was performed in the Pomp–Siemens cabin with hot air and a warm water mattress, the patient being covered with plastic film to avoid cooling by perspiration. The heat treatment lasted for* 2 hr *at* 41.8–42.0°C. *Toxicity, such as liver damage and respiratory problems, was considerable. There were two fatalities. Hyperthermia gave an improved therapeutic effect in* 6 *of the patients. Considerable pain relief was observed in* 8 *of* 10 *patients. Whole-body hyperthermia at* 42°C *can be effective but the potential toxicity limits its use to those patients with severe complaints for whom no other palliative treatment is available.*

INTRODUCTION

HYPERTHERMIA in the range of 40–46°C has long been known as a cell-killing modality [1]. The effect of hyperthermic treatment depends on the height of the temperature and the duration of temperature increase [2]. It has been shown experimentally that hyperthermia *in vivo*, especially mild heat treatment (<43.5°C), selectively kills malignant cells [3] as a result of the poor physiological conditions in tumours [4]. In combination with radiotherapy, hyperthermia has an additional effect: the relatively radioresistant cells such as hypoxic cells, cells in S phase or cells in areas with a low interstitial pH [5–7] are especially heat-sensitive [7–10]. Besides the additional effect of hyperthermia, there is an enhancing influence on the effect of radiotherapy, the enhancement ratio dependent on temperature, treatment duration, time interval between the two modalities and tissue type [11–14]. In addition to a directly radiosensitizing action, the enhancing effects is due to inhibition of repair mechanisms in cells following sublethal or potentially lethal damage by radiotherapy [15–18]. It has been shown in experimental rodent tumour systems that a therapeutic gain can be obtained, when a tumour is not selectively heated, by giving the hyperthermia treatment a few hours after radiotherapy [12, 14, 19]. Hyperthermia also has additional and enhancing effects in the combination with chemotherapy, although different mechanisms play a role. These include an increase in the activation of the cytotoxic process, the inhibition of cellular repair processes and an increase in cell permability to the drug [20]. One of the problems in the clinical application of hyperthermia is the technique of inducing hyperthermia in tumour tissue. At the start of this investigation the only possibility for deep-seated tumours was to heat the patient's entire body. In the past, this was achieved by the injection of bacteria, bacterial toxins or mixtures of these or other pyrogenic materials. With this method, however, it was not possible to give controlled hyperthermia; neither the degree nor the duration of the temperature increase could be regulated and toxicity was considerable. This subject has been extensively reviewed by McKenzie *et al.* and Neumann *et al.* [21, 22].

Whole-body hyperthermia by means of external energy input was first applied by Lampert, as reported by Kirsch and Schmidt [23]. He found that the temperature should not exceed a maximum of 42°C to avoid cardiovascular failure. This maximum temperature is now generally

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accepted for long-duration whole-body hyperthermia treatment.

Whole-body hyperthermia can be induced by energy input via the surface of the patient, such as by using paraffin wax [24, 25], hot air and radiofrequency [26] or water perfused blankets or suits [27–30]. Another method of inducing hyperthermia is employed by Parks *et al.* [31], who warmed their patients by heating the blood circulating in an extracorporeal circuit. All of these authors have reported their experiences with these methods and the conclusion is that whole-body hyperthermia at a temperature of 42°C is feasible and that hyperthermia administered under these conditions can be effective.

The intention of the present study was to outline a technique for, and investigate, the benefits of the clinical application of whole-body hyperthermia.

Reports by other investigators [24, 29, 30] indicate that only a minimal benefit can be expected from whole-body hyperthermia alone. This was confirmed by the results of our early treatments and we therefore decided to treat succeeding patients, when possible, with the combination that seemed the most promising on the basis of animal experiments and preliminary clinical experience [25], i.e. hyperthermia and radiotherapy.

As the two treatment modalities were given with a time interval of at least 16 hr, there was no need for radiotherapy dose reduction; patients therefore received optimal radiotherapy in addition to hyperthermia.

MATERIALS AND METHODS

The 27 patients who were entered into this study were characterized by a poor prognosis and a good general condition.

