Overview

Hyperthermia: a Potent Enhancer of Radiotherapy

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ABSTRACT:

Hyperthermia is generally regarded as an experimental treatment with no realistic future in clinical cancer therapy. This is totally wrong. Although the role of hyperthermia alone as a cancer treatment may be limited, there is extensive pre-clinical data showing that in combination with radiation it is one of the most effective radiation sensitisers known. Moreover, there are a number of large randomised clinical trials in a variety of tumour types that clearly show the potential of hyperthermia to significantly improve both local tumour control and survival after radiation therapy, without a significant increase in side-effects. Here we review the pre-clinical rationale for combining hyperthermia with radiation, and summarise the clinical data showing its efficacy. Horsman, M. R., Overgaard J. (2007). Clinical Oncology 19, 418–426

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Key words: Clinical trials, hyperthermia, pre-clinical models, radiation, radiosensitisation

Introduction and Historical Background

The use of heat to treat cancer is probably one of the oldest cancer therapies known. In fact, the first recorded application can be found in the Edwin Smith Surgical Papyrus, an Egyptian papyrus that can be dated back some 5000 years [1,2], in which a patient with breast cancer was treated with heat. Since the 17th century there have been numerous reports of tumour regressions in patients suffering with infectious fever [3], and probably the most famous example illustrating the potential use of fever-induced treatment to control tumour growth was Coley’s toxin back in the 1800s [4]. The first real attempt to deliberately use hyperthermia to treat cancer was made by Westermark in 1898 [5], when he used water-circulating cisterns to treat inoperable carcinomas of the uterus with temperatures of 42–44°C. Since then, hyperthermia has been extensively investigated in both pre-clinical and clinical studies. However, despite this long history, hyperthermia is often considered as an experimental treatment with no realistic future in clinical cancer therapy. This is a totally erroneous evaluation. Although hyperthermia per se is probably only useful in palliative situations and has no role to play in the curative treatment of human tumours [6], unless extremely high thermal ablation temperatures can be achieved [7], there is definitive evidence that when hyperthermia is combined with other treatments significant improvements in clinical outcome are possible. This is especially true for the combination of heat and radiation [8], and in fact hyperthermia is probably one of the most effective radiation sensitisers known.

Combining Heat and Radiation

in vitro and in vivo

It has been shown in vitro that the enhancement of radiation damage by heat generally occurs in all cell types regardless of whether they are neoplastic or normal [9]. This interaction between heat and radiation is dependent on a number of factors. These include heating temperature, heating time, and sequence and time interval between the two modalities, as illustrated in Fig. 1. Generally, the higher the temperature used the larger the effect seen. With exposure time there is a similar increase with increased heating, although a saturation effect can sometimes be seen [9]. Figure 1 also shows the influence of sequence and timing between the radiation and heat treatment. It is a controversial issue as to whether irradiating immediately before or after heating is superior and this is clearly illustrated in Fig. 1, in which irradiating before heating is best for HA-1 cells, whereas for EMT6 the reverse schedule is better. The consensus is that irradiating during the heating period maximises cell killing [11] and that as the interval between heat and radiation increases, regardless of sequence, the radiosensitisation by heat is rapidly lost (Fig. 1). The exact mechanism by which heat sensitises cells to radiation is not known, but most evidence suggests that heat primarily interferes with the cells’ ability to deal with radiation-induced DNA damage [12,13].

