Cancer Treatment Reviews 41 (2015) 742–753

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

Local hyperthermia combined with radiotherapy and-/or chemotherapy: Recent advances and promises for the future

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ARTICLE INFO

Article history:
Received 21 March 2015
Received in revised form 16 May 2015
Accepted 20 May 2015

Keywords:
Hyperthermia
Clinical trials
Radiotherapy
Chemotherapy
Thermal dose
Treatment planning

ABSTRACT

Hyperthermia, one of the oldest forms of cancer treatment involves selective heating of tumor tissues to temperatures ranging between 39 and 45 °C. Recent developments based on the thermoradiobiological rationale of hyperthermia indicate it to be a potent radio- and chemosensitizer. This has been further corroborated through positive clinical outcomes in various tumor sites using thermoradiotherapy or thermoradiochemotherapy approaches. Moreover, being devoid of any additional significant toxicity, hyperthermia has been safely used with low or moderate doses of reirradiation for retreatment of previously treated and recurrent tumors, resulting in significant tumor regression. Recent *in vitro* and *in vivo* studies also indicate a unique immunomodulating prospect of hyperthermia, especially when combined with radiotherapy. In addition, the technological advances over the last decade both in hardware and software have led to potent and even safer loco-regional hyperthermia treatment delivery, thermal treatment planning, thermal dose monitoring through noninvasive thermometry and online adaptive temperature modulation. The review summarizes the outcomes from various clinical studies (both randomized and nonrandomized) where hyperthermia is used as a thermal sensitizer of radiotherapy and-/or chemotherapy in various solid tumors and presents an overview of the progresses in loco-regional hyperthermia. These recent developments, supported by positive clinical outcomes should merit hyperthermia to be incorporated in the therapeutic armamentarium as a safe and an effective addendum to the existing oncological treatment modalities.

Introduction

Hyperthermia, one of the oldest forms of a cancer treatment known to mankind, was first mentioned in the Edwin Smith Surgical Papyrus around 5000 BC [1]. The Indian medical treatises of *Charak Samhita* and *Sushrut Samhita* scripted in about 3000 BC also mentions hyperthermia as a therapeutic modality [2]. Hippocrates too, had acknowledged the potential of "heat" for cancer treatment and had stated that tumors which cannot be cured by heat must be deemed incurable. Several reports of tumor regression following high fever secondary to bacterial infections, like erysipelas are available in the 19th century [3–5]. However, with the discovery of penicillin in 1930s, as high fever secondary to these infections became a rarity, the phenomenon of tumor regressions following high fever too became infrequently reported.

According to the Kadota Fund International Forum 2004, hyperthermia is usually defined as a modest elevation of temperature in the range of 39–45 °C [6]. Temperatures beyond this are considered as thermal ablation. The resurgence of hyperthermia for cancer therapy came subsequent to the several *in vitro* and *in vivo* studies carried out during the latter half of the last century following systematic evidence of a thermal dependence of cell kill and its potentiation by radiotherapy [7–9]. This prompted clinicians to use

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http://dx.doi.org/10.1016/j.ctrv.2015.05.009
0305-7372/

hyperthermia either alone or in combination with radiotherapy or chemotherapy for various tumor sites. Nonetheless, by the end of the last century, there was a subtle dampening in the enthusiasm for hyperthermia in clinical practice. This was due to a lack of proper heating and temperature monitoring equipment and some equivocal reports on treatment outcomes that could be attributed to unsatisfactory heating techniques [10–13].

Since the beginning of this century, there has been resurgence in hyperthermia with insights redefining the biological rationale of hyperthermia, immunomodulation at higher temperatures along with the availability of better hard and software permitting safer and more effective hyperthermia treatment delivery. The present review summarizes these developments that make hyperthermia a potent and viable complement to the existing treatment modalities in future oncology management.

Hyperthermia can be used both as a thermal sensitizer and thermal ablator. In this article, we intend to focus primarily on the developments related to hyperthermia as a thermal sensitizer adjuvant to radiotherapy and-/or chemotherapy in solid tumors. Thus, certain thermoablative techniques like high-intensity focused ultrasound and radiofrequency ablation are outside the scope of this review.

Mode of action of hyperthermia

Thermobiological rationale of hyperthermia

Various *in vitro* and *in vivo* studies conducted during 1970s to 2000s have conclusively shown that radiation induced damage is enhanced by hyperthermia at 41–43 °C. These have been very well summarized in various reviews [7–9]. Primarily, the thermal sensitizing effects with radiotherapy are due to (a) increased sensitivity of hypoxic, nutritionally deficient cells in low pH (b) inhibition of radiation induced DNA damage repair (c) sensitization of the "S" phase cells and (d) an enhanced intrinsic sensitivity of some tumor cells to hyperthermia (e.g. sarcomas, melanomas). All these contribute to a relative radioresistance with conventional photon therapy and hence addition of hyperthermia to radiation could yield a supplementary effect on tumor cytotoxicity.

