Pilotstudie zur Thermo-Chemotherapie

ein Service des Teams der

Hyperthermie Tagesklinik Bochum

Pilotstudie einer Ganzkörper-Hyperthermie kombiniert mit Chemotherapie bei Patienten mit metastasierten, vorbehandelten, progredienten Mamma-,Ovarial- und Kolon-Rektum-Karzinomen

Pilot Study of Whole-Body Hyperthermia Combined with Chemotherapy in Patients with Metastasised Pretreated Progressive Breast, Ovarian, and Colorectal Carcinomas

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Zusammenfassung

Hintergrund: Da die Wirksamkeit einiger Zytostatika bei erhöhten Temperaturen zunimmt, wurde in einer Pilotstudie die praktische Durchführbarkeit und Verträglichkeit sowie die remissionsinduzierende Wirksamkeit einer Thermo-Chemotherapie (TCT) in Chemotherapie-refraktären Patienten mit soliden Tumoren untersucht. **Patienten und Methoden:** Bei 19 Patienten mit metastasierten Adenokarzinomen (Mamma n = 7, Ovarial n = 5, Kolon-Rektum n = 7), die gegenüber einer Standard-Chemotherapie refraktär waren und eine Krankheitsprogredienz aufwiesen, wurden insgesamt 28 TCT-Behandlungen bei einer maximalen rektalen Temperatur von 42,0 – 42,3 °C mittels eines IRATHERM-2000-Hyperthermiegerätes durchgeführt in Kombination mit einer Hyperglykämie-induzierten Laktatazidose, Hyperoxygenierung und simultaner Poly-Chemotherapie entsprechend der systemischen Krebs-Mehrschritt-Therapie (sKMT). **Ergebnisse:** Das IRATHERM-2000-Gerät ermöglichte einen raschen Anstieg der Körperkerntemperatur innerhalb von 90 – 120 Minuten und eine hohe Temperaturkonstanz während der 60- bis 95-minütigen Hochtemperatur-Plateauphase. In erfahrenen Händen erwiesen sich die TCT-Behandlungen gemäß dem Konzept der sKMT als sichere und gut durchführbare Therapieverfahren. Partielle Remissionen (mittlere Dauer drei, Bereich 1 – 6 Monate) wurden in 9 Patienten und eine Krankheitsstabilisierung bei 7 Patienten erreicht. Drei Patienten zeigten eine weitere Tumorprogredienz. Toxische Nebenwirkungen waren mäßiggradig ausgeprägt mit einer Leukozytopenie WHO-Grad I – III bei 5 Patienten sowie einer Thrombozytopenie und Anämie Grad I und II bei zwei bzw. 6 Patienten. Übelkeit/Erbrechen des WHO-Grades II und III erlitten 6 Patienten trotz antiemetischer

Summary

Background: Since the efficacy of some cytostatic agents can be enhanced by hyperthermia, a pilot study has been performed to examine the feasibility, tolerability, and remission inducing potential of thermo-chemotherapy (TCT) in chemotherapy refractory solid tumours. **Patients and Methods:** In 19 patients with metastasised adenocarcinomas refractory to standard chemotherapy (breast n = 7, ovarian n = 5, colo-rectal n = 7) and with progressive diseases, a total of 28 TCT-courses with maximal 42.0 to 42.3 °C rectal temperature have been performed using the IRATHERM 2000-heating equipment and have been combined with hyperglycaemia induced lactatacidosis, hyperoxaemia, and simultaneous polychemotherapy according the systemic Cancer Multistep Therapy (sCMT). **Results:** The IRATHERM 2000-equipment permitted a rapid rise of body-core temperature within 90 to 120 minutes and a high thermal constancy in the plateau phase of 60 to 95 minutes. The TCT treatments according to the sCMT concept proved to be a safe and practicable procedure with good tolerability in experienced hands. Partial remissions (median duration 3, range 1 – 6 months) have been achieved in 9 patients and disease stabilisation in 7 patients. Tumour progression continued in three patients. Side effects were moderate with WHO grade II – III leucocytopenia in 5 patients and grade I – II thrombocytopenia and anaemia in two and 6 patients, respectively. Nausea/vomiting WHO grade II – III has been experienced by 6 patients despite antiemetic prophylaxis. 8 Patients developed thermal dermal lesions of WHO grade I – III. **Conclusions:** This pilot study has confirmed that the TCT-courses applied are feasible without unexpected complications. They are good tolerable and have shown considerable efficacy.

