Introduction to hyperthermia – The potential of therapeutic overheating

By Holger Wehner

Hyperthermia undoubtedly represents a meaningful option for treating specific chronic diseases and cancer in various stages. Its efficacy has been documented by global empirical data gathered for decades as well as by numerous examinations and studies on the subject. Scientific data of different evidence levels on the use of hyperthermia for treating chronic diseases are available in the fields of dermatology (scleroderma),[24] gastroenterology (ulcerative colitis, Crohn's disease), pulmonology (asthma),[25,10] metabolic disorders,[26, 27] morbid obesity and hypertension [24, 30, 32, 33] as well as rheumatology or immunology [2, 31, 34, 36] and in pain therapy, especially for the treatment of fibromyalgia [29, 35]. The role of hyperthermia has also been examined in the context of detoxification efforts.[28] As can easily be discerned, the feasible application range of hyperthermia is exceedingly broad, and the method – when properly applied – is capable of generating sustained prognostic improvement in a multitude of health conditions, including, but not limited to oncology.

Hyperthermia is an exciting medical area that is in constant motion as research is conducted all over the world. In the future, whole-body hyperthermia may become especially relevant for infectious diseases caused by bacteria or viruses. The first associated studies[10] have already revealed interesting aspects (HIV, hepatitis, spirochetes [syphilis, Lyme disease]).[37, 38] Distinct equipment technologies with a range of different energy sources are available for the treatment of various diseases. For example, scientific data indicate that water-filtered infrared A radiation should be favored for dermatological applications and for treating fibromyalgia.[29]

Fourth pillar of oncology

A cancer diagnosis continues to mark a drastic incursion in the life of affected patients. Driven by fear of death and the tortures of therapy, patients keep looking for additional assistance. Considering that the potential of hyperthermia has been discussed extensively over the past decades, the medical profession is now called

upon to demonstrate its competence and to jointly promote the effort for prognostic improvement together with all disciplines of the corresponding tumor entity. As numerous polls and surveys have shown, patients greatly appreciate this effort. By now, a growing body of studies has proven that hyperthermia is far more than just a complementary therapy – it is in fact an important part of integrative concepts. The ability of hyperthermia to increase radiation sensitivity is certainly among the undisputed aspects supporting this statement.

Hyperthermia treatment options are now available on a nationwide scale in Germany, with over 200 inpatient and outpatient medical facilities established. Some 150 of these are organized in professional associations, the majority in the *Deutschen Gesellschaft für Hyperthermie e.V. (German Society of Hyperthermia).* Knowledge gain has advanced significantly, although the *Federal Joint Committee* has not yet integrated hyperthermia into basic care, allegedly for lack of sufficient evidence of efficacy. The data that delayed the integration of hyperthermia into basic care in 2005 (!) had been gathered in the previous decade. As a result, patients may have to forgo cost coverage or reimbursement in the current German healthcare system in 2018 because we are relying on a state of expertise that was relevant two decades ago! Knowledge is evolving rapidly, as further proof of the serious aspects and academic rigor of this therapy option. In 2007, Professor Bamberg[1] stated the following at a press conference associated with the meeting of the European Society for Hyperthermic Oncology (ESHO) in Prague:

When properly applied, hyperthermia can be considered the fourth pillar of cancer treatment to complement surgery, radiation and chemotherapy. Especially in the case of advanced tumors, we can achieve amazing results with hyperthermia in combination with other methods: The spectrum ranges from significant quality of life improvements and extended survival to complete cures of some tumor types.

Insight into methodological diversity

A therapy option that offers as many possibilities as hyperthermia will naturally have detractors, but the times of relying on historical data and at best, sharing empirical treatment protocols are long gone. It is of great relevance for users and referring

physicians to understand the potential this therapy option holds for improving the prognosis in all stages of various cancers, ranging from adjuvant, or even neoadjuvant therapy, to palliative use.

This context is significant, both with regard to thermo-chemotherapy and for using hyperthermia as an addition to radiotherapy. Even when using complementary options, certain aspects must be taken into account for integrating hyperthermia. The potential of this tried-and-tested, helpful therapy option should be made accessible to as many therapists and patients as possible, as the old and unfounded opinion of critics that the method “is not much use” has clearly been reduced to absurdity. Of course, not everything that is feasible is also desirable and helpful. We must avoid any unfortunate combination of individual therapy steps to prevent disadvantages for patients. For this purpose, quality standards were developed over the last two decades and professional bodies have generated guidelines.

