Hyperthermia Combined with Chemotherapy – Biological Rationale, Clinical Application, and Treatment Results

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Key Words

Hyperthermia · Thermochemotherapy · Phase II/III studies, clinical results

Schlüsselwörter

Hyperthermie · Thermochemotherapie · Phase-II/III-Studien, klinische Ergebnisse

Summary

There is substantial evidence from preclinical data that the antitumor cytotoxicity of selected chemotherapeutic agents either alone or combined with radiation can be enhanced by appropriate heat exposure (40–44 °C) of cells or tumor tissues. Based upon these results the integration of hyperthermia as an additional treatment modality, given simultaneously with systemic chemotherapy or in combination with radiochemotherapy, is currently tested at the clinic. Regional hyperthermia combined with chemotherapy or radiochemotherapy showed impressive results (phase II studies) at clinical relevant temperatures in locally advanced tumors of different entities in terms of objective response rate, local tumor control and relapse-free survival. Clinical protocols of well-designed phase III trials on combined treatment modalities integrating hyperthermia are rather limited but for some tumors confirm its clinical benefit. In general, the clinical approach to use hyperthermia has gained much more interest within in the field of medical oncology. One of the major reason is the substantial technical improvements made with the available commercial equipment for local or regional heating, especially in case of deep-seated lesions or systemic heating. Further testing of the potential of hyperthermia combined with chemotherapy or radiochemotherapy in prospective randomized trials are warranted. At this time, hyperthermia as an adjunct to conventional treatment strategies is recommended in the setting of clinical protocols. The results of prospective trials should answer the question for which types of local advanced or metastatic tumors hyperthermia becomes standard as part of a multimodal treatment strategy.

Zusammenfassung

Die Ergebnisse der präklinischen Forschung zeigen, daß die therapeutische Effektivität ausgewählter Zytostatika sowie deren Kombination mit Bestrahlung unter hyperthermen Bedingungen (40–44 °C) in Tumorzellen und Tumorgeweben gesteigert wird. Auf dieser thermobiologischen Grundlage wird derzeit im Bereich der Klinik die Integration einer Hyperthermie als zusätzliche therapeutische Möglichkeit mit simultan applizierter systemischer Chemotherapie oder in Kombination mit Radiochemotherapie untersucht. Im Rahmen von Phase-II-Studien wurde für die Thermochemotherapie und Radiochemotherapie bei klinisch relevanten Temperaturen in lokal fortgeschrittenen Tumoren verschiedener Entitäten beeindruckende Resultate erzielt, wobei die objektive Ansprechrate, die lokale Tumorkontrolle und das rezidivfreie Überleben die wesentlichen Endpunkte darstellten. Klinische Ergebnisse von prospektiv randomisierten Phase-III-Studien unter Einbeziehung der Hyperthermie in multimodale Therapieansätze liegen nur vereinzelt vor, zeigen aber für einige Tumorentitäten einen deutlichen Vorteil zugunsten der Hyperthermie. Insgesamt ist im Bereich der internistischen Onkologie ein zunehmendes klinisches Interesse an der Hyperthermie festzustellen. Einer der wesentlichen Gründe ist der technische Fortschritt im Bereich kommerziell erhältlicher, ausgereifter Systeme zur lokalen bzw. regionalen Hyperthermie besonders für tiefliegende Tumoren oder Ganzkörperhyperthermie. Eine weitere Überprüfung der Hyperthermie kombiniert mit systemischer Chemotherapie oder Radiochemotherapie in prospektiven Phase-III-Studien ist dringend notwendig. Zum jetzigen Zeitpunkt sollte die klinische Anwendung der Hyperthermie als zusätzliche Maßnahme zu konventionellen Behandlungsstrategien im Rahmen klinischer Protokolle erfolgen. Die Ergebnisse derartiger Studien werden die Antwort geben, für welche Art von lokal fortgeschrittenen oder metastasierten Tumorentitäten eine Hyperthermiebehandlung als Teil eines multimodalen Vorgehens einen klinischen Standard darstellt.