Their ages ranged from 20 to 69 yr, with a mean

Table 1. *Patient characteristics*

Patient No., sex and age	Tumour histology	Previous therapy	Present therapy	No. of WBHT	Results
1 F 53	undiff., breast ca	S, R, C, H	HT*	2	progr.
			HT**+C(1)	1	NC
2 F 62	breast adeno ca	S, R, C, H	HT	1	NC
			HT+C(1)	1	NC
3 M 30	malign. melanoma	S, C	HT	1	NC
4 M 50	malign. melanoma	S, R, C	HT	3	NC
			HT+R(30)	–	NC
5 M 51	lung adeno ca	none	HT+R(49)	3	CR
6 M 42	lung adeno ca	none	HT+R(50)	2	CR
7 M 57	lung squam. cell ca	none	HT+R(46)	2	PR
8 F 54	rectal adeno ca	S, R, C	HT+R(20)	2	PR
9 F 52	breast adeno ca	S, R, C, H	HT	1	progr.
			HT+R(18)	–	CR
10 M 44	colon adeno ca	S, R	HT+R(19.5)	2	PR
			HT+C(2)	1	NC
11 M 62	pleural mesothelioma	none	HT+R(19.5)	1	CR
12 M 20	osteosarcoma	S, R, C	HT	1	NC
			HT+R(67)	–	NC
13 F 34	pharyng. adenocystous ca	R	HT+R(55–65)	1	CR
14 M 35	fibrosarcoma	none	HT+R(60)	1	PR
15 F 39	cervical squam. cell ca	R, C	HT+R(20)	2	NC
16 F 62	colon adeno ca	S, R	HT+C(2)	3	PR
17 M 51	lung adeno ca	none	HT+C(2)	1	NC
18 F 51	sinus adenocystous ca	S, R	HT+R(9)	1	NE (†)
19 M 44	leiomyosarcoma	S	HT**+R(20)	1	NE inop.–op.
20 F 56	colon adeno ca	S	HT+R(64.5)+C(2)	2	NC
21 M 51	pleural mesothelioma	none	HT+R(24)	1	progr.
22 M 57	rectal adeno ca	S, R, C	HT+R(15–20)	1	NC
23 M 38	leiomyosarcoma	S	HT+R(60)	2	NC
24 M 56	gastric adeno ca	S	HT+R(20)	1	NE inop.–op.
25 F 65	kidney adeno ca	S, R	HT+R(15–20)	2	NC
26 F 51	kidney adeno ca	S, R, H	HT+R(15)	1	NC
27 M 69	pleural mesothelioma	none	HT+R(2)	1	NE (†)

S = Surgery; R( ) = radiotherapy (dose in Gy); C( ) = chemotherapy (1 = melphalan, 25 mg; 2 = 5 fluorouracil, 10 mg/kg bodyweight); H = hormonal therapy; HT = hyperthermia; progr. = progression; NC = no change; PR = partial response; CR = complete response; NE = not evaluable; inop. = inoperable; op. = operable.
*40.5°C; **41.5°C.

of 49.5 yr. Previous case histories ranged from 1 month to 17 yr, with a mean of 28 months. For other patient characteristics see Table 1.

After verbal informed consent, an extensive pretreatment examination was conducted including heart and lung function tests and technetium 99^m liver and brain scanning. Patients with brain metastases and those with heart and liver function disturbances were excluded from this study. Treatment of those with diminished lung function was extensively deliberated by the team and adequate post-hyperthermia care provided. Tumour treatment consisted of whole-body hyperthermia (WBHT) alone (6 treatments) or WBHT combined with either chemotherapy (5 treatments) or radiotherapy (22 treatments).

If given in combination with chemotherapy, melphalan, 25 mg, or 5-fluorouracil, 10 mg/kg body weight, was given at the moment that a rectal temperature of 41.0°C was reached. When combined with radiotherapy the WBHT treatment was given within a radiotherapy series following a conventional scheme of 5 fractions per week, fraction size 1.5–2.5 Gy, with the exception of patient No. 4, who received 2 fractions of 5 Gy during the 3 weeks in which the WBHT treatments were given. For the induction of WBHT the Pomp–Siemens cabin was used. The construction of this cabin is described in a separate publication [32]. We did not use the radiofrequency coil as the radiofrequency energy interfered with the monitoring equipment.

An additional source of external heating in the form of a water mattress was added and energy loss by evaporation of transpiration fluid was prevented by covering the patient with plastic film. This method was developed during the first 19 treatment sessions. The patient was hospitalised one day before the treatment session. Zero-time blood samples were collected, and a control thoracic X-ray and ECG were done. Tumour dimensions were measured by calipers where possible and/or recorded by X-ray photographs, planigrams or CT scanning. The rectum was emptied by enema to ensure reliable rectal temperature monitoring. On the morning of the treatment the patient was given premedication and prevented from cooling by use of an aluminium foil blanket. Following sedation with diazepam, an intra-arterial catheter was introduced into the radial artery, a Swan Ganz catheter into the pulmonary artery and, in 9 patients for 11 treatments, a catheter was placed in one of the hepatic veins. Anaesthesia was induced with methohexitone; the patient was paralysed, intubated and ventilated and anaesthesia was maintained with an N_2O/O_2 (66%/33%) mixture, humidified and warmed up to 40–42°C. This was supplemented with fluothane or enflurane in some patients. Warmed fluid was administered at a mean rate of 525 ml/hr; this consisted of alternating crystalloid and colloid solutions, with cold plasma and a 20% mannitol solution at the start of cooling.