Furthermore, hyperthermia with its properties as mentioned above, shares the radiobiological advantages as evident in high linear energy transfer (LET) radiations, like ^{12}C particle. Robinson therefore described hyperthermia as a "poor man's high-LET radiation" [14]. Thus, in combination with protons (physical dose profile similar to that of ^{12}C ions), hyperthermia (with its high-LET properties comparable to ^{12}C ions) could even mimic ^{12}C ion therapy [14].

Chemotherapeutic agents and hyperthermia appear to have a three-way interaction. Some drugs like 5-flurouracil, methotrexate, taxanes have an independent action and hence may not be potentiated with hyperthermia. An additive action on tumor cell kill with increasing temperature is evident with drugs like doxorubicin, cyclophosphamide, ifosphamide, gemcitabine, etc. A distinct sensitization and synergistic action at temperatures of 41–43 °C could be appreciated with cisplatin, carboplatin and bleomycin [15].

Even though these observations are based on *in vitro* studies for tumors heated at or beyond 43 °C, Dewhirst et al., have indicated that even in the temperature range of 39–42 °C, biological effects of hyperthermia could be evident through inhibition of radiation induced damage repair, changes in perfusions, re-oxygenation, induction of heat shock proteins (HSP) and immunomodulation [16]. This could reset the biological rationale for thermal therapy and may permit the use of hyperthermia even at lower temperatures that are easily achievable and better tolerated by the patients during hyperthermia treatment sessions.

Immune modulation induced by hyperthermia

In addition to the various thermoradiobiological effects that have been discussed above, it has been lately shown that local hyperthermia has also the capability of inducing systemic anti-tumor immune responses [17]. The latter had been described in the past only after whole-body hyperthermia. The mode of action is related to mechanisms induced by fever as a component of the acute phase immune response to injury or infection [18,19]. Innate immune responses are induced by binding of pathogen associated molecular patterns (PAMPs) to Toll-like receptors (TLRs), such as prototypic pattern recognition receptors. In cancer, whole body hyperthermia might additionally improve the adaptive immunity to tumor antigens by induction of dendritic cell (DC) maturation, activation, migration, increasing the tumor antigen presentation and stimulating the activation and trafficking of leukocytes, just to mention as some of the main modes of such immune interactions [20].

Local irradiation in association with mild hyperthermia has been demonstrated to result in systemic effects through immune mediated abscopal effects [21,22]. The local modification of the phenotype of the tumor cells and their microenvironment might render the tumor immunogenic. The key players in this scenario in the tumor microenvironment are the damage associated molecular patterns (DAMPs); danger signals such as high mobility group box 1 (HMGB1) protein, adenosine triphosphate (ATP) and HSP70. HMGB1 and HSP70 bind both to TLR4 and thus enhance the processing of tumor antigens by DCs and their cross-presentation to T cells [23,24]. HSP70, being a chaperone, has cyto-protective tasks inside the cell. It stimulates the immune system by activating DCs and NK cells when present in the extracellular space [25,26]. Since HSPs are much conserved and bear the ability to activate antigen presenting cells (APCs), they provide a unified mechanism for response to internal and external stimuli [27]. HSP70 chaperone peptides are a part of the stress response and thus can transfer tumor proteins to DCs, which could then cross-present these antigens and initiate an adaptive immune response [28].

Thus, tumor peptides bound to HSP70 are delivered to DCs that act as antigen-presenting cells and free HSP70 could stimulate the consecutive cross-presentation of tumor antigens to cytotoxic CD8+ T cells. The latter specifically kills the tumor cells. Combination of hyperthermia with radiation results in a significant increased release of HMGB1 and HSP70 and consecutive activation of DCs [24,29,30]. Additionally, immunogenic cell death forms such as necroptosis, a programmed form of necrosis, might also get induced [31]. The activation of innate and adaptive immune responses against the tumor by the hyperthermia induced released HSP70 is summarized in Fig. 1.

Besides inducing immunogenic cancer cell death, hyperthermia might also directly activate immune cells present in the tumor and its microenvironment [32]. Hyperthermia especially improves DC functions during immune activation and has therefore the capability to deliver tumor antigens and to directly activate DCs [33]. This could even lead to a dynamic immunomodulation by hyperthermia in combination with radiotherapy resulting in enhanced tumor regression as has been reported recently in a patient of liposarcoma [34]. Thus, hyperthermia in multimodal tumor therapy settings can be also considered as immune therapy for cancer, mirroring "*in situ* tumor vaccination" [32,35,36]. This supplements the known radio- and chemosensitizing capabilities of hyperthermia.

Hyperthermia delivering technology

The application of clinical hyperthermia can be either divided as a whole-body, regional or local. The heating techniques are often characterized as superficial or deep (>4 cm from the skin surface)