In vivo the situation is slightly more complicated, with the heat-induced enhancement of radiation damage generally considered to be the result of two mechanisms. One is a direct radiosensitisation, as seen in vitro. However, in
tumours there is an additional indirect mechanism that results from the heat killing the radioresistant hypoxic cell population. A tumour’s vascular supply is structurally and functionally abnormal when compared with that of the normal tissue from which it is derived [14], and as a result is unable to meet the oxygen and nutrient demands of the growing tumour mass. This results in the development of areas that are nutrient deprived, low in oxygen, and highly acidic [14]. Cells that survive in these adverse conditions are often referred to as hypoxic and have not only been identified in both animal [15] and human [14] solid tumours, but are also known to have a significant negative effect on the tumour response to radiation therapy [16]. Several in vitro studies have reported that cells under hypoxic conditions are more sensitive to the lethal effects of hyperthermia than cells in a well-oxygenated environment [17–19]. Under well-defined nutrient conditions, acute hypoxia alone does not have any significant influence on the cellular response to hyperthermia [19–21]. However, prolonged oxygen deprivation or chronic hypoxia will increase cellular heat sensitivity [19,22,23]. Prolonged hypoxia generally leads to metabolic changes, which in turn alter several other parameters, such as acidity, and it is these changes that are responsible for the increased sensitisation to hyperthermia [17,20,22,24].

Factors Influencing the Response to Single Treatments

The difference between the enhancement of the radiation response via a direct heat radiosensitisation or hyperthermic cytotoxicity is illustrated in Fig. 2. Generally, for tumours the thermal enhancement of the radiation response is greatest when the radiation and heat are administered simultaneously (i.e. the time when hyperthermic radiosensitisation is probably greatest) and decreases with the introduction of an interval between the heat and radiation. This reduction typically reaches a nadir at around 4 h when heat is administered after irradiation (i.e. the time when hyperthermic cytotoxicity predominates), but may take slightly longer when the reverse schedule is used. Clearly, there are some tumour models shown in Fig. 2 that do not seem to show these time-dependent differences. However, this may simply reflect the fact that in those studies a truly simultaneous heat and radiation were not given, as was the case for the two studies that showed the greatest enhancement [27,28]. There is also evidence that even when irradiating immediately before or after heating there is a significant reduction in the enhancement obtained compared with that observed when the radiation is given in the middle of the heating period [6].

Also illustrated in Fig. 2 is the effect of scheduling and timing on the response of various normal tissues to the combination of heat and radiation. As for the tumour, a simultaneous application gives rise to the greatest enhancement and as the time interval between irradiating and subsequent heating is increased so the enhancement decreases, almost completely disappearing with a 4 h interval. When heating is administered before irradiation, there is also a reduced enhancement, although the effect seems to be persistent as the time interval increases and is certainly still present with a 4–6 h interval. The fact that there is some thermal enhancement of radiation damage in tumours when heat is administered 4 h after irradiating, but little or no effect in normal tissues, is additional confirmation that with this time interval and schedule the effect in tumours is primarily due to hyperthermia killing radiation-resistant hypoxic cells, because unlike tumours most normal tissues are devoid of any significant hypoxia [14]. The presence of a somewhat larger enhancement when the heat is administered before radiation may be indicative of a persistent thermosensitisation mechanism.

Regardless of whether the combination of radiation and heat is given in a simultaneous or sequential schedule, the thermal enhancement of both tumours and normal tissues will be dependent on the heating time and temperature. This is illustrated in Fig. 3. For a simultaneous treatment,
the relationship is very simple, in that the higher the temperature and the longer the heating time, then the larger the thermal enhancement, and this is true for both tumours and normal tissues. As such, no therapeutic advantage is to be expected from a simultaneous treatment if the tumour and normal tissue are heated at the same temperature. This is not the situation with a sequential treatment. In tumours there is an enhanced response with increasing temperature and time, but as the temperature increases so the degree of difference diminishes and eventually a saturation level is reached. Although this plateau is at a relatively low level when compared with the enhancements seen with a simultaneous treatment, the fact that a sequential treatment has little or no effect in normal tissues means that there is a substantial therapeutic benefit.

Clinically Relevant Issues with Thermoradiosensitisation

The combination of heat and radiation in a clinical regimen will probably be in a fractionated schedule. It has been shown from studies in vitro, and with both tumours and normal tissues in vivo, that hyperthermia may induce a temporary resistance to a subsequent heat treatment.

