Non-oncological & oncological whole-body hyperthermia and a new immunological road to attack cancer? - some treatment procedures

Alexander von Ardenne Dr. rer. nat.
Von Ardenne Institute of Applied Medical Research, Germany

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Non-oncological & oncological whole-body hyperthermia and a new immunological road to attack cancer? -some treatment procedures

There is an increasing number of publication-based non-oncological indications in which the application of modern whole-body hyperthermia (WBH) can bring about an alleviation for the patients. Some of these indications are arterial hypertension, chronic back pain, fibromyalgia syndrome, psoriatic arthritis, ankylosing spondylitis, systemic scleroderma and major depressive disorder. This presentation wants to inform about the procedure in the mentioned indications. In a first Table 1 "**Publication-Based Treatment Procedures for WBH for some Non-Oncological Indications**" are the main parameters for the WBH procedure given with some remarks and together with the publications behind the procedure.

Furthermore, the application of WBH adjuvant to the conventional methods for the treatment of cancer patients - surgery, radiotherapy and chemotherapy - could be helpful. By WBH before operation, which increases the microcirculation and activates the immune system, the risk of wound infection after surgery is reduced. WBH increases with its intensified perfusion the oxygen partial pressure in tumors for higher x-ray sensitivity. WBH combined with chemotherapy for the treatment of cancer patients in a therapy resistant, metastatic or advanced stage of solid malignancies can improve the response rate and increases the quality of life.

Last but not least a view onto the immune system. It is still not proved by (published) clinical trials with cancer patients but there is a good probability that WBH with temperatures until fever-range supports the efficacy of checkpoint inhibitors. Also, not proved by clinical trials is the proposal of Hatfield & Sitkovsky to activate the cytotoxic T-cells to kill cancer cells by increasing the Oxygen partial pressure in the tumor, followed by a reduced adenosine concentration in the tumor microenvironment, and in connection with an adoptive immunotherapy. Fever-range WBH could support this process by increasing the killing efficiency of the cytotoxic T-cells. In a second Table 2 "**For Discussion: Treatment Procedures regarding Adjuvant Treatment of Cancer Patients with WBH**" is given a proposal of the main parameters for the WBH procedure with the rationale of the procedure and remarks together with the associated publications.

For all the mentioned indications and procedures are currently two leading devices used, realizing body-core temperatures from mild until extreme WBH (s. Fig 1 and Fig 2):

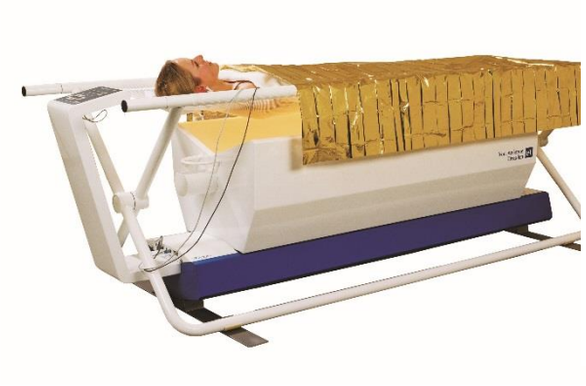

Fig 1 Ardenne-IRATHERM®1000; **exclusively** water-filtered infrared-A radiation is used radiation
www.iratherm.de

Fig 2 Heckel-HT3000; **regional** water-filtered infrared-A used
www.hydrosun.de

Table 1 Publication-Based Treatment Procedures of Whole-Body Hyperthermia for some Non-Oncological Indications

Indication	**Target-Temperature T(rectal)**	**Heating-Up Phase**	**Plateau Phase; (Retention)**	**Resting Phase**	**Number of Sessions**	**Monitoring**
	°C	**min**	**min**	**min**		
Arterial Hypertension	38,3	30	0	30	8 (2 x /week) or 8 (every 2 days)	T(axill), Pulse