Following the induction of anaesthesia, rectal, oesophageal, nasopharyngeal, intramuscular and subcutaneous thermocouple probes were placed; probes were also placed between the skin and water mattress, against the tympanic membrane and, where possible, in the tumour. Thermometry was performed with an Ellab medical thermocouple system (accuracy, 0.1°C) at 10–12 sites and the apparatus was adapted with a temperature display unit from which the temperatures of 10 different probes could be read off simultaneously. For safety two additional independent thermometry systems were used. One was an intra-oesophageal thermistor which forms a part of the Hewlett-Packard compact monitor. The other one was part of the cardiac output monitoring system, recording the temperature in the pulmonary artery.

In some patients it was possible to place one or more pH electrodes intratumorally, using the method described by van den Berg *et al.* [33].

A bladder catheter was introduced to enable monitoring of urine output during hyperthermia. Special cushions filled with polystyrene grains were placed at pressure sites to protect against decubitus and, finally, the patient was wrapped in plastic film. Through this 'preparatory phase' the water mattress was perfused with water at a temperature of 44–46°C.

Heating was started by closing the hood of the cabin and raising the temperature in the cabin to 60–65°C. The temperature was maintained at 41.8–42.0°C for 2 hr ('plateau phase'). Cooling was achieved by opening the cabin, blowing cool air over the unwrapped patient and circulating cold water through the mattress.

Before, during and after the heat treatment arterial, venous, mixed venous and hepatic venous blood samples were taken.

On the first evening following WBHT the patient was transferred to the intensive care unit. If there were no complications the patient was dismissed from the hospital 2–3 days following treatment. To help in assessing the side-effects of the treatment blood and urine samples were collected for 3 days following hyperthermia.

Response criteria as recommended by WHO [34] were used, and these can be summarised as follows: complete response, complete disappearance of all tumour for a period of at least 4 weeks; partial response, a decrease in tumour size of at least 50% for a period of at least 4 weeks; no

change, a decrease in tumour size of less than 50% or an increase in tumour size of less than 25%; and progression, an increase in tumour size of more than 25%, with objective response including partial and complete response.

RESULTS

The hyperthermic treatment

A rectal temperature of 41.5°C was reached 75–165 min after the start of heating, the average time required being 114 min when the complete set-up of hot air, warm water mattress, warmed inhalation gases and infusion fluids and covering with plastic film was used. The temperature could easily be maintained at 41.8–42.0°C for 2 hr. A fairly homogeneous temperature distribution was obtained, with a mean difference of 0.5°C between the rectal or oesophageal and the subcutaneous temperature, at plateau. The temperature data will be reported elsewhere. Patients Nos 1 and 19 purposely received lower heat doses: due to our lack of familiarity with the technique the first patient was given three 2-hr treatments at 40.5, 41.5 and 41.5°C respectively, and patient No. 19 received one treatment of 2 hr at 41.5°C as we feared a toxic overload should his massive tumour suddenly become necrotic.

A temperature decrease to 39°C was achieved 45–55 min after the start of cooling. An example of the temperature curve from one patient (No. 13) is given in Fig. 1. Intratumoral pH was determined in 4 patients during 7 WBHT treatments. No significant changes in pH values were observed during the treatment. The results of these pH determinations are given in Fig. 2 and a comparison of tumour pH and arterial pH is given in Table 2. Laboratory testing of blood samples taken during the treatment showed significant decreases in haemoglobin (Hb) and haematocrit (Ht) values and in total calcium (Ca), inorganic phosphate (Pi) and magnesium (Mg^{2+}) levels. The decrease in total calcium was related to a decrease in total protein content; the ionised calcium level remained the same during and immediately following WBHT. The glucose content increased up to a mean maximum of 13.9 mmol/l immediately after the start of cooling. Urine output was greatly decreased, to less than 10 ml/hr in some patients. Urea and creatinine blood levels increased, but kidney function disturbances appeared to be temporary. The results of the laboratory determinations are given in Table 3. Changes in cardiovascular functions will be reported elsewhere [35]. Changes in some of the parameters can be summarized as follows: (1) the pulse rate increased from a mean of 93 beats/min before induction of anaesthesia to a maximum of 146 at the end of the plateau phase; (2) the mean systemic arterial pressure decreased from a mean of 88 mm Hg to a minimum of 61 mm Hg after 15 min of cooling. Most patients were relatively hypotensive during

