Thermometric Parameters to Guide Hyperthermia Treatment

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Hyperthermia (HT) is a cancer treatment modality which targets malignant tissues by heating to 40–43 °C. In addition to its direct antitumor effects, HT potently sensitizes the tumor to radiotherapy (RT) and chemotherapy (CT), thereby enabling complete eradication of some tumor entities as shown in randomized clinical trials. Thermometric parameters of HT are considered to have potential as predictive factors of treatment response.

hyperthermia thermometric parameters clinical evidence

1. Introduction

Hyperthermia (HT) is a clinical treatment for cancer which extraneously and intrinsically heats malignant cells to a temperature of 40–43 °C for a suitable period of time [1][2]. Heat delivered to tumor tissues can act as a cytotoxic or sensitizing agent to enhance their remission or at least regression by utilizing several biological mechanisms and pleiotropic effects when combined with other conventional cancer treatment techniques, such as radiotherapy (RT) and/or chemotherapy (CT).

The biological effects of HT, which all favor its use in combination with RT and CT, include direct cytotoxicity, radiosensitization, chemosensitization, and immune modulation. HT-induced cell lethality is predominantly a result of conformational changes and the destabilization of macromolecule structures including the disruptions in cell metabolism, inhibition of DNA repair, and triggering of cellular apoptotic pathways [3][4][5][6]. The direct HT-induced cell lethality is known to be intrinsically tumor-selective for hypoxic cells [7].

The effectiveness of HT combined with RT and/or CT has been investigated in many clinical studies with different tumor types. Unfortunately, to date, there is no consensus on HT delivery when combined with these cancer treatment modalities, resulting in substantial heterogeneity of the HT treatment protocols applied. Any comparison of these studies in terms of outcome should be made with caution in view of this heterogeneity in HT protocols. A good understanding of thermometric parameters and their interpretation is mandatory in this regard. However, there is inconclusive clinical evidence about the relationship of thermometric parameters with both tumor and normal tissue responses to HT in combination with RT and/or CT. The reason for this is that thermometric parameters are inconsistently reported or analyzed in prospective clinical studies and the retrospective analyses are conflicting. For instance, minimum tumor temperature was identified as a prognostic factor in a few studies [8][9][10]. However, another study showed that different metrics such as temperature achieved in 90% (T_{90}), 50% (T_{50}),

and 10% (T_{10}) in the target volume were more strongly correlated with cancer response than minimum achieved temperature [11].

3. Evidence for Predictive Values of Thermometric Parameters in Preclinical Studies

3.1. Heating Temperature

The responsiveness of a tumor to HT is determined by different heat-induced mechanisms at the cellular level. The oxygenation rate is affected by temperature, as a higher rate was reported at 41–41.5 °C in comparison to higher temperature (at 43 °C) in rodent tumors, human tumor xenografts, canine, and human tumors [12]. Heating at 40 °C potentiated the cytotoxicity of CT drugs in human maxillary carcinoma cells [13], and the cytotoxicity was further increased on heating to 43.5–44 °C [14]. In contrast, another preclinical study showed no such dependency at 41–43.5 °C [15].

3.2. Heating Duration

Temperature fluctuations, such as a decrease by 0.5 °C, have been shown to have a strong effect on the extent of cell kill, which was compensated by doubling the heating duration [6][16]. Therapeutic ratio, defined as the ratio of thermosensitive liposomal doxorubicin delivered to the heated tumor increased from 1.9-fold with 10 min heating to 4.4-fold with 40 min heating [17].

4. Evidence for the Predictive Values of Thermometric Parameters in Clinical Studies Combining HT with RT

Numerous prospective and retrospective clinical studies have been conducted to assess the efficacy of HT in combination with RT for treating superficial and deep-seated tumors. The design of most clinical studies was based on the translation of experimental findings aiming to reproduce benefit of HT when combined with RT.

The difficulty of performing invasive measurements was illustrated by a randomized phase III study by Chi et al. [18] in which only 3 out of 29 patients with bone metastases had directly measured intratumoral temperature. In the study by Nishimura et al. [19], the HT session was defined as effective if an intratumoral temperature exceeded 42 °C for more than 20 min. However, according to the Arrhenius relationship, this is not considered long enough to induce a significant biological effect [20].

Another obstacle during HT is the non-standardized methodology for describing the temporal and spatial variance of temperature fields. Several groups have investigated the correlation between various temperature metrics. The study by Oleson et al. showed that T_{min}, tumor volume, radiation dose, and heating technique play significant roles in predicting treatment response for patients treated with RT in combination with HT [8].

5. Evidence for Predictive Values of Thermometric Parameters in Clinical Studies Combining HT and CT

The added value of combining CT with HT has been established, not only in in vitro and in vivo studies, but also in clinical studies. Randomized clinical studies, which demonstrate that the combination of CT and HT results in improved clinical outcome in comparison with single modality treatment [21][22][23][24], confirm the preclinical findings [25].

The effectiveness of CT drugs has been enhanced by HT in a variety of clinical situations, such as localized, irradiated, recurrent, and advanced cancers, but only few indications are really promising. Long term outcome data, e.g., regarding the combination of CT with HT for bladder cancer, underline the clinical efficacy of this treatment strategy [24]. Chemosensitization by HT is induced by specifics biological interactions between CT drugs and heat. The increased blood flow and the increased fluidity of the cytoplasmic membrane of the cells induced by HT increase the concentration of CT drugs within malignant tissues.

6. Evidence for Predictive Values of Thermometric Parameters in Clinical Studies Using RT and CT in Combination with HT

Clinical malignancies, in particular advanced and inoperable tumors, can be treated using triplet therapy consisting of CT, RT and HT as a maximal treatment approach.

The optimal combination of CT, RT, and HT in a single framework is complex, be-cause so many biological processes underly the interactions between the three modalities. In addition, clinical factors often influence the optimal combination of RT and CT. A template with fundamental specifications for designing a clinical study with the trimodal treatment is proposed by Herman et al. [26].

Even though there is no consensus as to the optimal scheduling of trimodal treatment, clinical studies to date integrate HT in combination with daily RT and CT drugs based on the concept that CT should interact with both RT and HT. Scheduling CT weekly is most feasible in terms of maintaining an optimal t_{int} between HT sessions, drug administration, and RT fraction [26].

7. Conclusions

It emerged that the sequencing of HT and RT varies more than the sequencing of HT and CT. Only a few standards seem to exist with regard to the sequence of HT with RT and CT in a triplet for specific CT drug, RT fractionation and thermal dose. According to the evaluated studies, t_{int} is a critical parameter in clinical routine, but no clinical reference values have been established. Of note, a constant t_{treat} of 60 min throughout the HT treatment course was described in most clinical studies. The most important parameter seems to be temperature itself, which correlates with thermal dose. Revealing the relationship between thermal dose and treatment response for different

cancer entities in future clinical studies will lead to the improved application of heat to promote the synergistic actions of HT with RT and CT. It is suggested that it become mandatory for new clinical study protocols to include the extensive recording and analysis of thermometric parameters for their validation and overall standardization of HT. This would allow for the definition of thermometric parameters, in particular of thresholds for temperature descriptors and thermal dose.

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