Remark
↓ systolic by 22 mmHg, ↓ diastolic by 12 mmHg, 10% nonresponder

Literature

· Mischke M. Wirkungen einer einmaligen bzw. seriellen Infrarot-A-Hyperthermie bei Patienten mit arterieller Hypertonie der WHO-Stadien I und II. Diss. Humboldt-Universität Berlin 18.07.1991
· Meffert H, Scherf HP, Meffert B. Milde Infrarot-A-Hyperthermie: Auswirkungen von Serienbestrahlungen mit wassergefilterter Infrarotstrahlung auf Gesunde und Kranke mit arterieller Hypertonie bzw. systemischer Sklerodermie. Akt Dermatol, 1993;19:142-148

Chronic Back Pain	38,5	45	15	30	7 (1 x /week)	T(rect), T(axill), Pulse

Remark
prä/post 1 year: analgetics consumption < 10%

Literature

· Weller E, Ullrich D. Infrarot-A-Hyperthermie-Anwendung bei

Patienten mit Analgetica-Abusus wegen chronischer Rückenschmerzen. Vortrag auf dem 95. Kongreß der Gesellschaft für Phys Med und Rehab 5.10.1990

Fibromyalgia Syndrome	38,1	40	15	30	6 (2 x /week), or 6 (every 2 days) or 6 consecutive days	T(axill), Pulse

Remark

prä/post 6 month 20% below basic painacc. to "Fibromyalgia Impact Questionaire"/FIQ

Literature

· Brockow T, Wagner A, Franke A, Offenbächer M, Resch KL. A Randomized Controlled Trial on the Effectiveness of Mild Water-filtered Near Infrared Whole-body Hyperthermia as an Adjunct to a Standard Multimodal Rehabilitation in the treatment of Fibromyalgia. Clin J Pain 2007;1:67-75

· Walz J, Hinzmann J, Haase I, Witte T. Ganzkörperhyperthermie in der Schmerztherapie – eine kontrollierte Studie an Patient. mit Fibromyalgiesyndrom. Schmerz 2013;1:38-45

· Romeyke T, Stummer H. Multi-modal pain therapy of fibromyalgia syndrome with integration of systemic whole-body hyperthermia – effects on pain intensity and mental state: A non-randomised controlled study. J Musculoskel Pain 2014;4:341-55

· Schleenbecker HG, Schmidt KL. Zur Wirkung einer iterativen milden Ganzkörper-hyperthermie auf den Fibromyalgieschmerz. Phys. Rehab. Kur Med, 1998;8:113-117

Psoriatic Arthritis	38,5	45	15	30	6 (in 8 days) or 6 consecutive days	T(rect), T(axill), Pulse

Remark

prä/post 6 month alleviation of pain, ↓ Disease-Activity Score (DAS 28) 3 month
(DAS28 = activity and function parameter)

Literature

· Lange U, Schwab F, Müller-Ladner U, Dischereit G. Wirkung iterativer Ganzkörperhyperthermie mit wassergefilterter Infrarot-A-Strahlung bei Arthritis psoriatica – eine kontrollierte, randomisierte, prospektive
Studie. Akt Rheumatol 2014;05:310-16

Axial Spondyloarthritis	38	30	15	120 in bed	6 (2 x /week)	T(axill), Pulse

Remark

prä/post 3 months pain reduction

Literature

· Stegemann I, Hinzmann J, Haase I, Witte T. Ganzkörperhyperthermie mit wassergefilterter Infrarot-A-Strahlung bei Patienten mit axialer Spondyloarthritis. Orthopäd. & Unfallchirurg. Praxis 2013;10:458-463

Ankylosing Spondylitis	38,5	45	15	30	6 (in 8 days) or 6 consecutive days	T(rect), T(axill), Pulse

Remark

↓ disease activity index (BASDAI) 3 month, ↓ blood sedimentation rate 3 month, ↑ TLR-4, IL-10

(BASDAI = Bath AS Disease Activity Index

Literature

· Lange U, Müller-Ladner U, Dischereit G. Effectiveness of whole-body hyperthermia by mild water-filtered infrared-A radiation in ankylosing spondylitis – a controlled, randomized, prospective study. Akt Rheumatol 2017; 2:122-128

