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Editorial Comment

A future for hyperthermia in cancer treatment?☆

O.S. Nielsen*, M. Horsman, J. Overgaard

Department of Oncology and Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus C, Denmark

Knowledge about heat treatment of tumours is as old as the written text in medicine. Thus, the Edwin Smith Surgical papyrus, which was probably the first medical textbook dating back more than 5000 years, contains a description of a patient with a tumour in the breast treated with hyperthermia (cautery) [1]. In the last decades of the nineteenth century, hyperthermia underwent a renaissance triggered by observations that patients with high fever due to erysipelas, in some instances, demonstrated spontaneous regression of tumours. This led the New York surgeon William B. Coley to develop his 'Mixed Bacterial Toxin' and thereby he became the father of both the modern use of hyperthermia and the non-specific immunotherapy for the treatment of cancer. Concurrent with Coley's interest, a more direct local application of hyperthermia was performed by others who demonstrated that moderately elevated temperatures ($<45^{\circ}C$) could induce significant regression and even the disappearance of tumours. Subsequently, this treatment principle was developed throughout the first part of our century, not only as a modality by itself, but also in combination with radiotherapy. As early as 1912, Müller published a well conducted 'phase 2' study with 100 patients where the principle of 'thermal penetration' of X-rays was shown to be beneficial [2].

The current interest in hyperthermia came into the limelight in the early 1970s, where substantial research activities were begun addressing both the biological and clinical usefulness of this modality. This was mainly in combination with radiotherapy, but to a smaller extent, also involved studies on heat–drug interactions. The effect of hyperthermia was specifically related to the tumour microenvironment and an almost selective destruction of tumour cells in a hypoxic and, consequently, acidic environment. Even more prominent was the very substantial enhancement of radiation damage; for example, a heating of 43.5°C for 1 h could yield an enhancement ratio of approximately 5 [3–5]. The problem of the effect, however, was two-fold, namely that it was not selective for tumours and that it requested the elevated temperature to be present at the time of radiation. This addresses the Achilles heel of hyperthermia, namely the enormous difficulties related to the heating of a localised area. It is definitively against nature and the body will do whatever is possible to avoid such focal heating. Thus, the use of hyperthermia, despite these impressive biological effects, was held back by the major problems related to the delivery of the heat, aptly phrased as: "The biology is with us, the physics are against us".

Despite these problems, the biological exploration was followed by the initiation of a number of multicentre clinical trials, mainly addressing the interaction between heat and radiotherapy [3,6]. In Europe, the studies were primarily initiated by the European Society of Hyperthermia and Oncology (ESHO). Due to the difficulties of achieving heating of deep-seated tumours, most trials were performed on relatively superficial lesions such as melanoma, neck nodes and recurrent breast [3,6–8]. The early trials should, therefore, mainly be considered to show the proof of principle, and although they may have had a substantial loco-regional and palliative effect, they had only a limited influence on survival. However, improvements in the heating methodology have allowed better heating of deep-seated tumours, especially in the pelvis. Furthermore, the results of the recently published Dutch randomised trial [9] and a similar smaller study by Harima and colleagues [10] clearly showed that not only a substantial improvement in loco-regional control, but also a better survival was achieved for the treatment of patients with uterine cervix and other advanced pelvic tumours. Therefore, combined use of hyperthermia and radiation has not only been shown to have a biological rationale, but also a clinical potential in the appropriate situations. In a time of evidence-based oncology, hyperthermia has proved its value and deserves a greater focus and exploration. Similarly, its use in combination with

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* Corresponding author. Tel.: +45-8949-2555; fax: +45-8949-2550.

E-mail address: osn@oncology.dk (O.S. Nielsen).

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tumour necrosis factor-alpha (TNF-α) needs to be further studied.

Not all aspects of hyperthermic treatment may be useful and prophylactic hyperthermic limb perfusion with cytotoxicity is such an example. Although widely used in malignant melanoma, a well-designed large multicentre randomised trial has clearly evaluated such an approach to be of no significant value [11]. The specific role of heat as a sensitiser of melphalan is less clear and may be another story.

The potential role of hyperthermia is not only limited to its interaction with traditional treatment modalities. There are a number of exciting areas in which it may have a new role to play, such as gene therapy. One of the major challenges in the current development of gene therapy strategies is the ability to regulate the expression of therapeutic genes to adequate levels. Several preclinical studies have now shown that such controllable gene expression can be achieved by the use of heat-inducible promoters [12,13].

Another new area where hyperthermia seems useful is in combination with vascular targeting therapies. Numerous clinical trials are currently in progress investigating the potential of anti-cancer agents that can either inhibit the formation of new blood vessels by angiogenesis, or damage the already established tumour blood supply. More recent studies have now shown that the antitumour activity of such vascular targeting therapies can be significantly enhanced by combination with hyperthermia [14,15]. Other hyperthermia combination approaches, such as with chemotherapy, are not necessarily new, but there are clearly new drugs/combinations that may have potential in this regard.