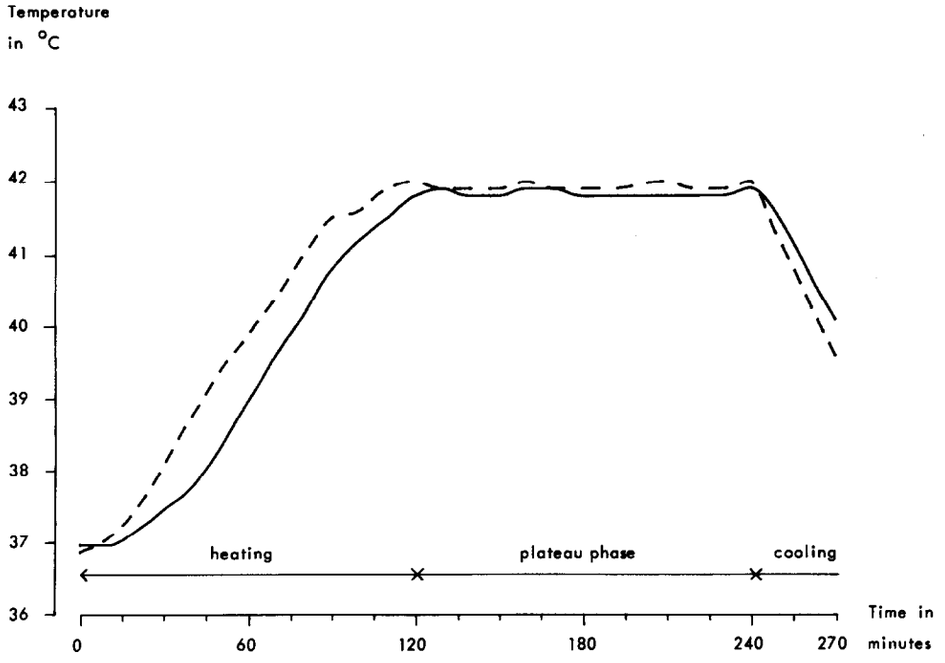

Fig. 1. Typical course of rectal and oesophageal temperatures during WBHT. Temperature course during WBHT in patient No. 13: —— rectal temperature; ---- oesophageal temperature.

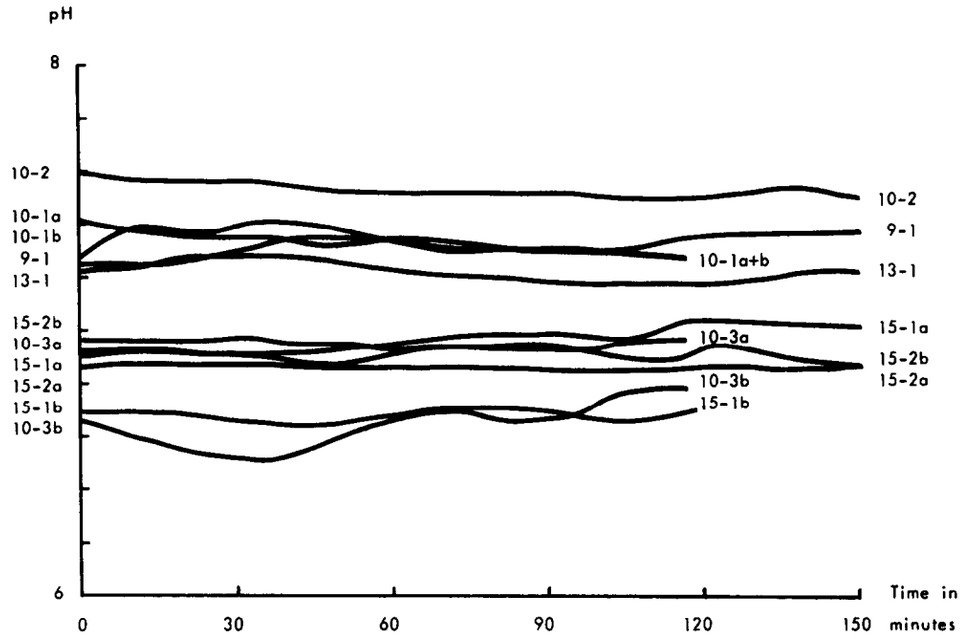

Fig. 2. Course of tumour pH in 4 patients during 7 WBHT treatments. Time 0 = start plateau phase; time 120 = start cooling. Patient No. and treatment No. per patient is indicated with the curves.

Table 2. Comparison of tumour pH and arterial pH

Patient No.	Treatment	Tumour pH		Arterial pH	
		Start plateau	Start cooling	Start plateau	Start cooling
9	1	7.25	7.36	7.26	7.35
10	1	7.41;7.27	7.28;7.28	7.28	7.28
	2 (2 weeks)*	7.59	7.51	7.38	7.41
	3 (2 months)*	6.92;6.66	6.97;6.79	7.33	7.32
13	1	7.22	7.23	7.53	7.49
15	1	6.90;6.69	7.04;6.71	7.37	7.29
	2 (1 week)*	6.86;6.96	6.86;6.94	7.34	7.32

There is no significant difference in pH values at start plateau and at start cooling; a paired T test gave $2P$ values of 0.4077 for the tumour pH and 0.8400 for the arterial pH. The difference between tumour and arterial pH is significant ($2P = 0.0001$).
*Time interval from previous WBHT.

cooling and for a few hours following WBHT; (3) the cardiac output increased from a mean of 5.75 l/min at start heating to a mean of 12.67 l/min during plateau phase; and (4) the arterial pH during plateau phase ranged from 7.24 to 7.53, with a mean value of 7.39. Clinical difficulties during WBHT were encountered in 2 patients. Patient No. 3 developed acidosis with ventricular tachycardia during cooling, which was secondary to insufficient spontaneous ventilation. Administration of bicarbonate solved this problem. In patient No. 26 we were forced to interrupt the hyperthermia treatment session and start cooling 10 min before schedule when the ECG showed periods of asystole. This patient showed no other signs of cardiac problems during and following cooling.