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Prophylaxe. Thermische Hautschäden des WHO-Grades I – III traten bei 8 Patienten auf. **Schlussfolgerungen:** Diese Pilotstudie zeigte, dass die applizierten TCT-Behandlungen gut durchführbar und komplikationslos sowie gut verträglich sind bei bemerkenswerter Wirksamkeit. Daher kann eine TCT eine effektive alternative Behandlungsmethode mit nur mäßiggradigen, gut tolerierbaren Nebenwirkungen darstellen.

Schlüsselwörter:
Ganzkörperhyperthermie · Thermo-Chemotherapie · Mammakarzinom · Ovarialkarzinome · Kolorektale Karzinome · Nebenwirkungen · Klinische Ergebnisse

Therefore TCT may represent an effective alternative treatment modality with moderate, well tolerable side effects.

Key words:
Whole-body hyperthermia · Thermo-chemotherapy · Breast cancer · Ovarian carcinomas · Colorectal carcinomas · Toxicity-Clinical results

Introduction

Hyperthermia (HT) with an increase of tissue temperatures (range 40 – 44 °C) potentially induces tumour cell death by a spectrum of molecular, metabolic, cellular, and tumour tissue changes including confirmational changes of cellular proteins and enzymes, synthesis of heat shock proteins, stimulation of immune responses. decrease of pH and ATP supply as well as alterations of microenvironment, cytokine production, and blood flow [1 – 5].

Although HT alone has shown no valuable clinical effects concerning longer lasting tumour remissions [6], preclinical and clinical data have shown, that HT not only enhances the efficacy of some cytostatic drugs [1,5,6] but also potentiates the effects of ionizing irradiation [5 – 7]. Therefore, HT has been integrated into multimodal anticancer strategies as local/regional HT combined with radiation or chemotherapy or radiochemotherapy [5 – 7] as well as systemic whole-body HT (WBH) combined with chemotherapy [6,8]. The clinical applicability, side effects, and efficacy of local and regional HT combined with radiotherapy and/or cytostatic agents have been evaluated in valid phase III studies [5,6]. The more complex and hence potentially more toxic procedure of WBH with simultaneous chemotherapy, called thermo-chemotherapy (TCT) is the subject of several recent phase I/II studies in patients with incurable metastatic and/or refractory cancer [8], mainly with breast cancer [8], sarcoma [9,10], ovarian cancer [8,11 – 13], colorectal cancer [8,14,15], gastrointestinal cancer [8,16,17] and malignant melanoma [8].

We retrospectively analysed the feasibility, toxicity, and efficacy of TCT performed in a pilot study (parts have been presented recently [18]), in which patients with pretreated breast, ovarian, and colorectal adenocarcinomas received TCT for remission induction because of tumour progression under or relapse after standard chemotherapy.

Patients and Methods

Patient selection

Patients with histologically confirmed advanced and/or metastatic solid tumors, age between 30 – 75 years and Karnofsky-index > 60% were eligible. Progressive relapses after or tumour progression while on standard chemotherapy as well as measurable tumours and tumour parameters, respectively, have been required.

Further prerequisites were: time intervals to last cytostatic treatment of more than three weeks; adequate bone marrow function (WBC > 4.0 k/ml, hemoglobin > 10 g/dl, platelet count > 100 k/ml); adequate hepatic and renal function, absence of clinically relevant coronary heart disease, serious dysrhythmias, and severely compromised respiratory status, exclusion of central nervous system metastases.

The demographic profiles, tumour histologies, and location of metastases of the 19 patients treated between December 1995 and December 1999 are listed in Table **1**. Written informed consent was obtained from each patient.

Pretreatment evaluation

Actual documented tumour staging included complete history and physical examination, chest-X-ray, computerized axial tomography scan of brain, chest and abdomen, a full analysis of blood chemistry including tumour markers and haematological parameters, full pulmonary function test, and exercise electrocardiography.

WBH treatment procedure

Heating was applied by external water-filtered infrared-A-radiation with dominant wave lengths of 850 to 1300 nm (IRATHERM® 2000, von Ardenne Institut für Angewandte Medizinische Forschung GmbH, Dresden, Germany). Five radiator pairs, three at dorsal and two at ventral position, are controlled individually. The patient lies, freely accessible, in a semitransparent tent. The technical-physical aspects and thermal parameters of this heating device have been analysed [8,19,20].