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Introduction

The clinical application of hyperthermia with an increase of tissue temperatures (range 40–44 °C) has been integrated into multimodal anticancer strategies. This innovative treatment approach within the field of medical oncology is based on the evidence that hyperthermia enhances not only the radiosensitivity of tumors, but also the therapeutic effects of anticancer drugs, even in drug-resistant cells. Beside direct cytotoxicity of heat and thermal enhancement of drug efficacy, hyperthermia might be potentially useful to modulate the immune response against heated tumor cells at moderate temperatures by inducing the expression of heat shock proteins (HSP). Profound research has produced a scientific basis for the simultaneous application of hyperthermia in combination with ionizing radiation and/or systemic chemotherapy. The rational for *regional hyperthermia* (RHT) is based upon direct heat cytotoxicity and thermal enhancement of radio- and/or chemosensitivity within not well-perfused areas of the individual tumor. These areas usually are hypoxic and drug supply is limited but reaching highly effective temperatures (42–43 °C) due to low convection of heat. *Whole-body hyperthermia* (WBH) is usually applied simultaneously with systemic chemotherapy to patients having metastatic disease with the intention of thermal enhancement of drug sensitivity. This method is used not to target the heating field to individual tumors but to increase the core temperature of the patient's body (range 40–41.8 °C). At present the combination of RHT and chemotherapy or radiochemotherapy is administered within clinical protocols (phase II/III) in order to improve local tumor control and relapse-free survival in patients with high-risk, locally advanced tumors of different entities. WBH is currently tested in phase I/II protocols to evaluate feasibility and toxicity and to determine further the efficacy in patients with metastatic disease refractory to conventional chemotherapy.

Thermobiology

Cell survival studies have shown that heat-induced cytotoxicity is dependent on temperature and time of exposure. For an isoeffect induced in a specific cell type or tissue by heating for different times at different temperatures, a strong time–temperature relationship exists, showing a large increase of cytotoxicity at higher temperatures (42.5–45 °C). Cells exposed to more moderate temperatures (< 42.5 °C) are resistant to continuous heat exposure (2–4 h), which means they become thermotolerant [1]. Thermotolerance can also be induced at higher temperatures but its development requires time intervals of approximately 6–12 h at 37 °C before second heat exposure. The cellular status of thermotolerance is reversible and is greatly diminished about 48–72 h after the triggering heat dose has been applied. Thermosensitivity itself, but also the development of thermotolerance are influenced by various environmental parameters as pH, oxygen, nutritional supply, but also by the proliferative status of cells [2, 3]. The target for heat cytotoxicity is considered to be at the level of cellular proteins [4]. Whether the major interaction of hyperthermia and cellular proteins occurs at the level of the structure of membranes, cytoplasm, cytoskeleton or nucleus, still is an open question. One of the most exciting fields of thermobiology is our better understanding of the so-called 'thermal stress response' that relates to the early activation of heat shock genes encoding the preferential synthesis of HSP [5]. Under normal conditions and in response to stress, HSP are implicated in protein–protein interactions such as folding, translocation and prevention of inappropriate protein aggregation [6]. An emerging field is the role of HSP in the stimulation fo the immune response against cancer in which members of different HSP families (e.g. HSP70, HSP90-related glycoprotein gp96) are involved [7]. When purified from cells, it has been shown that they are associated with a broad range of peptides derived from that particular cell, such that the HSP chaperon the antigenic repertoire of the cells from which they are purified [8]. Immunotherapy of mice with preexisting cancers using HSP preparations derived from autologous cancer resulted in retarded progression of the primary cancer, a reduced metastatic load, and a prolongation of the life-span [9]. The role of HSP may be also interesting in that the heat-inducible HSP70 expressed on the cell surface of certain tumor cells acts as positive recognition signal for natural killer (NK) cells [10]. Therefore, beside direct cell cytotoxicity, hyperthermia has the additional potential for use in immunotherapy in clinical applications.