Toxicity

General toxicity. Following cooling, the patients were transferred to the intensive care unit where they remained until the next morning. During this period most patients showed neurological disorders in the form of hyperexcitability and agitation. This was probably related to the low Mg^{2+} serum level (Table 3). Gastrointestinal disorders such as vomiting and diarrhoea occurred in 23 of 27 patients. Decreased levels of potassium (K^+) and Ca were corrected by intravenous supplementation. Electrolyte losses in the urine did not explain the decrease in serum levels. Some patients required transfusion of red blood cells. Patients with no complications could be mobilised from the first day following whole-body hyperthermia. Coagu-

Table 3. Changes in relevant mean laboratory values during and following WBHT

	-24 hr	Mid-plateau	¼hr cooling	+ 24 hr	+ 48 hr
Electrolytes					
Na^+ (mmol/l)	139.9	134.5	134.0	137.6	139.6
Cl^- (mmol/l)	100.9	104.7	102.8	107.9	105.4
K^+ (mmol/l)	4.29	4.61*	3.50*	3.74*	3.72*
total Ca (mmol/l)	2.34	2.02*	2.00*	2.08*	2.14*
free Ca (mmol/l)	1.39	—	1.32	1.30*	1.30*
Mg^{2+} (mmol/l)	0.92	—	0.66*	0.69*	0.85*
P^- (mmol/l)	1.12	0.65*	0.58*	0.91*	0.81*
Haematology					
haemoglobin ((mmol/l)	7.8	6.4*	6.5*	6.7*	7.2*
leucocytes (10^9/l)	9.0	—	17.2*	9.0	8.8
Coagulation					
platelets (10^9/l)	262	222	127*	89*	100*
fibrinogen (g/l)	4.5	—	2.8*	2.9*	3.9
Glucose (mmol/l)	6.6	8.6*	13.0*	7	5.7
Total protein (g/l)	71	56*	54*	58*	62*
Enzymes					
alk. phophatase U/l	29.7			31.6	34.3
acid phosphatase U/l	5.71			5.11	5.73
SGOT U/l	12.9			48.4*	210*
SGPT U/l	13.6			27.9*	141*
LDH U/l	157			243*	437*
-iso 5 (liver) (%)	3.9			9.0*	11.6*
CPK U/l	21.7			156*	99*
Kidney functions					
urea (mmol/l)	4.8		6.2	7.2*	5.8*
creatinine (μmol/l)	81		142	91,8	87,2

Output in urine (mmol/24 hr)	24 hr before WBHT	day of WBHT
Ca	2.61	2.55
Na	93	186*
K	51	89*
Mg	2.22	1.12

Remarks: All -24 hr values were within normal range.
*Significant change with regard to -24 hr values (Student's t test, $2P<0.05$).

lation parameters showed evidence of a low-grade disseminated intravascular coagulation in 6 patients, i.e. a decreased fibrinogen level, a decreased number of thrombocytes and an increase in fibrinogen degradation products (FDP) above 20 mg/l, which was maximal 24 hr following WBHT. The partial thromboplastin time was more than doubled in only 3 patients. There was only 1 patient with clinical evidence of coagulation problems following the second WBHT treatment; the puncture in the femoral vein, through which a hepatic vein catheter had been introduced, haemorrhaged for several hours. This patient had, however, no increase in FDP levels. Some degree of liver damage was observed in most patients. Serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT) and lactate dehydrogenase (LDH) levels increased significantly, with maxima at 48 hr post-treatment. The relevant laboratory values are presented in Table 3.

Circumoral Herpes simplex infection was observed in 10 of 27 patients following their first WBHT treatment and in 4 of 13 patients following subsequent treatments. In one patient (No. 25), the Herpes infection spread to the eye. This Herpes keratitis could be controlled and did not cause permanent damage. Second-degree burns developed in 9 patients; decubitus was seen at the site of the coccyx in 2 patients and on the back of the head in 2 others. Burns occurred at pressure sites caused by infusion lines, thermocouple lines or sites where the skin was directly exposed to hot air streams, and could be prevented by careful insulation and cushioning.

A generally experienced subjective side-effect was fatigue, lasting from 3 to 14 days, similar to that following febrile disease.