In the present issue of the *European Journal of Cancer* [16,17], Issels and his colleagues present two important phase 2 trials of neoadjuvant chemotherapy combined with regional hyperthermia in patients with primary, recurrent or inadequately-resected high-risk soft-tissue sarcomas of adults. One of the most important factors in the treatment of soft tissue sarcomas is the necessity of treatment planning within the framework of a multidisciplinary approach, which has been acknowledged by an increasing number of sarcoma centres. In soft-tissue sarcomas, local treatment is still of the utmost importance for cure. However, in the last decade, the treatment of patients with resectable extremity sarcomas has shifted from radical to more extremity saving procedures by the use of combined surgery and adjuvant radiotherapy [18], thereby improving the functional outcome and probably also the quality of life. At present, the use of limb-sparing surgery and postoperative irradiation has become the standard treatment in many of these patients. However, their anatomical location and invasiveness may prevent an adequate resection or the use of radiotherapy due to toxicity. In addition, the role of neoadjuvant or adjuvant chemotherapy in these patients has been continuously debated and, at present, no firm conclusions are possible [19,20]. A meta-analysis of adjuvant chemotherapy showed an improved disease-free survival, but no effect on overall survival [21]. However, recent data indicate that in some of these high-risk patients, adjuvant chemotherapy may improve survival [22]. Data from an ongoing randomised European Organization for Research and Treatment of Cancer (EORTC) study evaluating the effect of adjuvant chemotherapy are awaited. Finally, other treatment modalities such as regional hyperthermia and local perfusion should be investigated as a way of improving the outcome in these locally advanced sarcomas.

High-risk patients with large, high-grade and deep-seated soft-tissue sarcomas remain at an increased risk of developing distant metastases despite local control [19]. However, there is also strong evidence that local recurrence in these patients has an unfavourable impact on survival [23,24]. In the two studies by Issels and colleagues, they have studied the activity and safety of neoadjuvant regional hyperthermia combined with chemotherapy in patients with primary advanced or recurrent high-risk soft-tissue sarcomas.

In the first study (RHT-91 protocol), 59 patients received four cycles of EIA consisting of etoposide, ifosfamide and doxorubicin combined with concurrent hyperthermia [16]. The regional hyperthermia was applied using an electromagnetic deep regional-heating device and the aim was to achieve a maximum tumour temperature of $\geqslant 42^{\circ}C$ for a period of 60 min. Following this treatment, those patients judged to be resectable underwent surgery. If the tumour showed signs of response, four additional cycles of combined EI and hyperthermia were given. All patients not pre-irradiated also received external beam radiotherapy. Treatment-related toxicity was acceptable. Median survival was 52 months and the 5-year survival rate was 49% (95% confidence interval (CI): 36–61%) — values quite impressive in this group of patients. The data was in favour of the patients responding to EIA combined with hyperthermia.

In their second paper (RHT-95 protocol), a similar high-risk patient group (54 patients) received the same treatment as in the RHT-91 protocol with the exception that the patients did not receive hyperthermia after surgery [17]. This study showed an inferior local failure-free survival rate compared with the RHT-91 protocol, but no difference in overall survival. Thus, post-surgical hyperthermia may be critical for local control. These two phase 2 trials may indicate that hyperthermia may have a future in the treatment of high-risk patients with soft tissue sarcomas. However, the two trials cannot demonstrate that hyperthermia is needed to improve outcome. To prove its use in routine clinical oncology, data from randomised phase 3 trials are needed. The authors are to be commended that they have been able,

together with ESHO and the EORTC Soft Tissue and Bone Sarcoma Group to initiate a randomised multicentre phase 3 intergroup study comparing chemotherapy combined with hyperthermia, similar to the treatment schedule used in the phase 2 trials with the same treatment without hyperthermia thereby assessing the effect of adding hyperthermia to the chemotherapy. The results of this important study will help define the impact of hyperthermia on local tumour control and survival in patients with soft-tissue sarcomas. If positive, hyperthermia will definitely have a role in cancer treatment, not only in soft-tissue sarcomas, but probably also in other solid tumours.

The role of hyperthermia in oncology cannot be defined at this moment. Obviously, it will be limited to specific scenarios, but taking into consideration the enormous resources and activity, which are placed in various technologically advanced and difficult treatment modalities, it is evident that there should also be a platform for hyperthermia. This does not belong in every oncological clinic, but a number of dedicated centres, which working in collaboration with the EORTC and ESHO should be identified and maintained within the European community, and, most importantly, have secured the necessary support. The papers presented in this issue of the journal shed important light on the potential role of hyperthermia in soft tissue sarcomas, but only the ongoing randomised trial will either refute or strengthen the current evidence that hyperthermic oncology is a useful modality which belongs in the current cancer treatment armamentarium.

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