Hyperthermia based on sensitivity assays?

The treatment of chronic diseases, including cancer, is highly complex and requires the coordinated interaction of all disciplines, both in the areas of conventional and empirical medicine. In my experience, there are no true "alternative" therapies. Rather, success is the result of finding the right combination of therapy options from many areas, in a customized scope. Hyperthermia is one of these options. Publications about different forms of hyperthermia treatment have shown evidence of increased efficacy in most commonly used chemotherapy/radiation regimens, but is hyperthermia effective for every patient/tumor? Is there a test procedure to estimate the therapeutic effect? This article discusses these questions.

Numerous drugs have been developed in recent years to specifically target cancer cells (antibody/immunotherapy drugs). While many of these drugs can initially inhibit tumor growth, it is not uncommon for the cancer to later relapse or progress. A number of good and reliable publications about "chemosensitivity assays" are available to avoid "unnecessary therapies with little chance of success," These have already been sufficiently examined for conventional chemotherapies and in part are integrated into treatment choices.

So far, such an assay procedure is largely unavailable for the complementary use of hyperthermia. Is there such an option, and to which extent is it evidence-based and reliable? Should there be/is there a therapeutic consequence for "hyperthermia practitioners" if these measurements have no effect? This article discusses these questions in greater detail. The first assays of the hyperthermia effect ("heat shock proteins") are being examined under laboratory conditions.

Hyperthermia in oncological therapy

There are four basic forms of hyperthermia:

1. Active hyperthermia (fever therapy): This option nowadays is greatly restricted, but infusions of mistletoe extracts still play a significant role in holistic and particularly anthroposophic oncology.

2. Whole-body hyperthermia (passive form with the use of equipment): Whole-body hyperthermia (WBHT) involves heating the entire body to temperatures of 39 – 40°C (moderate form) or to 41.5 – 42.5°C (extreme form).

3. Local hyperthermia: Local hyperthermia can be achieved with external, intra-luminal or interstitial methods. The external application of heat is used for superficial hyperthermia and loco-regional deep hyperthermia. In the case of interstitial hyperthermia, the energy is typically transmitted by laser or high-frequency currents.

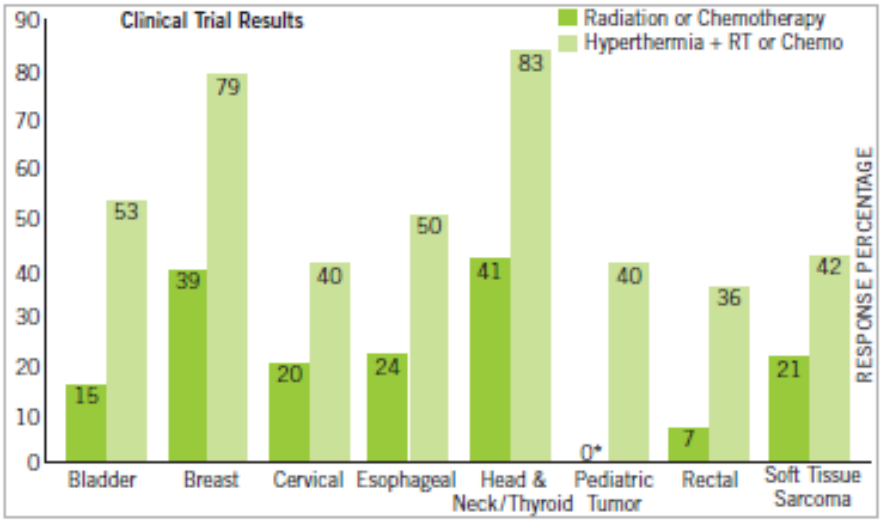
4. Regional hyperthermia: partial body hyperthermia can be induced with capacitive coupled electrodes or radiative high-frequency methods.

The various forms of hyperthermia can be combined depending on the indication, for example, active HT together with passive, equipment-controlled WBHT. There are even options to involve local hyperthermia in certain body regions (e.g. in the liver or lung).

Clinical outcome

Studies consistently have shown higher rates of complete remission when radiation therapy is combined with hyperthermia compared to radiotherapy alone. The addition of hyperthermia to radiation and chemotherapy has been examined in more than 28 randomized, controlled clinical studies.

Another 35 studies also showed significantly better results in combined therapy with HT. Especially in the treatment of patients with highly malignant primary brain tumors (gliomas, WHO Grade III and IV), complete, long-term partial remission rates were achieved in patients with advanced, therapy-resistant cases, which are very promising and are far superior to previous methods (▶ Fig. 1).



Use of hyperthermia forms based on "sensitivity assays"?

Why are sensitivity assays important?

- To decide which drugs/therapy options should be used for certain types of cancer.
- Because micro-metastases remain after therapy.
- Because there is a much-needed interest in individual cancer therapy.
- Because it can achieve the best effect in an individual patient's cancer.
- Because the test is performed on the patient's own cancer cells.
- Because the test identifies "accumulators" or "rapid metabolizers."
- Because tumors are subject to constant change and have about 300 mutations in their cells.
- Because these tests offer guidance in clinical practice.
- Because this test points out changed and new tumor biology (antibody presence, hormone status, immunological properties, genetic shifting etc.) and much more

Why are heat shock proteins a marker for sensitivity assays?