Severe toxicity. Two patients died following treatment. Patient No. 18 remained lethargic following treatment, and laboratory findings on the following days showed that she had sustained

extensive liver damage which progressed until she succumbed 5 days after WBHT. Post-mortem examination showed massive liver necrosis and hardly any signs of tumour necrosis. The other patient, No. 27, showed progressive dyspnoea from the second day following WBHT. Despite artificial respiration, antibiotics and corticosteroid therapy his condition deteriorated and he died 7 days after WBHT. Post-mortem examination showed that this patient had developed an adult respiratory distress syndrome (ARDS). Extensive retrospective analysis of the available data on both patients yielded no indications in either the previous case histories or the pretreatment examinations that could have alerted us to the possibility of these calamities occurring in these patients.

Patient No. 14 experienced considerable liver damage, with a maximum SGOT of 1380 U/l (norm <19 U/l) and clinical jaundice, but recovered on the third day. Three other patients (Nos 12, 13, 21) had SGOT levels >300 U/l but no clinical signs. Two patients, Nos 9 and 26, were seriously dyspnoeic immediately after WBHT and had to be artificially ventilated for 12–24 hr. Both of these patients suffered from carcinomatous lymphangitis of the lungs and had impaired ventilation before hyperthermia. Two patients, Nos 1 and 3, developed third-degree burns during WBHT. In the first patient this could be attributed to the additional local tumour heating with microwaves during anaesthesia, which as a result of 'standing waves' probably caused an unobserved hot spot. Patient No. 3 had burns on his toes, probably due to poor regional circulation and an excessively high local temperature in the unisolated skin.

Patient No. 21 appeared to have brain metastasis following treatment. This was suspected when he developed a hemiparesis 48 hr after WBHT. CT scanning showed multiple edematous brain metastases. Brain scanning had not been included in the pretreatment examinations of this patient as we erroneously assumed that the likelihood of brain metastasis from a pleural mesothelioma was negligible. Corticosteroid therapy and subsequent radiotherapy of the brain gave a rapid recovery.

Tumour responses

(1) Following WBHT alone, tumour response was evaluable in 6 patients (Nos 1–4, 9, 12). No patients gave an objective response.

(2) Following WBHT combined with chemotherapy, evaluable in 5 patients (Nos 1, 2, 10, 16, 17), only patient No. 16 gave a partial response.

(3) Following WBHT combined with radiotherapy, evaluable in 18 patients (Nos 4–15, 20–23, 25, 26), 5 patients (Nos 5, 6, 9, 11, 13) gave a complete response and a partial response was observed in 4 others (Nos 7, 8, 10, 14), the total response being 9 of the 18. In patient No. 5 the effect of WBHT and radiotherapy could be compared with that of radiotherapy alone. Following the combined therapy the homolateral cervical lymph nodes of his lung adenocarcinoma showed a complete response lasting for 10 months (at which point he died of tumour progression in another part of the body). The heterolateral lymph nodes, which appeared outside the radiation field after the combined treatment and were treated 2 months later, showed only a partial response lasting for 6 months following an equal dose of radiotherapy alone. The tumour response following WBHT and radiotherapy was not evaluable in 4 patients. In patients Nos 18 and 27 this was due to the fact that they died 5–7 days following treatment. Patients Nos 19 and 24 had surgical treatment of their tumours after completion of the radiotherapy course. These two patients had been considered inoperable before treatment but became operable after the combined treatment. Patient No. 19 had a local recurrence of leiomyosarcoma 9 months after surgery and patient No. 24 is presently free of disease following surgical treatment 12 months ago.

Of the 16 non-responders, 14 died at an average of 5 months (3 weeks–11 months) following WBHT. Patients Nos 22 and 23 are still alive after 17 and 14 months respectively. The patients with a partial response all died at 4–22 months, with a mean of 11 months, following WBHT. The patients with a complete response have survived for 9–31 months, with a mean of 17 months, following WBHT, except for patient No. 9, who died within 1 month from progression of carcinomatous lymphangitis in the lungs, and patient No. 13, who is still alive and free of disease 32 months after WBHT.

Palliative effect

An outstanding palliative effect was obtained in 4 of the 13 patients suffering disabling pain from their tumours (Nos 8, 9, 10, 19). A less remarkable but still worthwhile palliation occurred in 5 patients (Nos 2, 14, 22, 23, 27). Some pain relief was obtained in the remaining 4 patients (Nos 10, 15, 16, 21). The palliative effect lasted for 1–4 months.