Skin and body-core temperatures were recorded online and continuously measured by several probes attached to the skin and one rectal sensor. The output of infrared-A-radiation was individually adjusted to achieve a continuous increase of temperature. The target maximum body-core temperature of 42.0 – 42.3 °C was reached at least after two hours heating and kept for a plateau phase of 60 to 95 minutes depending on the patient's vital parameters and clinical situation. Cutting off heating resulted in spontaneous cooling down to 39 °C in about two hours (Fig. **1**).

Tab. 1 Patients characteristics and response data after thermo-chemotherapy.

Patienten-Charakteristika und Ergebnisse der Thermo-Chemotherapie.

Patient	*Age (years)*	*Sex*	*Tumour histology*[1]	*Metastases*[2]	*Chemotherapy pretreatment* *Substances*	*Duration (months)*	*Thermo-chemotherapy* *Cytostatics*[3]	*Courses*	*Response* *PR (months)*	*NC (months)*	*Survival time (months)*
1.	52	f	BC	O	TAM; CMF, ADM/ MMC, MEG	36	MMC/VDS	1	5	–	11
2.	32	f	BC	P, N	EC, CMF	12	MMC/VDS	1	3	–	10
3.	54	f	BC	O, D	EC	17	MMC/VDS	1	–	–	2
4.	53	f	BC	PL, H, O	TAM, CMF, ADM/ VCR, Mitox.	40	EC	1	2	–	4
5.	58	f	BC	O, N, D	HD-CXT (EC, CMF), PACL.	6	FEC	2	–	1	14
6.	52	f	BC	H	BMF	3	FEM	1	–	15	27
7.	40	f	BC	PL, PER, D	CMF, Goserelin, Mitox, EC	72	MIC	1	–	2	39
8.	44	f	OC	PER	PACL./CARBO	14	MIC	1	4.5	–	9.5
9.	60	f	OC	PER	DDP/ADM	8	MIC	1	1	–	2
10.	65	f	OC	PER, PI	DDP/CYCLO, TREO, PACL/CARBO, MEG, 5-FU/CF	27	MIC	3	–	3	16
11.	59	f	OC	PER	DDP/CYCLO, TAM, PACL, TOPO	34	MIC	1	1	–	30 +
12.	65	f	OC	PER	PACL/CARBO, TOPO, GEM, TAM	44	MIC	2	2	–	10
13.	60	f	Colon	H, P	MMC, 5-FU/CF, RAL/IRINO	21	MMC/5-FU/ CF	2	2	2	5
14.	50	f	Colon	H	5-FU/CF, OXALI, 5-FU/CF	21	MMC/5-FU/ CF	1	1	–	3
15.	74	m	Colon	H	5-FU/CF	5	MMC/5-FU	1	1	–	7
16.	63	m	Rectum	H	IRINO	14	MMC/5-FU/ CF	4	4	–.	12
17.	50	m	Rectum	H	5-FU/CF, IRINO	9	MMC/5-FU/ CF	1	1	3	15
18.	59	m	Colon	H	5-FU, MMC/5-FU	10	FAM	1	1	3	19
19.	64	f	Rectum	H, P	5-FU	5	FAM	2	2	–	10

Abbreviations: [1] BC = Breast carcinoma, OC = Ovarian carcinoma, [2] D = Skin, H = Liver, N = Lymphnodes, O = Skelett, P = Lung, PER = Peritoneum/intraabdominell, PL = Pleura, [3] TAM = Tamoxifen, CMF = Cyclophosphamide/Methotrexat/5-FU, ADM = Adriamycin, MMC = Mitomycin C, MEG = Megestrolacetat, EC = Epirubicin/Cyclophosphamide, VCR = Vincristin, Mitox = Mitoxantron, HD-CXT = High-dose chemotherapy, PACL = Paclitaxel, BMF = Bendamustin/Methotrexat/5-FU, CARBO = Carboplatin, DDP = Cisplatin, CYCLO = Cyclophosphamide, TREO = Treosulfan, 5-FU = 5-Fluoro-Uracil, CF = Calcium folinic acid, TOPO = Topotecan, GEM = Gemcitabine, RAL = Raltitrexed, IRINO = Irinotecan, OXALI = Oxaliplatin, VDS = Vindesine, FEC = 5-FU/Epirubicin/Cyclophosphamide, FAM or FEM = 5-FU/ Adriamycin or Epirubicin/Mitomycin C, MIC = Mitomycin/Ifosfamide/Cisplatin