Heat shock proteins (HSP) assist other proteins with folding or maintaining their secondary structure under extreme conditions. They are generated in increased numbers when cells are exposed to heat, radiation or other types of harmful chemicals. In those cellular stress situations, HSP stabilize the cellular proteins to protect them against denaturation and to accelerate the degradation of proteins that are no longer functional via the proteasome.

Studies have found that an elevated production of HSP is correlated with resistance to hyperthermic therapy forms. Examples of relevant HSPs include HSP27 (HSPB1), HSP70 (HSPAlA) or HSAP90, which can serve as a marker for the projected success of hyperthermia (▶ Tab. 1).

If (cancer) cells are capable of protecting themselves against stress factors (ionizing radiation, toxic drugs, heat), the therapies are not very effective, meaning the cancer cells in the cell compounds have developed a survival strategy. As a consequence, an effective therapy shows a good primary effect, but cannot cause any further damage to cancer cells. For the affected patients, that means that the cancer comes to a standstill after a regression, and then continues to grow in spite of continuing tumor-toxic therapies. The risk of metastatic growth or further progression and relapse is much higher in that case because the immune system continues to be suppressed under the therapies.

Relevant HSPs for sensitivity assays

HSP27 (HSPB1):
Up-regulation associated with:
•Progression
•Metastatic growth
•Poor prognosis
•Resistance

HSP70 (HSPAlA):
•Metastatic growth
•Antiapoptotic properties

HSP90:
•Involved in all typical characteristics of cancer.

Conclusion of the authors from the publications:
Increased HSP production correlates with resistance, including to hyperthermic therapy forms.

Objectives of preparatory testing:

- Individualized treatment for patients, based on tumor biology criteria and sensitivities
- Avoidance or reduction of side effects
- Better quality of life
- Lower psychological stress
- Avoidance of time lost to tumor progression
- Lower therapy costs
- Longer survival times, with better quality of life

Predictability based on such assays:

There is a large data volume on the specificity and sensitivity of such tests, as highlighted in the following statement quoted from Kurbacher CM et al [1]:
"The predictive accuracy for ovarian and breast cancer is over 90%, with a positive predictive value of 85-90% and a negative predictive value close to 100%." – That is a high predictive value!

How can this resistance be overcome?

Here is a selection of possible options:

1.Quercetin:
In cell cultures, quercetin has shown inhibitory properties on tumor cell lines of

"As a specialist for radiation therapy radiology and palliative medicine, the most important aspect to me is for patients to say after a conversation that they can see "a path for themselves" and feel more confident. I am a seeker. I am always searching for the right, the most successful approach for my patients. That is what drives me, every day. My experience as a physician, and my hope as a human."

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different tumor entities (breast, endometrial, lung, oral, ovarian and prostate cancers).

In combination with hyperthermia, quercetin prevents the formation of the heat shock protein HSP 70 and has been shown to increase, for example, the sensitivity of Ewing tumor cells to heat-induced cytotoxicity.

2. Hyperthermia therapy in intervals
Since the 1980s, countless publications have demonstrated the effect of thermal, electrical and electromagnetic fields on various tumor cells, either alone or in combination with chemotherapy and/or radiation. The discovery of HSP can be traced back to this research as well. The formation of HSP in the cell nucleus, transport through the cell, and presentation on the cell surface occurs in cellular stress situations. Once these triggers are no longer present, HSP formation decreases and returns to a "normal" level 24-48 hours later.

This insight can be helpful for the application of HT to counter resistance effects; for example, by performing HT every second or third day.

Discussion:
There is evidence that HSP have both a positive ("immunological triggering") and a negative effect (resistance to various forms of therapy) in cancer therapy.

However, high temperature appears to play a more important role in the generation of HSP in hyperthermia application than with moderate temperatures under 39-40°C, as appears to be the case in the application of mild/moderate whole-body hyperthermia or capacitive HT devices.

When a high degree of resistance is found in the primary diagnosis or in sensitivity assays, the first question is how to overcome it and whether the use of hyperthermia is still justified or whether hyperthermia is not indicated, as would be the case with negative assays for drugs.

There are many different assay procedures. We have to be aware that some show excellent sensitivity and specificity, while others are less suitable.
Nevertheless, they can be help us reach decisions in our daily medical work.

Conclusion

Preparatory assays are a useful option to help therapists reach a decision that, to the best of their knowledge and belief, is in the interest of patients and in accordance with the latest scientific criteria.

Individualized therapy for the affected patients, based on tumor biology criteria and sensitivities, can help to avoid or reduce side effects, improve quality of life, reduce psychological stress, prevent lost time due to tumor progression, lower therapy costs and result in longer survival times with better quality of life. Testing in advance is therefore recommended.

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The main focus of Dr. Sahinbas' medical practice is on local and whole-body hyperthermia as well as complex-complementary infusion therapies as an integrative component of cancer therapy and the treatment of chronic diseases. In the case of cancer therapy, his therapies are supplemented with conventional treatments such as dose-adjusted chemotherapy and/or radiation. The patients Dr. Sahinbas sees in his practice come from all age groups and suffer from oncological illnesses as well as rheumatic and autoimmune diseases.

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