DISCUSSION

Method

The method described above for the induction of WBHT is clinically useful. The mean time of 114 min necessary to raise the rectal temperature to 41.5°C is comparable with the time mentioned by

other authors [24, 27–30, 36] using the technique of transcutaneous energy input. The plateau temperature of 41.8–42°C was easily controllable by adjusting the air and water temperatures. The advantage of the transparent perspex hood is that the patient can be obsrved *in toto*. As we did not use the (originally included) 27-MHz radio-frequency coil for additional whole-body heating, it was possible to continuously monitor the patient's cardiovascular functions. The original intent of our programme was to heat the patient's whole body up to a relatively non-toxic temperature with additional local tumour heating with 433-MHz microwaves. This was done with our first patient. She underwent her first treatment unanaesthetised, but this appeared to be unbearable for her; therefore subsequent WBHT treatments were given under general anaesthesia. During this patient's third treatment a local hot spot must have occurred, probably caused by a 'standing wave' by reflection on underlying ribs, resulting in a severe third-degree burn. Our present experience with local hyperthermia indicates that there is a sizable risk of the occurrence of a burn if the energy input is not immediately decreased when the patient feels pain, even if the measured temperatures are relatively low. This led to the decision to never again use local hyperthermia by microwaves in an anaesthetised patient unless better temperature monitoring systems are developed.

We observed no tumour pH changes during WBHT. This contrasts with the findings of Bicher *et al.* [37], who found a decrease in pH values in mouse tumours after 1 hr at 43°C, and Song *et al.* [38], who reported a decrease in pH in rat tumours following one or more hours at a temperature of 43°C or more. Both groups of authors, however, used a higher treatment temperature than we did. Our observations do not contrast with the findings of Vaupel [39], who saw pH drops at temperatures above 42°C in smaller mouse mammary carcinomas but not in the larger tumours, i.e. >1.1 g, and Dickson and Calderwood [40], who saw no pH changes in the rat Yoshida sarcoma following 60 min at 42°C.

In view of the fact that we did not observe a decrease in tumour pH during treatment, no additional therapeutic effect through this mechanism can be expected with the method used by us.

Profits and losses

In order to assess the value of WBHT, the toxicity of the treatment has to be weighed against the positive therapeutic effects.

Toxicity. When we started investigating WBHT we expected to have to deal with some degree of toxicity but that we would be able to avoid major toxicity by excluding patients who were in a poor general condition. Not many problems were encountered during the treatment. In patient No. 3 the cardiac arrhythmia during cooling was due to acidosis caused by respiratory insufficiency. This could be prevented in subsequent patients by artificial ventilation. The cardiac arrythmia in patient No. 26 was unexpected but appeared to be rapidly reversible by cooling. The problems arising during the first few hours following WBHT were the same as observed by other authors. Gastrointestinal disturbances such as diarrhoea and vomiting were sequels to almost every treatment. Decreased levels of K^+, Ca, Mg^{2+} and Pi were found following every treatment. These findings are in agreement with those of other authors [25, 27–30]. In most cases, only K^+ and Ca^{2+} were corrected for by intravenous administration. In general, normal levels were again reached by 72 hr following WBHT.

Transient hyperexcitability and agitation were seen in 19 patients following 23 WBHT treatments and were, retrospectively, probably the results of a magnesium deficiency. It was necessary to administer diazepam to 12 patients to subdue them. Other than this restlessness and the clinical manifestation of brain metastasis in patient No. 21, we found no neurological disorders.

The decrease in total serum calcium gave no clinical sequelae, as the ionised calcium remained within normal limits. The decreased total calcium content probably resulted from the decrease in total protein. Sites of decubitus developed in patients Nos 7, 8, 10 and 11, but could be avoided in subsequent patients by careful use of cushions.

Disseminated intravascular coagulation (DIC) was observed by Pettigrew *et al.* [24], who described 4 patients who died following WBHT with evidence of DIC, and by Barlogie *et al.* [29], who saw a low-grade DIC in 4 patients. Although we did find a decrease in the number of platelets and in the fibrinogen levels following every WBHT treatment, these were accompanied by an increase in fibrin degradation products (FDP) above 20 mg/l in only 6 and above 40 mg/l in only 3 of 45 treatments. The only patient with clinical coagulation problems had no elevation of FDP.

Circumoral Herpes simplex infection occurred in 10 of the 27 (37%) patients following WBHT. This is within the range of earlier reported observations: 40% [28] and 50% [24, 29]. Some degree of liver damage occurred in most of our patients, as judged from the increase in serum transaminase levels.

Two patients suffered post-treatment clinical

jaundice and one of them died with massive liver necrosis. Pettigrew *et al.* [24] related liver damage to the height of the applied temperature; he did not observe increases in SGOT levels with a treatment temperature below 41.8°C. Levin and Blair also [25] reported that they saw no liver problems after they had restricted the treatment temperature to a maximum of 41.5°C. We could not find a correlation with hyperthermia dose in our patient series. Larkin *et al.* [27] observed SGOT increases in many patients, but they treated patients who already had increased SGOT levels before WBHT. One of Levin and Blair's [25] patients died with massive liver necrosis, but this patient had used phenobarbitone for many years and the authors attributed the liver failure to this. Extensive analysis of our patient's case history and of all the treatment parameters did not result in a clear indication of the cause of the massive liver damage. In contrast to the experiences mentioned above, Barlogie *et al.* [29], Bull *et al.* [30] and Moricca *et al.* [28] found no significant changes or only minor elevations in SGOT levels in a total of 48 patients at treatment temperatures of 41.8–42.0°C. A discussion of this problem is presented by Wike-Hooley *et al.* [41].