· Zauner D, Quehenberger F, Hermann J, Dejaco C, Stadner MH, et al. Whole-body hyperthermia treatment increases interleukin 10 and toll-like receptor 4 expression in patients with ankylosing spondylitis: a pilot study. Int J Hyperthermia 2014; 6:393-401

Systemic Scleroderma	38,3	30	0	30	15 (2 x /week) or 15 (every 2 days)	T(axill), Pulse

Remark

in the follow-up period of two years for about 50% of the female patients the frequency and severity of Raynaud attacks were sustained reduced

Literature

· Meffert H, Scherf HP, Meffert B. Milde Infrarot-A-Hyperthermie: Auswirkungen von Serienbestrah-lungen mit wassergefilterter Infrarotstrahlung auf Gesunde und Kranke mit arterieller Hypertonie bzw. systemischer Sklerodermie. Akt Dermatol, 1993;19:142-148

· Förster J, Fleischanderl S, Wittstock S, Storch A, Meffert H. Letter to the Editor: Infrared-Mediated Hyperthermia is Effective in the Treatment of Scleroderma-Associated Raynaud's Phenomenon. J Investig Dermatol, 2005;6:1313-16

Major Depressive Disorder	38,5	110	60	0	1	T(rect), T(axill), Pulse

Remark

a single session of whole-body hyperthermia produced a significant antidepressant effect apparent within a week of treatment that persisted for 6 weeks after treatment.

Literature

· Janssen CW, Lowry CA, Mehl MR, Allen JJB, Kelly KL, Gartner DE, Medrano A, Begay TK, Rentscher K, White JJ, Fridman A, Roberts LJ, Robbins ML, Hanusch KU, Cole SP, Raison CL. Whole-Body Hyperthermia for the Treatment of Major Depressive Disorder – A Randomized Clinical Trial. JAMA Psychiatry 2016; 8:789-95

· Meesters Y, Beersma DGM, Bouhuys AL, vdHoofdakker RH. Prophylactic Treatmet of Seasonal Affective Disorder (SAD) by Using Light Visors: Bright White or Infrared Light. Soc Biol Psychiatry 1999; 46:239-246

Table 2 For Discussion: Treatment Procedures regarding Adjuvant Treatment of Cancer Patients with Whole-Body Hyperthermia

Procedure	**Rationale**	**Target-Temperature T(rectal)**	**Heating-Up Phase**	**Plateau Phase; (Retention)**	**Resting Phase**	**Number of Sessions**	**Monitoring**
		°C	**min**	**min**	**min**		
Surgery + Whole-Body Hyperthermia	whole-body hyperthermia before surgery activates the immune system and reduces the risk of a postoperative infection. Hypothesis: better wound care on the side of the body-own immune defense	+ 0,35	30	0	0	1 x right before surgery	T(axill)

Remark

421 patients with clean breast, varicose vein, or hernia surgery randomized in control- and treatment group. Whole-body hyperthermia device was left in situ until just before surgery.

Follow-up: 2 and 6 weeks postoperatively: wound infections were reduced from 14% (control group) to 5% (hyperthermia group). post OP: hyper gr. TNF-**α**, HSP 's 60+90 increased

Literature

· Melling AC, Ali B, Scott EM, Leaper DJ. Effects of preoperative warming on the incidence of wound infection after clean surgery: a randomised controlled trial. Lancet 2001;358:876-80

· Sulyok L, Fleischmann E, Stift A, Roth G, Eichinger DL, Kasper D, Spittler A, Kimberger O. Effect of preoperative fever-range whole-body hyperthermia on immunological markers in patients undergoing colorectal cancer surgery. Br J Anaesth 2012; 5:754-61
· Wong PF, Kumar S, Bohra A, Whetter D, Leaper DJ. Randomized clinical trial of perioperative systemic warming in major elective abdominal surgery. Br J Surg 2007; 4:421-26