Heat and Chemotherapy Interaction

By combining heat exposure with anticancer drugs, a cooperative effect can be observed, dependent on the specific chemotherapeutic agent. In general, selected cytotoxic drugs showed an enhanced inhibition of clonogenic cell growth in vitro at higher temperatures. The magnitude of the thermal enhancement ratio (TER), which is defined as the ratio of the dose of a drug causing a given level of cell death in the presence of absence of hyperthermia, depends on the treatment temperature, time of exposure and drug concentration. Excellent reviews on the interaction of hyperthermia with a wide range of anticancer agents in models employing cells in tissue culture or rodent tumors have been presented by Hahn [11], Dahl [12] and Urano [13]. Despite the complexity of the underlying mechanisms for the observed thermal enhancement, the phenotype of interaction can be classified into 3 categories using isobologram analysis of in vitro data [14]: 1. independent; 2. additive; 3. synergistic. The term noninteractive (= independent) describes a situation in which hyperthermia and the individual drug appear to act by independent mechanisms. For some agents, the slope of the survival curve changes smoothly with continuously increasing temperature, meaning that hyperthermia results in the additivity of damage by increasing the cytotoxic mechanism (= additive). A third group of drugs shows distinct threshold effects: little or no sensitization at low temperatures, but marked sensitization occurring at 42 °C or higher (= synergistic). The classification for selected anticancer drugs whose modes of action fall into one of these categories is shown in table 1.

Antimetabolites (e.g. 5-fluorouracil, methotrexate) do not seem to be the optimal candidates for combination with hyper-

thermia because the combined effect of heat and drug exposure upon cell survival is equal with the effect of each individual treatment alone (=independent action). In addition, both taxanes (paclitaxel and docetaxel) did not show any significant thermal enhancement of cytotoxicity using different time intervals between the administration of taxanes and hyperthermia. The efficacy of alkylating agents (e.g. cyclophosphamide, ifosfamide and melphalan) but also of the nitrosoureas (e.g. BCNU) was enhanced by hyperthermia, both in vitro and in vivo. Maximal effects occurred when the agents were scheduled simultaneously with hyperthermia in vitro (endpoint: clonogenic survival) and immediately before hyperthermia in vivo (endpoint: tumor growth delay). In vivo the TER was the same for temperatures between 40.5–42.5 °C, with only a slight increase at higher temperatures of 42.5–44.5 °C. The importance of appropriate timing and sequencing for the evaluation of heat and drug interaction was recently shown for gemcitabine (= 2',2'-difluorodesocycytidine). Simultaneous application led to decreased cytotoxicity, whereas an interval of 24 h between dFdCyd and hyperthermia led to an enhanced cell killing [15]. For cisplatin (CCDP) and analogues (e.g. carboplatin) a potentiating effect of hyperthermia on cytotoxicity has been demonstrated already at relatively low temperatures of 40.5 °C. Overcoming chemoresistance has been extensively studied within the past, especially using CDDP-resistant cells [16]. In regard to the potential benefit that drug-resistant cells can be recruited for effective therapy by combining chemotherapy with hyperthermia, it was important to show that chemoresistance against several anticancer drugs (e.g. mitomycin C, anthracyclines, BCNU, melphalan) including CDDP could be reversed at least partially by the addition of heat [17]. The effect of thermotolerance and its interference with drug sensitivity of cells is still controversially discussed. However, hyperthermia did not induce cellular p-glycoprotein expression [18], and heat sensitivity of human leukemia clones displaying multidrug resistance was not altered [19]. In conclusion, there is substantial evidence from preclinical data that the antitumoral cytotoxicity of selected chemotherapeutic agents can be enhanced by appropriate heat exposure to cells or tumor tissues.

Clinical Application

First, clinical hyperthermia can be divided into two almost separate domains: WBH versus RHT. The clinical application of heat can be induced by electromagnetic field technique, ultrasound, or perfusion methods. Lately, noninvasive WBH can be administered with an Aquatherm radiant heat device (Cancer Research Institute, New York, NY, USA), achieving systemic temperatures up to 41.8 °C [20]. At present noninvasive RHT is most commonly performed using single microwave or ultrasound applicators for superficial hyperthermia and arrays of multiple applicators for deep heating [21]. Preferential heating of different tumor regions is achieved by the lower convection of heat from relatively poorly vascularized areas of tumors compared to their surrounding tissues. During hyperthermia treatments the measurement of the actual temperature distribution in the tumor or immediately adjacent tissue is crucial to the clinical evaluation of the quality of RHT