Heating up the human body for therapeutic reasons nowadays can be achieved in many different ways. That is why we distinguish between local, regional, partial body and whole-body hyperthermia, based on the form of application. Differentiations are also made based on technical aspects. Within whole-body hyperthermia, this ranges from contact heat and infrared C to infrared B and infrared A radiation, which enables the gentlest physiological warming of the organism.[7, 8, 9, 12, 13] Local or regional hyperthermia must respect physical characteristics. In principle, the following applies: the higher the frequency, the greater the potential for superficial warming. Accordingly, it takes either lower frequencies or suitable antenna systems to reach deep-seated tissue, and reviewed procedures and appropriate equipment technology are in place to ensure exactly that.

Application examples

Nowadays, **local hyperthermia** can be used both for surface hyperthermia (e.g. to treat a recurring tumor in scar tissue) or for local transcutaneous applications in deeper locations. Thermal ablation methods offer the necessary options. For example, thermal ablation of a liver, lung or bone metastasis can be performed with a laser beam at temperatures up to 110°C. Radiofrequency ablations for the same locations are already part of standard surgical routine. The target temperature for

local hyperthermia, but also for hyperthermal lavage, is frequently around 43°C or even reaches 50°C and above (the literature mentions values up to 80°C, for example in prostate hyperthermia). **Regional deep hyperthermia** aims for temperatures above 42°C.

Mild and moderate temperature ranges (Fig.1) are distinguished from extreme ranges in whole-body hyperthermia. These choices also require a definition of the therapeutic goal. The work by SCHMIDT [2] created a solid base for immunological aspects in professional discussion, while REPASKY [3], BULL [4] and GAIPL [5], to name just a few, added important impulses and insights with regard to whole-body hyperthermia and hyperthermia in general. The lowest temperature found in the literature in the context of direct tumor cell impact is 41.5°C as stated by OVERGAARD[6], albeit under the aspect of sensitivity increases based on tumor tissue acidification. VON ARDENNE[7] had previously reached and published the same findings. From today's point of view, it is recommended to aim for temperatures above 42°C to achieve these effects. In the interest of avoiding tissue destabilization and direct cell damage, it can be postulated that each tenth of a degree in temperature increase above the mark of 42.0°C is relevant. That prompted VON ARDENNE [7] and his collaborator, STEINHAUSEN, to define a clinical routine that allows for the safe application of 42.3°C in this group. These data were supported by an additional phase-I study[18]. After clinical testing, this specific therapy option resulted in a study on advanced colorectal cancer at Charité Hospital[13] with specific emphasis on systemic cancer multi-step therapy, i.e. the synchronous effort to achieve tumor acidification and oxygenation (thermal sensitivity). In pursuit of temperature escalation, a few teams developed whole-body temperatures above 43°C.[10,11] However it must be noted in the evaluation of such temperatures that they can only be reached very briefly. In addition, it is important to consider study data (VAUPEL[39]) that may limit the target temperature (with the exception of thermal ablation) to 42.5°C (adenosine accumulation).

Hyperthermal bladder, peritoneal and pleural lavage nowadays are included in the options of regional therapy. Thanks to the increasing maturity of technical systems, targeted hyperthermia applications can be performed safely in modern human

medicine.

With regard to whole-body hyperthermia, deliberations ranging from immune stimulation (killer cells) under near-fever conditions to the work of BULL[4], which resulted in improved response rates for different tumor entities, in part with near-fever long-term hyperthermia (6 to 8 hours), are as interesting as the evidence that poly-chemotherapy is more effective in the treatment of pleural mesothelioma under extreme whole-body hyperthermia [21]. The list of these examples would be incomplete without the previously cited work of WUST et al. on colorectal cancer.