Radiotherapy + Whole-Body Hyperthermia	whole-body hyperthermia after total body irradiation enhances the hematopoiesis and the recovery of the neutrophils	39,5	?	360	cooling by air convection down to 38 °C. Discharge approx. 2 h after cooling	1 x 2 h after total body irradiation	T(rect), T(axill), cardiovascular "Critical Care Monitoring"

Remark

Animal experiment: 2h after total-body irradiation (3 or 6 Gy) 6h whole-body hyperthermia and conscious sedation (a.o. midazolam + fentanyl):
signif. increase in the rate of neutrophil recovery in blood ✚ in hematopoietic stem cells of bone marrow ✚ in neutrophil progenitors.
Increased G-CSF concentration in the serum ✚ in the bone marrow ✚ in the intestinal tissue.
Increased concentration of IL-17 ✚ IL-1β ✚ IL-1**α** in the intestinal tissue

Literature

· Capitano ML, Nemeth MJ, Mace TA, Ruf CS, McCarthy PL, Segal BH, Repasky EA. Elevating body temperature enhances hematopoiesis and neutrophil recovery after total body irradiation in an IL-1-, IL-17-, and G-CSF-dependent manner
Blood 2012; 13:2600-9
· Zaidi HK, Patil MS, Bhatt MB, Badewadikar RS, Subramanian M, Rajan R, Kaklij GS, Singh BB. Effect of whole-body hyperthermia on radiation therapy of transplanted fibrosarkoma in Swiss mice. Int J Hyperthermia 2001; 5:428-38
· Shen RN, Hornback NB, Shidnia H, Wu B, Lu L, Broxmeyer HE. Whole-body hyperthermia: a potent radioprotector in vivo. Int J Radiat Oncol Biol Phys 1991; 3:525-30

Chemotherapy + Whole-Body Hyperthermia	whole-body hyperthermia raises the chemotherapy-induced tumor-response by combination with special chemotherapy protocol (here: Cisplatin, Gemcitabine and Interferon-**α**: proof in preclinical model followed by phase I/II study)	40,0	60	360	cooling by air convection down to 38 °C. Discharge approx. 2 h after cooling	up to 7 sessions	T(rect), T(axill), T(skin), cardiovascular "Critical Care Monitoring"

Remark

37 patients with therapy-resistant, metastatic or advanced solid malignancies.

Conscious sedation (a.o. midazolam + fentanyl):

43% response rate (best: pancreas ca. with 5/7) ✚ LQ-improvement w.r.t. pain, weight, fatigue.

Extreme whole-body hyperthermia (Trect > 42°C) in the scope of the systemic Cancer Multistep Therapy is not considered here

Literature

· Bull JMC, Scott GL, Strebel FR, Nagle VL, Oliver D, Redwine M, Rowe RW, Ahn CW, Koch SM. Fever-range whole-body thermal therapy combined with cisplatin, gemcitabine and daily interferon-α: A description of a phase I-II protocol. Int J Hyperthermia 2008; 8: 649-662

· Kraybill WG, Olenki T, Evans SS, Ostberg JR, O'Leary KA, Gibbs JF, Repasky EA. A phase I study of fever-range whole-body hyperthermia in patients with advanced solid tumors: correlation with mouse models. Int J Hyperthermia 2002; 3:253-66

· Hildebrandt B, Dräger J, Kerner T, Deja M, Löffel J, Stroszczynski C, Ahlers O, Felix R, Riess H, Wust P. Whole-body hyperthermia in the scope of von Ardenne's systemic cancer multistep therapy (sCMT) combined with chemotherapy in patients with metastatic colorectal cancer: a phase I/II study. Int. J. Hyperthermia 2004; 3:317-33

Next Steps?

Checkpoint Immunotherapy (Immunoncolog. Therapy) + Whole-Body Hyperthermia	checkpoint-inhibitors reduce the suppression of cytotoxic T-cells and activate these to damage cancer cells. Preclinically: killing efficiency of T cells against cancer cells reaches its maximum at 39.5 °C (≈ 3 times higher than at 37 °C)	39,5	45	60	60 preferably in bed (thermally well insulated) to increase the thermal dose	e.g. 6 sessions (in 2 weeks Mo, We, Fr)	T(rect), T(axill), cardiovascular "Critical Care Monitoring"

Remark

Currently focused on melanoma patients.