Table 1. Interaction between hyperthermia and anticancer drugs

Independent	Additive	Synergistic
5-Fluorouracil	doxorubicin	cisplatin
Methotrexate	mitoxantrone	carboplatin
Actinomycin D	cyclophosphamide	mitomycin C
Cytarabine	ifosfamide	bleomycin
Taxanes	melphalan	
	BCNU	
	gemcitabine	

[22]. So far, noninvasive methods for temperature measurements in deep-seated tissues are under investigation [23]. From temperature measurements acquired as temperature versus time and temperature versus depth plots, time-averaged temperatures can be calculated at each site monitored. In addition, the time-averaged temperatures above 20, 50 and 90% of the monitored points (reported in terms of T_{20}, T_{50}, and T_{90}) allow comparison of different RHT treatments in clinical protocols with regard to the quality of heating [24]. More recently, the clinical application of the thermal isoeffect dose (TID) concept has been applied in retrospective analysis of clinical data to guide future clinical studies in which different treatment protocols for different times at different temperatures are converted into equivalent minutes at 43 °C (EM_{43}) [25].

Regional Hyperthermia Combined with Radiation

Within the past, the most often performed treatment modality involving hyperthermia was its local or regional application with radiation. Now substantial clinical data exist, demonstrating for the treatment of locally advanced superficial tumors of different entities the improved efficacy and relative lack of normal tissue toxicity of combined radiation and hyperthermia treatments as compared to radiation therapy alone [26]. In addition to the results of numerous phase II studies, more recently the results of European phase III randomized multicenter trials became available. For example, in superficial tumors, an advantage of the combined treatment was shown for recurrent or metastatic melanoma [27] and recurrent breast cancer [28]. In melanomas there was an increase in complete response (CR) or 35–62% with an 2-year local control rate of 28 versus 46%. The overall 5-year survival rate was 19%, but 38% of the patients for whom all known disease was controlled, survived 5 years. The cooperative study of the Medical Research Council (MRC, UK) and the Princess Margaret Hospital (Ontario, Canada) demonstrated in recurrent breast cancer an increase in CR of 41–59% with a 2-year control rate from 20 to 50%, but no statistical difference in overall survival.

Regional Hyperthermia Combined with Chemotherapy

In the last few years radiation therapists start to accept RHT as an useful adjunct to their modality, motivated largely by

the results of these studies. Completed clinical protocols on the combination of RHT and chemotherapy are rather limited, but this approach has now gained much more interest within the field of medical oncology. One of the main reasons are the substantial technical improvements made in available commercial equipment for local or regional heating especially for deep-seated lesions and for systemic heating. Another reason is related to the more general acceptance of using multimodal strategies in the treatment of locally advanced cancers in order to obtain optimal local control and to prevent distant metastases. The advanced stages (e.g. T3/4 N1/2) or tumors in unfavorable anatomic locations often prevent primary resection with adequate margins, and the toxicity of radiotherapy limits the use of potentially therapeutic doses. Therefore, based on the benefits of heat-induced enhancement of drug-efficacy, the integration of RHT as an additional treatment modality given simultaneously with systemic chemotherapy is currently used in the clinic.

RHT given as an adjunct to systemic chemotherapy has been proven feasible with promising results in phase II trials. In table 2 results are given of several selected studies which have been extended to well-designed phase III trials already started, mainly in Europe. The most relevant aspects of these trials and further applications of thermochemotherapy for different tumor types will be discussed below.

Stomach and Pancreatic Cancer

Multi-institutional studies on clinical RHT combined with chemotherapy of stomach and pancreatic cancers have been performed in Japan using an 8-MHz-radiofrequency heating device (Thermotron RF8, Yamamoto Co., Osaka, Japan). This system most commonly used for hyperthermia in Japan achieves temperatures within the range of 40–43 °C in deep-seated tumors [29]. A total of 33 patients with stomach cancer (29 of them stage IV) and of 22 patients with pancreatic cancer (stage III/IV) received RHT twice weekly combined with mitomycin C and 5-fluorouracil [30]. Primary tumor response was 39% (3 CR/10 PR, partial response) and 36% (3 CR/5 PR), respectively. In addition, objective complaints (e.g. abdominal pain, ascites, passage disturbance, nausea, vomiting) were improved in 66% of all cases. Although follow-up was limited, among pancreatic cancers 2 patients survived disease-free longer than 30 months and 4 patients were still alive with no regrowth of tumors. These results and also the promising results reported by Shibamato et al. [31] using thermoradiotherapy in nonresectable pancreatic cancer warrant further clinical investigation.