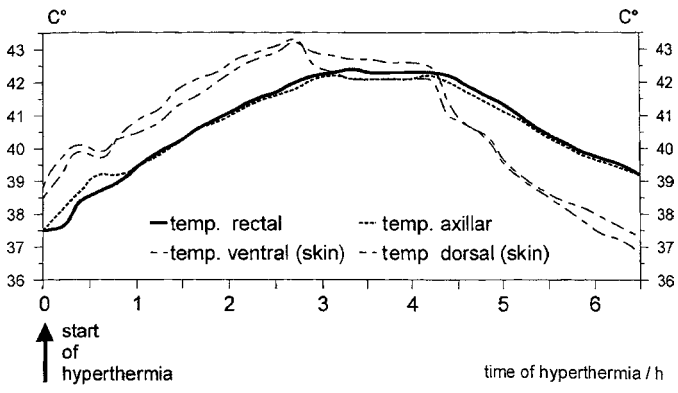

Fig. 1 Temperature profile of whole-body hyperthermia in patient number 13.

Temperaturverlauf der Ganzkörper-Hyperthermie bei Patient Nr. 13.

TCT has been performed according to the sCMT concept [8,19,20]. By infusions of 5 – 10% glucose solutions hyperglycaemia with subsequent lactatacidosis was achieved to reach a two to three-fold increase of blood lactat levels inducing decreases of pH-values of peripheral venous blood (Fig. **2**) as well as tumour tissue [4,8].

Blood pressure, ECG, and oxygen saturation were monitored continuously. Venous blood samples for measuring glucose level, pH-value, and electrolytes where withdrawn every 15 minutes, for haematocrit and lactat determination every 30 minutes.

Capillary blood gas samples were taken several times before, during and after reaching the maximal temperature plateau phase. Diuresis was supported by intermittent furosemid doses and the mean arterial blood pressure kept between minimally 60 and maximally 100 mmHg.

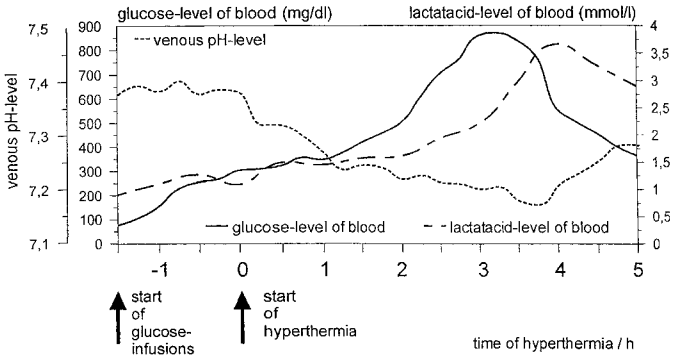

Fig. 2 Hyperglycaemia induced lactatacidosis during whole-body hyperthermia in patient number 13.

Hyperglykämie-induzierte Laktatazidose während der Ganzkörper-Hyperthermie bei Patient Nr. 13.

WBH was done under analgosedation with permanent intravenous application of fentanyl, benzodiazepine, and DHB. Patients breathed spontaneously, occasionally supported by a guedel tube and received high dosages of oxygen over a laminar flow applicator. No severe respiratory insufficiency had to be treated.

Patients remained under intensive care for 24 hours after WBH and additional 2 to 4 days in our hospital to assure regular hydration and electrolyte balance by appropriate infusion therapy; they received low molecular weight heparin subcutaneously as thrombosis prophylaxis and oral aciclovir medication as prophylaxis or treatment of herpes virus infections. When infusional or other medical supports are not longer required, the patients were discharged into ambulatory controls at weekly intervals.