Simultaneously during application of checkpoint-inhibitors a number of whole-body hyperthermia sessions should run in phases of high efficacy of checkpoint-inhibitors under consideration of the pharmacodynamics of the checkpoint-inhibitors (time constant betw. application & inhibition?).

Attention SE: activation of cytotoxic T-cells by checkpoint-inhibitors attracts systemically and it attracts therefore also against normal cells in inflammation regions!

Literature

Still no clinical publication available! → However, hint to meaningfulness:

· Schadendorf D. Entscheidungsfindung für die klinische Praxis: Aktuelle Konzepte und Behandlungsalgorithmen mit Immun-Checkpoint-Inhibitoren beim Melanom. Oncol Res Treat 2016;39/4:8-12

· Larkin J, Sileni VC, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015; 373:23-34

· Weigelin B, activating serial killers of cancer cells with artificial fever: Hyperthermia as supporting strategy for immunotherapy of cancer. Symposium - Modern Hyperthermia, Krakow, 14.11.2015

· Kobayashi Y, Ito Y, Ostapenko VV, Sakai M, Matsushita N, Imai K, Shimizu K, Aruga A, Tanigawa K. Fever-range whole-body heat treatment stimulates antigen-specific T-cell responses in humans. Immunology Letters 2014; 162:256-61

Adoptive Immunotherapy + Respiratory Hyperoxia + Whole-Body Hyperthermia	hypoxia in tumors leads to high adenosine concentration in the tumor microenviron-ment and activates in zytotoxic T cells immunosuppressive factors such as PD-1 and CTLA-4. Respiratory	39,5	45	60	60 preferably in bed (thermally well insulated) to increase the	e.g. 6 sessions (in 2 weeks Mo, We, Fr)	T(rect), T(axill), cardiovascular "Critical Care Monitoring"

	hyperoxia is said to reverse this process. Preclinically: killing efficiency of T cells against cancer cells reaches its maximum at 39.5 °C (≈ 3 times higher than at 37 °C)				thermal dose		

Remark

Mice-study: The combination of „Adoptive Immunotherapy "(Kjaergaard 2003) and long-lasting inhalation of 60 % O2 enabled the complete regression of 11-day old established pulmonary tumor in all mice of the treatment group. Whereas > 250 tumors per mouse were counted in the control group (Hatfield 2015).

In patients with a weaker immune system, a further increase of the killing efficiency of the T-cells by whole-body hyperthermia could be helpful (Weigelin 2015, Kobayashi 2014).

Literature

Still no clinical publication available! → However, hint to meaningfulness:

· Hatfield SM, Kjaergaard J, Lukashev D, Schreiber TH, Belikoff B, Abbott R, Sethumadhavan S, Philbrook P, Ko K, Cannici R, Thayer M, Rodig S, Kutok JL, Jackson EK, Karger B, Podack ER, Ohta A, Sitkovsky MV. Immunological mechanisms of the antitumor effects of supplemental oxygenation. Sci Transl Med 2015; 7:277ra3027:435-36

· Kjaergaard J, Peng L, Cohen PA, Shu S. Therapeutic efficacy of adoptive immunotherapy is predicated on in vivo antigen-proliferation of donor T-cells. Clin Immunol 2003; 108:8-20

· Weigelin B, activating serial killers of cancer cells with artificial fever: Hyperthermia as supporting strategy for immunotherapy of cancer. Symposium - Modern Hyperthermia, Krakow, 14.11.2015

· Kobayashi Y, Ito Y, Ostapenko VV, Sakai M, Matsushita N, Imai K, Shimizu K, Aruga A, Tanigawa K. Fever-range whole-body heat treatment stimulates antigen-specific T-cell responses in humans. Immunology Letters 2014; 162:256-61