Soft-Tissue Sarcomas and Bone Tumors

First results were obtained from a phase II study comprising 38 adult patients mainly with soft-tissue sarcomas [32]. These patients had relapsed after prior surgery and radiation and had not responded to previously given chemotherapy alone. The local response rate was 37%. A drug combination of ifosfamide and etoposide (VP 16) has been used combined with RHT as second-line treatment. Beside long-term tumor control in some of the patients, the analysis of tumor temperatures (e.g. T_{20}, T_{50}, T_{90}) achieved with the BSD system showed significant higher temperature parameters in responders versus non-

responders, respectively. These results were confirmed in an extended trial recruiting 65 patients with chemopretreated sarcomas [33]. The consecutive phase II protocol (RHT-91) was designed as a neoadjuvant study where the EIA regimen (etoposide + ifosfamide + adriamycin) was given to 59 patients with high-risk soft-tissue sarcomas (size >8 cm, grade II/III, extracompartmental) for 4 cycles prior to surgical resection. After first initial analysis showing no severe toxicity or unexpected treatment side effects [34], the evaluation of clinical and pathohistological response was 47%. At present, 29 patients are alive and the median follow-up of all patients is more than 3.5 years. The estimated rate of the 5-year overall survival is 46% [35]. Further, the EORTC Soft Tissue And Bone Sarcoma Group (STBSG) is testing this multimodal concept as a first-line treatment of high-risk soft-tissue sarcomas in adults in a multicenter prospective randomized phase III trial (EORTC 62961 / ESHO RHT-95) as an intergroup study with the European Society of Hyperthermic Oncology (ESHO). Patients meeting all of the eligibility criteria at first presentation (tumor size ≥5 cm, grade II or III, extracompartmental) or in addition after inadequate surgery (resections with microscopic/macroscopic residual tumor) will receive neoadjuvant chemotherapy either combined with or without RHT. WBH achieved by reinfusion of extracorporeal heated blood combined with ifosfamide and carboplatin (CBDCA) showed 6 PR in 19 patients with metastatic disease [36]. In a consecutive phase II study the ICE regimen (ifosfamide + carboplatin + etoposide) was given. In 12 sarcoma patients with distance disease, 7 partial responses were observed [37]. Noninvasive WBH achieved with an Aquatherm radiant heat device has been combined with carboplatin in patients with refractory cancers [38]. It is noteworthy that WBH did not affect the pharmacokinetics of carboplatin in that trial. Also, in repeated pair courses, there was no significant difference in the myelosuppression caused by carboplatin with or without WBH. More recently, the application of melphalan and WBH at 41.8 °C for 60 min was well tolerated and the clinical results served as the basis to further elucidate the potential role of WBH as and adjunct to systemic chemotherapy in advanced cancer patients [39].

Pediatric Cancers

The application of regional hyperthermia as part of combined modality therapy in pediatric patients, especially with tumors that failed to respond to standard regimen, has been proven feasible with several drug combinations. A multicenter study of the German Society of Pediatric Oncology and Hematology (GPOH) recruited 34 patients (mean age 11 years) mainly with deep-seated advanced soft-tissue sarcomas and Ewing tumors. Among 25 patients with locally advanced tumors, 12 patients of this group achieved no evidence of disease (NED), including 7 patients with CR [40]. Follow-up of these patients showed long-term tumor control ranging from 7 to 64 months. RHT in combination with cisplatin-based systemic chemotherapy in recurrent of refractory extracranial nontesticular germ cell tumors of children and adolescents was found to induce objective tumor response in 70% of patients.

In comparison to a matched cohort, the probability of event-free survival was shown to be superior for these patients [41].

