Regional hyperthermia

Multimodal tumor treatment

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Regional hyperthermia (= elevation of regional body temperature) is a treatment modality with few side effects, which in combination with radio-/chemotherapy can significantly improve the prognosis in locally advanced tumor disease.

In the mid-19th century, the German surgeon Carl W. Busch reported on a patient whose malignant facial sarcoma had clearly regressed in size after an erysipelas-related episode of fever. This observation led to the administration of bacterial vaccines to tumor patients to artificially induce fever.

Since controlled and reproducible hyperthermia was not technically feasible for a long time, this modality initially fell into therapeutic obscurity. In retrospect, these studies may mark not only the modern beginning of hyperthermia, but also of immunotherapy in oncology.

Technical advances made procedures such as whole-body hyperthermia possible and finally resulted in radiative regional hyperthermia, which has since found its way into international oncology guidelines. At the Grosshadern Campus of the Ludwig-Maximilians-University Medical Center (LMU) in Munich, targeted hyperthermia of tumors in combination with chemotherapy or radiotherapy has been employed successfully since 1986. The Division of Hyperthermia, headed by Lars Lindner, M.D., PhD., is working intensely on potential clinical applications of hyperthermia and has conducted groundbreaking studies on this topic.

Hyperthermia effects

The rationale for raising the temperature in tumors to 40–44°C is not only to sensitize the tumor cells to chemotherapy and/or radiotherapy but also to induce a synergistic effect. These effects can also be demonstrated in vitro for the various chemotherapeutic agents and explained by increased reactivity with the cellular targets (e.g. increased alkylation of DNA by ifosfamide). In the context of radiotherapy, this improves tissue oxygenation and, above all, blocks cell repair mechanisms, thereby enhancing the effect of radiotherapy. At temperatures above 42.5°C, there is also direct thermal cytotoxicity due to protein denaturation, especially in the hypoxic parts of the tumor. The increased blood flow associated with this temperature rise can also increase the local concentration of active substances. And last, hyperthermia triggers a cellular stress response and adaptive tumor-specific immune response, which enhance the anti-tumor effect.

Procedural workflow and technical principle

Hyperthermia is administered solely in combination with radio-/chemotherapy. Once indicated by a specialized tumor board, multispecialty planning along the quality guidelines of the European Society of Hyperthermic Oncology (ESHO) is mandatory. Prior to initiation of treatment, the target area must be defined by up-to-date imaging. Targeted temperature elevation is achieved by coupling electromagnetic waves through special applicators with a ring-shaped antenna surrounding the patient's body. This setup utilizes the physical effect that electromagnetic waves can be used to heat water-containing tissues for therapeutic purposes. There are two types of hyperthermia: superficial (tumor depth up to 3 cm) and deep hyperthermia using ring applicators. Both applicators feature a water bolus between the patient and the applicator, which allows the electromagnetic waves to couple with the tumor tissue while cooling the skin surface. The goal is to heat the entire tumor tissue to 40–44°C for 60 minutes after a 30-minute warm-up period. Treatment response is primarily determined by the tumor temperature reached during therapy. Since several clinical trials have demonstrated a correlation between therapeutic success and temperature distribution in the tumor, precise temperature monitoring is vital. Only in special cases the initial hyperthermia sessions of the tumor still requires CT-guided thermoprobe implantation. In pelvic tumors, a correlation between non-invasive temperature measurement through the natural body cavities (rectum, bladder) and the actual temperature achieved in the tumor has been demonstrated. In superficial tumors, temperature sensors are applied to the surface of the skin. In the meantime, hybrid systems have been developed allowing temperature monitoring by MRI. Despite the fact that cells vary in their heat sensitivity, the cytotoxic effect can be calculated by the thermal dose as it follows a time-dependent dose-response relationship. Fortunately, hyperthermia is a modality with very few adverse events. The most common adverse events are reversible skin reddening and mild pain, especially due to the pressure of the water bolus. Since this modality increases the efficacy of radio-/chemotherapy, an increase in the adverse events of the latter is also possible theoretically. However, clinical trials have not yet been able to confirm this unequivocally. Due to an increased risk of burns, hyperthermia is usually contraindicated in patients with metal implants or medical devices near the hyperthermia field (e.g. in total hip replacements or cardiac pacemakers).

Fields of application

Soft tissue sarcoma

With about 4,000 new cases annually, soft tissue sarcomas account for less than 1% of all malignancies in Germany. In addition to the tissue of origin (e.g. fat, muscle and connective tissue), the prognosis is determined by tumor size, location, and degree of differentiation. In high-grade and locally advanced soft tissue sarcoma, the high risk of metastasis and local recurrence has resulted in multimodal regimens comprising preoperative chemotherapy, followed by surgery and radiotherapy and adjuvant completion of chemotherapy. Preoperative systemic therapy attempts to target micrometastases as early as possible, i.e. scattered tumor cells not yet visible on imaging, and to facilitate resection with adequate resection margin. A phase III trial in soft tissue sarcoma, initiated at LMU Munich, demonstrated for the first time the increased efficacy of systemic chemotherapy when combined with regional hyperthermia. Regional hyperthermia on two days per chemotherapy cycle was shown to significantly improve local tumor control. After a median follow-up of more than 11 years, these outcomes also translated into a significant prolongation of overall survival.