Thermo-chemotherapy (TCT)

All patients received cytostatic treatments during WBH, which was administered by short infusions about 30 minutes before reaching the maximal temperature plateau phase. Only 5-FU-doses were applied as 24-hour-infusions starting at the beginning of WBH. Dosages of chemotherapy regimes administered intravenously were as follows:

Mitomycin C (MMC) 10 mg/m^2 + Vindesine (VDS) 3 mg/m^2;

MMC 6 mg/m^2 + Ifosfamid 2 g/m^2 + Cisplatin 50 mg/m^2 (MIC);

MMC 12 mg/m^2 + 5-FU 2.5 g/m^2 + Calciumfolinic acid (Leukovorin®) 300 mg/m^2;

MMC 10 mg/m^2 + Adriamycin 50 mg/m^2 + 5-FU 2.5 g/m^2 + Leukovorin® 300 mg/m^2 (FAM);

Epirubicin 50 mg/m^2 + Cyclophosphamide 500 mg/m^2 (EC) + 5-FU 2.5 g/m^2 (FEC);

MMC 10 mg/m^2 + Epirubicin 50 mg/m^2 + 5-FU 2.5 g/m^2 (FEM).

Combination of dexamethasone and ondansetron has been used as antiemetic prophylaxis.

Posttreatment evaluation

Patients were monitored weekly for toxicity using the WHO common toxicity criteria for grading. Response to TCT-treatment was evaluated after a 4 to 6 weeks interval according to WHO criteria for reporting results of cancer treatment [21].

Results

Whole body hyperthermia (WBH)

Maximum body-core temperature of median 42.1 °C was obtained in 28 TCT-courses and kept up for median 80 minutes (Table **2**). Glucose infusions resulted in considerable increases of blood glucose levels in all patients and induced blood pH-value decreases by lactatacidosis (Table **2**).

Tab. 2 Summary of each two temperature and biochemical parameters of 28 thermo-chemotherapy courses in 19 patients.

Zusammenfassung von jeweils 2 Temperatur- und biochemischen Parametern der 28 Thermo-Chemotherapie-Behandlungen bei 19 Patienten.

Parameter	*Median*	*Range*
Maximum temperature during at least 60 minutes (°C)	42.10	41.96 – 42.27
Duration of maximum temperature plateau phase (minutes)	80	60 – 95
Maximum glucose concentration (mg/dl)	802	478 – 989
pH-decrease	0.219	0.111 – 0.302

Catecholamin requiring hypotensive situations, transitional psychosis or other side effects of WBH have not been observed.

Side effects

Whereas fever, infectious complications or toxicities of WHO grade IV have not been observed haematological side effects of WHO grade I to III as well as nausea/vomiting, thermal dermal lesions and herpes labialis of WHO grade I to III dominated within the toxicity spectrum (Table **3**). Anaemia and leucocytopenia were without clinical problems. Nausea and vomiting occurred in three patients due to cisplatin – containing chemotherapy despite antiemetic prophylaxis with ondansetron and dexamethason. Four patients complained about fatigue or asthenia of grade II. Perioral herpes simplex efflorescences of grade I/II appeared in 9 patients despite oral aciclovir prophylaxis. Thermal lesions of grade II/III in 4 patients healed under local treatment within 14 days.

Only about 13 % of our patients experienced side effects of WHO grade II and III. All toxicities resolved completely and were not aggravated in the 5 patients, who received more than one TCT-course.

Responses

In 13 of the 19 patients a single TCT-course has been performed, two courses in 4 and three or 4 courses in each one patient (Table

Tab. 3 Toxicity of thermo-chemotherapy (n = 19).

Toxische Nebenwirkungen der Thermo-Chemotherapie (n = 19).

	WHO-grades				
Side effect	*0*	*I*	*II*	*III*	*IV*
Hemoglobin	13	5	1	0	0
Leucocytes	10	4	2	3	0
Thrombocytes	17	2	0	0	0
Nausea/vomiting	13	0	4	2	0
Stomatitis	18	1	0	0	0
Diarrhoea	18	1	0	0	0
Fatigue/asthenia	13	2	4	0	0
Herpes labialis	10	7	2	0	0
Thermal skin lesions	10	5	3	1	0
Summary %	71.3	15.8	9.4	3.4	0

1) for a total of 28 TCT-courses. Median time interval between two TCT-courses was two months in the 6 patients, who received more than one treatment.

Nine patients experienced a partial remission with median duration of three months (range 1 – 6 months), and 7 patients showed disease stabilisation (no change). Three patients did not respond. Median survival time after TCT is 10 months (range 2 – 39 months) (Table **1**). Patient No. 11 is alive for 30 months after TCT.

Discussion

Different radiant heating devices for exogenous increasing of body-core temperatures are used to perform WBH. The WBH equipments Enthermics Medical Systems [22] and Aquatherm [6,23] make use of a tempered (about 60 °C) hot cylinder around the patients with 90% relative humidity of air. This cylinder emits long-wave infrared-C radiation.