Table 2. Hyperthermia combined with chemotherapy

Authors/Reference	Study	Entity	Number of patients	Hyperthermia	Chemotherapy	Results
Kakehi et al. 1990 [30]	phase II	stomach cancer	33	RHT/Thermotron 8 MHz	mitomycin + 5FU	3 CR + 10 PR (39%)
		pancreatic cancer	22		mitomycin + 5FU	3 CR + 5 PR (36%)
Issels et al. 1990 [32]	phase II (RHT 86) follow-up	sarcomas (pretreated with chemotherapy)	38	RHT/BSD 1000 60–110 MHz	VP 16 + IFO	6 pCR + 4PR + 4 FHR (37%)
1991 [33]		sarcomas (pretreated with chemotherapy)	65	RHT/BSD 1000 60–110 MHz	VP 16 + IFO	9 pCR + 4 PR + 8 FHR (32%)
1998 [35]	phase II (RHT 91)	high-risk soft-tissue sarcomas	59	RHT/BSD 2000 80–110 MHz	VP 16 + IFO + ADR (= EIA)	1 CR/6 pCR + 8 PR + 13 MR (47%) OS: 46%
	phase III (EORTC 62961)	high-risk soft-tissue sarcomas	44	RHT/BSD 2000 80–110 MHz	EIA ± RHT (randomized)	(12/98)
Eggermont et al., 1996 [52]	phase II	soft-tissue sarcomas	55	ILP	TNF + IFN + L-PAM	10 CR/35 PR (87%)
Wiedemann et al., 1994 [36]	phase I/II	sarcomas teratomas (metastatic)	19	WBH	IFO + CBDCA	6 PR (32%)
Wiedemann et al., 1996 [37]	phase II	sarcomas (metastatic)	12	WBH	IFO + CBDCA + VP 16	7 PR (58%)
Robins et al., 1997 [39]	phase I	refractory cancers (advanced or metastatic)	16	WBH/Aquatherm	L-PAM (dose-escalation)	1 CR/2 PR (19%)
Romanowski et al., 1993 [40]	phase II	pediatric sarcomas	34	RHT/BSD 2000 80–110 MHz	VP 16 + IFO + CBDCA	12 NED ('best response')/7 CR (duration: 7–64 months)
Wessalowski et al., 1998 [41]	phase II	pediatric non-testicular germ cell tumors	10	RHT/BSD 2000 80–110 MHz	CDDP + VP 16 + IFO (= PEI)	5 CR + 2 PR (70%) 6 patients alive without evidence of tumor (10–33 months)
Rietbroek et al., 1997 [42]	phase II	cervical cancer (recurrences)	23	RHT/array system 70 MHz	CDDP (weekly)	2 pCR/1 CR + 9 PR (52%)
Schilthuis et al., 1998	phase III (ESHO 97-1)	cervical cancer (recurrences)	5	RHT/array system 70 MHz	CDDP ± RHT (randomized)	ongoing study

RHT = Regional hyperthermia; EIA = etoposide + ifosfamide + adriamycin; ILP = isolated limb perfusion; WBH = whole-body hyperthermia; 5FU = 5-fluorouracil; VP 16 = etoposide; IFO = ifosfamide; ADR = adriamcyin = doxorubicin; CDDP = cisplatin; CBDCA = carboplatin; Bleo = bleomycin; L-PAM = melphalan; TNF = tumor necrosis factor-α; IFN = interferon-γ; p = pathohistological; CR = complete remission; PR = partial remission; MR = minor response; FHR = favorable histological response >75%; OS = overall survival; NED = no evidence of disease.

The results so far are encouraging and the study has been extended to patients with a poor response to first-line treatment.

Cervial Cancer
Recurrences of carcinoma of the uterine cervix develop in almost half of the patients treated for primary invasive cervical carcinoma (Figo stage IIIb/IVa). The majority of these recurrences occur without distant metastases in the pelvis. In this situation, radiotherapeutic or surgical treatment is seldom an option, because most of the patients have already received radiotherapy and very few are suitable for exenterated surgery. In a phase II trial performed within the Amsterdam Gynecologic Oncology Group (AGOG), 23 patients with previously irradiated recurrent carcinoma of the uterine cervix received weekly RHT and cisplatin [42]. The response rate was 52%, median duration of response 9.5+ months and the 1-year survival 42%. The overall

toxicity was moderate. The fact that 25% of the responding patients were able to undergo salvage surgery was also encouraging. Therefore, a prospective randomized trial comparing weekly RHT and cisplatin with cisplatin alone has been initiated in cooperation with several European institutions.