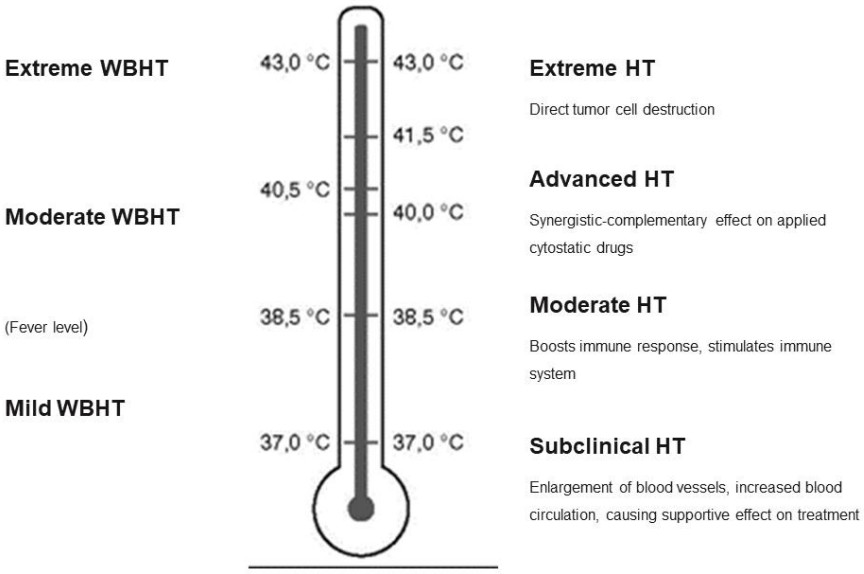

Fig. 1: Temperature level classification for whole-body hyperthermia

Comment regarding discourse

It would exceed the scope of an introductory article on hyperthermia that discusses the method in general terms to provide extensive, detailed information about the different forms of hyperthermia applications. Nevertheless, it is vital to explain this relevant therapy option in greater detail – and to sensitize others to its broad therapy potential. The frequently emotional debates on the subject, which continue in spite of successfully completed studies, keep pointing out the need for thoughtful communication within the professional world. Such poorly informed discussions are astonishing to anyone with extensive training in hyperthermia, as one would expect

at least some knowledge of existing studies. In the interest of the affected patients, it is essential to pursue questions and to make use of the options for gentle, additive treatment. As scientists, that will lead us to further questions, but answering them is the demand of our times. Undoubtedly, much examination is still required, both in basic research and subsequently, in clinical studies.

However, to deprive affected patients of current, up-to-date knowledge is almost negligent in view of the existing data situation. Impressive results of various scientific value have been published for different entities with regard to regional therapy in the last fifteen years. For patients affected by cancer, the studies listed in Table 1 may be reason for hope that their disease may respond to the option of hyperthermia.

- Impact of deep regional hyperthermia generated by devices with capacitive coupling (8 – 13.56 MHz) on brain tumors[14]
- Hyperthermia with BSD technology for soft tissue sarcoma[15]
- Regional hyperthermia with BSD technology[16] and capacitive coupling[17] for pancreatic cancer
- Deep regional hyperthermia and radiotherapy for cervical cancer[19, 19a]
- Hyperthermia for recurring chest wall tumors [20]

Table 1: Current studies on hyperthermia (selection)

Future research priorities

A close analysis of the professional discussion reveals that many potential synergies have not yet been used. Thus, the studies of ISSELS [15,16] document superior outcomes when hyperthermia is included in the treatment of soft tissue sarcoma. Because sarcomas frequently metastasize, it is essential to review the option of systemic, i.e. whole-body hyperthermia, and to consider its early use.

Temperature is an important criterion for the application of hyperthermia in the context of oncology. Since homogeneous measurements of temperature are undoubtedly easy to achieve in the use of whole-body hyperthermia, it seems obvious that results could be further improved if extreme whole-body hyperthermia were to be included in therapeutic strategies more frequently, potentially in

combination with regional applications (in the sense of a “hybrid treatment”).

Aspects of possible stray tumor cells and micro-metastases may represent another basis for discussion to be advanced. Similar thoughts also play a role with regard to intensifying the efforts to improve the prognosis of pancreatic cancers. The question of sufficient tissue temperature in a deep-seated abdominal location will be especially relevant for this particular tumor entity. So-called hybrid systems may offer potential in the future. Thus, it may be conceivable to combine regional and whole-body hyperthermia. Surely it cannot be insignificant whether the warming of a patient's body region starts at an average of 36.6°C or at 38.5°C after whole-body hyperthermia, for example in the mild to moderate temperature range. Whole-body hyperthermia, which is safe and causes no or little physical stress at this temperature level, could precede regional therapies. The increase of immunological phenomena [22] is likely to have a favorable impact on the desired results as well.

Summary

The body of scientific research on the topic of hyperthermia keeps growing. This work covers all levels, from basic research to clinical studies. Extensive studies on synergies with various cytostatic drugs[23] and radiation-sensitizing effects have paved the way for inclusion in clinical routine.[19, 20] The available studies document positive results for patients and encourage further efforts.

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