The skin transmission spectrum shows that only a spectrum range comprised of long-wave visible light and the adjacent infrared-A range (wave length 760 – 1400 nm) are able to penetrate the skin layers [19], whereas the infrared-B and infrared-C wave lengths are nearly unable to penetrate the skin, leading to energy and temperature concentrations in the upper-most layer of the skin and hence to conductance heat [19].

We applied the WBH equipment IRATHERM 2000 [8,19,20] using water-filtered infrared-A radiation with at least two advantages:

- Good ability to penetrate deep into the skin up to the capillary area of the corium, thus avoiding conductance heat of infrared B and C wave lengths,
- there is free access to the patient from all sides during all phases of WBH due to an open construction design.

Although the three available WBH equipments Enthermics, Aquatherm and Iratherm 2000 seem to be competitive in clinical practice [20], direct comparative studies are lacking. In several phase I/II-trials each of these three radiant heating devices have been applied to larger numbers of patients without serious complications [5 – 23]. Therefore, they represent safe and practicable WBH equipments with good tolerability in case of experienced application.

All three types of WBH procedures are common their combination with hyperoxaemia and simultaneous infusion of cytostatic drugs, but differ in the amount of infused glucose. According to the procedure of sCMT we induced high levels of hyperglycaemias to augment lactatacidosis in blood and tumour tissue [8]. Preclinical studies have shown that an acidic environment enhances heat-induced apoptosis [24] and that hyperglycaemia induced lactatacidosis combined with hyperthermia resulted in extensive tumour-growth inhibition [25].

The cytostatic agents infused during WBH (Table **1**) were selected with regard to the respective tumour entity and to their known increased efficacy under hyperthermic conditions [5].

With regard to toxicity it has been shown that WBH without chemotherapy is not associated with myelotoxicity [8]. It is of interest, that in our study as well as in other TCT trials the haematological toxicities after TCT do not differ from those secondary to chemotherapy alone [6,8,10 – 17]. It is hypothesised that myeloprotective cytokines are induced by WBH [26].

Nausea/vomiting, mucositis, and diarrhoea are considered to be mainly chemotherapy related, whereas asthenia/fatigue, herpes labialis, and dermal lesions are primarily caused by WBH. Thermal skin lesions of WHO I degree (erythemas) in 25% of the patients are in accordance with the observations of other WBH studies as well as the frequency of thermal lesions of WHO II (10 – 20%) and III degrees (< 5) [8,10,13,15,19,20,22,23].

We have seen no unexpected toxicities after administration of TCT, especially no fatal toxicities. Hyperglycaemias, lactatacidoses, and ph-decreases during WBH were tolerated without complications.

Several phase I/II TCT studies have been performed in patients with solid tumours, mainly suffering from advanced stages of breast cancer [8], colo-rectal carcinomas [8,14,15], ovarian carcinomas [8,11 – 13], soft tissue sarcomas [9,10], gastrointestinal carcinomas [8,16,17], and malignant pleural mesothelioma [27]. The response data of these trials compare favourably with our TCT results in our pretreated patients with breast, ovarian and colorectal carcinomas (Table **1**). In addition, these phase I/II-studies provide putative evidence that TCT enhances the antineoplastic effects of applied cytostatic agents and induces remissions even in pretreated patients usually classified refractory to the respective chemotherapy.

However, the question arose whether similar response rates as observed after TCT can be obtained by the application of either alternative potentially non-cross resistant cytostatic substances and/or dose-intensified chemotherapy regimes. In order to answer these questions randomized studies are warranted. To evaluate the effect of WBH we have prepared a study protocol for patients with advanced ovarian carcinomas which relapse shortly after or are refractory to first-line-chemotherapy with carbopla-

tin/paclitaxel. These pretreated patients will receive the chemotherapy combination of mitomycin C, ifosfamide, and cisplatin as second-line treatment at first under regular conditions and in case of ineffectiveness in combination with WBH as TCT.

To further substantiate whether TCT is more efficacious than chemotherapy alone, the majority of German hyperthermia performing physicians have constituted an interdisciplinary hyperthermia working group as a subgroup of the German Cancer Society and initiated several randomised phase III trials in patients with advanced small and no-small lung cancer, untreated malignant pleural mesothelioma, pretreated inoperable colorectal carcinomas and recurrent ovarian carcinomas.

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