Regional Hyperthermia Combined with Radiochemotherapy

An extension of multimodal therapy concepts incorporating hyperthermia is its combination with radiation *and* chemotherapy ('triple modality'), which seems to be feasible and effective as tested in several phase I/II trials. A few examples of trimodality studies should be discussed for the tumor entities given in table 3.

Table 3. Hyperthermia combined with radiochemotherapy

Authors/Reference	Study	Entity	Number of patients	Hyperthermia	Radio-chemotherapy	Results
Sugimachi et al., 1992 [44]	phase II/III	oesophagus carcinoma (preoperative)	53	LHT/Endoradiotherm 13–56 MHz	32 Gy + Bleo (3 weeks)	7 pCR (27%) with RHT (n = 27) 2 pCR (8%) without RHT (n = 20)
Amichetti et al., 1993 [46]	phase I/II	head and neck cancer (N2/N3)	18	LHT/BSD-MA 150 280–300 MHz	70 Gy + CDDP (7 weeks)	13 CR + 3 PR (89%)
Rau et al., 1998 [51]	phase II	rectum carcinoma (preoperative)	37	RHT/BSD 2000 90 MHz	45 Gy + 5FU/Lv (4 weeks)	5 pCR (14%) + 17 PR (46%)
Rau et al., 1998 [51]	phase III	rectum carcinoma (preoperative)	100	RHT/BSD 2000 90 MHz	45 Gy + 5FU/Lv (4 weeks) ± RHT (randomized)	ongoing study

LHT = Local hyperthermia; RHT = regional hyperthermia; Bleo = bleomycin; CDDP = cisplatin; 5FU = 5-fluorouracil; Lv = leucovorine; p = pathohistological; CR = complete remission; PR = partial remission.

Cancer of the Esophagus

From 1990 to 91 40 patients with locally advanced squamous cell carcinoma of the esopagus were treated with preoperative chemotherapy (bleomycin + cisplatin) either combined with (n = 20 patients) or without (n = 20 patients) hyperthermia in a prospective trial using a radiofrequency endotract electrode. Objective tumor regression, histopathological effectiveness of the preoperative regimen and improvement of dysphagia were substantially better in the treatment arm combined with hyperthermia [43]. However, the number of pathological CR with no viable cancer cells in the resected specimens were significantly increased when preoperative radiotherapy was also used in addition to thermochemotherapy ('triple modality') as has been shown in previous trials [44, 45].

Head and Neck Cancer

On the basis of the experience in hyperthermia-combined treatment of nodal metastases from head and neck cancer with the addition of either cisplatin or radiotherapy, the Radiotherapy Department of Trento (Italy) performed a phase II study on this disease using trimodal therapy combining hyperthermia, conventionally fractionated radical radiation and weekly low-dose infusion of cisplatin [46]. In 16 out of 18 patients treated in such a way, objective tumor response was 89% (13 CR / 3 PR) and acute local toxicity was mild. The trimodal therapy deserves further evaluation as a way to enhance the efficacy of radiation and chemotherapy for local control.