Survival was increased by 27% versus chemotherapy alone (absolute numbers of 5- and 10-year survival: 62.7 vs. 51.3% and 52.6 vs. 42.7%, respectively). An analysis of tumor specimens from these patients revealed that this mode of (neo-)adjuvant treatment had led to increased infiltration of immune cells into the tumor. Based on these impressive outcomes, the certified LMU Munich Sarcoma Center relies on hyperthermia as a standard component in the multimodal treatment of high-risk soft tissue sarcomas (> 5 cm, high-grade, deep location). A multispecialty tumor board may recommend chemotherapy plus hyperthermia even after surgery has already been performed. Unlike whole body hyperthermia, for which there are no controlled clinical trials, regional hyperthermia is listed in the current German S3 guideline "Adult Soft Tissue Sarcoma". Due to the limited availability of radiative devices and the meanwhile slightly modified standard of chemotherapy compared to the phase III trial, the following consensus has been stated: "Neoadjuvant chemotherapy (...) should/could be combined with deep hyperthermia." The treatments are reimbursed by the German statutory health insurance providers and offer patients with soft tissue sarcomas the chance to improve their prognosis by undergoing a treatment modality with few adverse events. At present, soft tissue sarcoma treatment is based on the synergistic effect of hyperthermia with conventional chemotherapeutic agents such as ifosfamide, dacarbazine and platinum-containing cytostatics. In recent years, LMU Munich initiated a phase II trial on hyperthermia and the sarcoma-specific chemotherapeutic agent trabectedin. Preclinical studies had previously established that the efficacy of trabectedin is significantly higher in the presence of a specific defect in DNA repair. Regional hyperthermia can induce this defect specifically in the tumor tissue and thus facilitate targeted therapy. The outcome of the clinical trial is eagerly awaited. Moreover, a phase I trial combining thermosensitive liposomes (TSL) with hyperthermia in soft tissue sarcomas is planned to start soon. This technique permits the thermal targeted release of chemotherapeutic agents encapsulated in nanocarriers into tumor tissue to increase local efficacy while reducing systemic adverse events. In cooperation with the LMU Munich Veterinary Medical Center, domestic cats with soft tissue sarcomas have already been successfully treated this way. This demonstrated a marked superiority over standard chemotherapeutic agents.

Modern hybrid system Temperature measurement by MRI monitoring

Pelvic tumors

Hyperthermia can also be used to increase the sensitivity of tumor tissue to radiotherapy. Especially following neoadjuvant radiotherapy, when the radiation dose must be reduced to avoid toxicity to normal tissues, a hyperthermia induced increase in efficacy is highly significant. A multicenter trial from the Netherlands studied locally advanced pelvic tumors (cervical, rectal and urinary bladder cancer) because despite radiotherapy, high local recurrence rates here result in an unfavorable prognosis. The addition of regional deep hyperthermia increased complete remissions across entities from 39% to 55%.

Cervical cancer in particular showed impressive outcomes, resulting in a significant survival benefit after 12 years of follow-up. While this disease has become rare in developed countries due to widespread HPV vaccination, it still constitutes the fourth most common cancer in women worldwide. The combination of hyperthermia and radiotherapy may be considered as a therapeutic option in cervical cancer where platinum chemotherapy is contraindicated or the potential radiation dose is inadequate.

Regional hyperthermia has also been shown to be beneficial in the treatment of locally advanced and recurrent rectal cancer. Last year, two German phase II studies were published, which reported good treatment outcomes without aggravated adverse events with the combination of preoperative radiochemotherapy and regional deep hyperthermia. Patients with higher temperatures in the tumor demonstrated better tumor regression. In rectal cancer with local recurrence and neoadjuvant radiotherapy, the addition of hyperthermia to maximize tumor regression and permit further resection with healthy resection margins could even constitute a new standard in cancer treatment. However, in view of the current discussion about not performing surgery once complete remission has been achieved, hyperthermia will also increasingly gain prominence in treatment of locally advanced de novo rectal cancer. Anal cancer represents another tumor entity with convincing clinical data on combined hyperthermia and radiochemotherapy. A phase II trial headed by Erlangen University is currently being conducted.

A phase II trial at Düsseldorf University Medical Center studying the effect of hyperthermia in children and adolescents with refractory or relapsed extragonadal germ cell tumors, deserves special attention. Here, the addition of hyperthermia to standard chemotherapy comprising cisplatin, etoposide and ifosfamide resulted in a very good long-term prognosis.

Superficial tumors

In a large multicenter trial, superficial tumors (breast cancer, malignant melanoma, and head and neck tumors) were treated with a combination of hyperthermia and radiotherapy. All tumor entities showed an improved response to treatment. Recurrent cancer with prior radiotherapy benefited particularly well. A phase III trial was even conducted in relapsed and metastatic malignant melanoma, where two-year local control was improved from 28% with radiotherapy alone to 46% when combined with hyperthermia. Dose-reduced radiotherapy with hyperthermia as a radiosensitizer may be considered in the above superficial tumors where healthy surgical resection margins are not possible. In some of these patients reimbursement by the German statutory health insurance providers can be simplified by including the patients in a case series.

Summary

Regional hyperthermia is an effective treatment modality with few adverse events to increase the efficacy of chemotherapy and radiotherapy through targeted temperature elevation. In soft tissue sarcoma, hyperthermia has become part of the standard multimodal regimen. When combined with radiation +/- chemotherapy, hyperthermia can also improve response rates in other pelvic tumors, notably cervical and rectal cancer, and in superficial tumors. Especially in the case of (neo-)adjuvant radiotherapy, the increase in efficacy through hyperthermia represents a valuable therapeutic option. Since soft tissue sarcomas are considered to have low immunogenicity, the combination of immunostimulatory hyperthermia and immunotherapy may offer a promising therapeutic approach in the near future ("Make cold tumors hot"). The therapeutic possibilities of regional hyperthermia are by no means exhausted. With continued development of radiative devices and optimization of temperature monitoring, it will be possible to apply thermal doses in an even more targeted manner in the future.

Literature available from the author

Information

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■ **Additional information**
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