Respiratory problems following WBHT occurred in two patients (Nos 9 and 26) with carcinomatous lymphangitis of the lungs; they had to be artificially ventilated for 24 hr. Oedema of the tumour metastases resulting in increased obstruction of the airway had probably occurred. One patient developed an adult respiratory distress syndrome (ARDS) and as a result died 7 days after WBHT. As far as we know, this syndrome following WBHT has only earlier been observed by Greenlaw *et al.* [42]. A hypothetical explanation for this is that, when one lung is mostly taken up by tumour, the greater part of the pulmonary circulation passes through the other lung. When the cardiac output increases during WBHT, the blood flow in the healthy lung reaches a very high velocity, the endothelial barrier is injured and protein leaks into the alveoli causing the respiratory distress syndrome [43]. Our patient No. 27 and Greenlaw *et al.*'s patient both had one lung completely replaced by tumour. The pretreatment ventilation parameters in patient No. 27, however, were only slightly diminished; we had therefore considered that he should be able to withstand the treatment.

Positive effects. WBHT alone produced no objective response in 6 patients. This seems to be in agreement with the findings of other authors who observed no [28] or only few [29] objective responses following WBHT alone. In one patient suffering considerable pain a palliative effect lasting 4 weeks was achieved. WBHT combined with chemotherapy resulted in a partial response lasting for 2 months in 1 of 5 patients. As the experimental experience in rodent tumours with the combination of whole-body hyperthermia and chemotherapy was still limited, we cautiously administered reduced dosages of relatively mildly toxic agents; therefore these results may not have been the optimum that can be achieved. The results of WBHT in combination with radiotherapy are much more promising. A complete response was achieved in 5 of 18 patients. It is very encouraging that 3 patients (Nos 5, 9 and 11) showed complete response following only 24, 18 and 19.5 Gy irradiation combined with 3, 1 and 1 WBHT treatments respectively.

Three of the 4 patients (Nos 8, 10, 14) with a partial response had also received low doses of radiotherapy of only 20, 19.5 and 20 Gy respectively. The reports of other authors on WBHT and irradiation are also promising. Larkin *et al.* [27] treated 1 patient with WBHT and radiotherapy, Pettigrew *et al.* [24] 3 and Levin and Blair [25] 8 patients; they observed 1, 3 and 5 responses respectively.

In our series it is curious that in the earlier patients the toxicity was relatively mild and seemed avoidable with growing experience and the therapeutic results were promising, while in the second half major toxicities occurred and the number of objective responses decreased. All the responders in the group receiving WBHT combined with radiotherapy were in the first 14 patients. The favourable results achieved in patients Nos 8 and 10, with intestinal carcinomas, had encouraged us to give the previously untreated patient No. 20 WBHT in combination with a full dose of 64.5 Gy and 5-FU in the hope of a cure. The tumour, however, completely failed to respond. The same applied for patient No. 21, from whom the same response was expected as seen in patient No. 11, who had a complete response following 19.5 Gy and 1 WBHT treatment, but the tumour of patient No. 21 progressed rapidly. The palliative effect following WBHT combined with radiotherapy in 8 of the 10 patients suffering pain was, however, worthwhile; the pain disappeared immediately following treatment, even in patients in which the tumour failed to respond, and was not evident for 1–4 months. From the response of patient No. 5, in whom a comparison between the effects of WBHT combined with radiotherapy and radiotherapy alone was possible, it is clear that WBHT treatment at 41.8°C can be an effective adjunct to radiotherapy. Also, we venture to ascribe the results achieved in patients Nos 8–11 and 14 to the WBHT treatment.

This means that the (microwave) deep-heating

methods that are presently being developed will almost certainly yield favourable therapeutic results.

The final conclusion from this study is that WBHT at 41.8–42°C, in combination with radiotherapy, can be an effective therapy regimen for cancer, in accordance with data obtained in experimental tumours. The results, however, are quite unpredictable. The minor complications of WBHT may be acceptable, but the possibility of the occurrence of fatal complications is not predictable, even with extensive pretreatment examination, and weighs heavily. It is possible that the results of further experimental investigation will indicate ways to prevent fatal complications. Until then, these conclusions imply that the application of WBHT is not indicated in patients without severe complaints and with a relatively good prognosis. In patients with a poor short-term prognosis, with disabling pain and with the possibility of additional treatment with a low dose of radiotherapy the small risk of fatal complications in WBHT has to be weighed by the patient against the good chance of a palliative effect.

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