Rectal Cancer

In rectal cancer, resection with negative margins is the major tool for achieving long-term survival. However, in locally advanced tumors (UICC stages II/III) local recurrences after surgery alone have been reported in up to 58% of patients [47]. For recurrent rectal cancer the prognosis is poor [48]. Efforts to improve the treatment results of locally advanced rectal cancers include preoperative radiotherapy or combined radiochemotherapy. Preoperative radiotherapy for locally advanced rectal carcinomas improved the resectability rate and the duration of local control [49, 50]. To further intensify
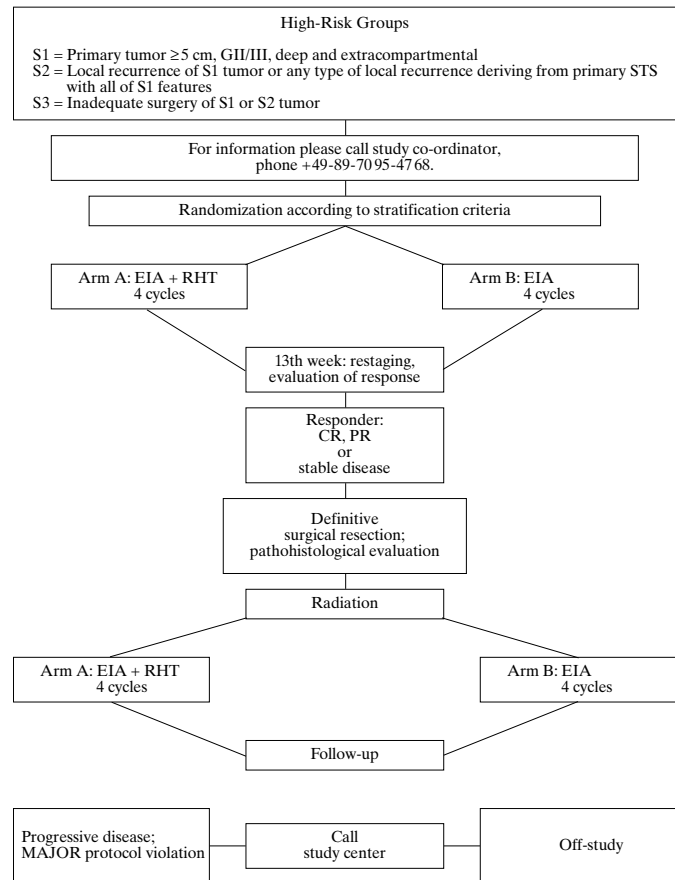

Fig. 1. EORTC 62961/ESHO RHT-95: High-risk soft-tissue sarcoma study; for information please call study co-ordinator, phone +49-89-70 95-47 68.

preoperative radiotherapy different regimens of combined chemotherapy and hyperthermia have been tested, showing encouraging results when compared with radiation or chemotherapy alone in historical controls. For example, in a prospective phase II study 37 patients with local advanced rectal

cancer (T_3/T_4) were treated with preoperative regional hyperthermia combined with radiochemotherapy [51]. The trimodal treatment was generally well tolerated. The overall resectability rate was 89%. The histopathological report confirmed no evidence of residual tumor in 5 resected specimens (5 pCR) and downstaging >50% of the tumor size as documented by CT or endorectal ultrasound in another 17 patients (17 PR). The survival rate after 38 months was 86% and none of the 31% of patients with negative margins (R0 resection) showed local recurrence, but 5 patients developed distant metastases. The contribution of regional hyperthermia to locoregional tumor control and overall survival within this preoperative setting is now to be proven in an ongoing phase III trial initiated by the same study group.

Conclusion

The distribution of temperatures (range 40–44 °C) achieved in human tumors by regional hyperthermia is heterogeneous mostly dependent on blood supply and tumor-specific parameters. Based upon preclinical investigations, the effects of hyperthermia are mainly due to enhancement of drug efficacy or thermal radiosensitization, and to a lower extent to direct cytotoxicity within areas of tumors heated up to more than 42.5 °C. The technical application of RHT is feasible and effective if combined with chemotherapy or radiochemotherapy, as shown in several clinical studies. Phase II/III trials showed impressive results at clinically relevant temperatures in locally advanced tumors of different entities in terms of objective response rate, local tumor control, and relapse-free survival. Further testing of the potential of regional hyperthermia combined with either of these modalities in prospective randomized trials is warranted.

The clinical experience using WBH is limited to first results of phase I/II studies but needs further evaluation in terms of toxicity and proven efficacy in metastatic disease not responding to first-line chemotherapy.

In general, hyperthermia as an adjunct to conventional treatment strategies can only be recommended in the setting of clinical protocols. The results of prospective trials should answer the question whether hyperthermia becomes standard as part of a multimodal strategy for the treatment of high-risk patients with locally advanced or metastatic tumors.

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