Fig. 2 – Left panel: thermal enhancement ratios (ratio of the radiation doses for radiation alone and radiation plus heat to produce the same effect) for different murine tumour models as a function of the time interval and sequence between heating (42.5°C; 60 min) and irradiation. The results are for mammary carcinomas (●), carcinoma NT (△), SQ carcinoma (○), sarcomas Fa (○), F (▽), and S (□). Right panel: thermal enhancement ratios (normalised to a percentage of the maximum effect) for different murine normal tissues as a function of the time interval and sequence between heating for 60 min at different temperatures and irradiation. The results are for intestine at 41.8°C (●), ear skin at 42°C (○) and 43°C (△), foot skin at 42.5°C (▲), and cartilage at 43°C (■). Figures redrawn from [25,26].

Fig. 3 – Left and centre panels: influence of heating time and temperature on the thermal enhancement ratio when heat and radiation are combined in either a simultaneous or sequential (heat 4 h after irradiating) protocol. Thermal enhancement ratios were determined from the ratios of the radiation doses for radiation alone and radiation plus heat to produce the same effect in C3H mammary carcinomas (closed symbols) or normal skin (open symbols) at the temperatures indicated. Right panel: thermal enhancement ratios for simultaneous or sequential heat and radiation treatments in tumours converted to an equivalent time at 43°C. Figures redrawn from [8,29].
Thermotolerance, a phenomenon often referred to as thermotolerance. The kinetics and degree of thermotolerance that develops is dependent on the cell type, the heating temperature, the time of heating, and the interval between successive heat treatments [30]. However, generally there is a lag phase that can be of a few hours’ duration before thermotolerance begins to manifest itself, after which thermotolerance increases, reaching a maximal effect within the first 24 h, and then decays. This decay can take anywhere from a few hours to several days before completely disappearing, depending on how quickly and to what degree the maximal effect occurs [30].

Thermotolerance can also affect the response to the combination of heat and radiation, regardless of whether a simultaneous or sequential schedule is used. Pre-heating a tumour and then subsequently irradiating and then simultaneously or sequentially re-heating, reduces the thermal enhancement compared with that seen without any pre-treatment (Fig. 4). Interestingly, the degree of ‘relative resistance’ in this example follows the same time course as seen with the development of thermotolerance for heat alone [30]. The role of thermotolerance when multifractional heat and radiation treatments are used is less clear. One pre-clinical study reported that if hyperthermia and radiation were combined in a fractionated schedule of five daily fractions, then the observed thermal enhancement was not significantly different from that obtained with a single fraction, regardless of whether the heat was administered simultaneously with radiation or 4 h later in a sequential regimen [33]. If the interval between fractions was extended to allow for thermotolerance to disappear, then the actual thermal sensitisation increased above that obtained with a single dose, reaching a maximum when a 5-day interval was used. This should not be considered as an improved response, because although the thermal sensitisation had increased, the response to radiation alone with a 5-day interval was actually reduced. These results contrast with those from another study, in which thermal sensitisation was reduced by giving one or four pre-treatments with hyperthermia [34]. In skin, the effect was unchanged when heat and radiation were given in two or five fractions, regardless of whether the heat followed immediately after irradiating or 3 h later [34,35]. Similar results were seen with fractionated heat and radiation in mouse ear, provided the heat was administered after irradiating [36]. If the heat was applied before the radiation in each combined treatment, a large reduction in thermal sensitisation was observed with increasing number of fractions.

Another clinical problem that needs to be considered is that during heat treatment considerable fluctuations in tissue temperature are often observed [9,37]. Experimentally this phenomenon has been examined by subjecting tissues to two consecutive heat treatments, one higher than the other. Exposure to a higher temperature followed by a lower is referred to as step-down heating (SDH), whereas the reverse treatment order is called step-up heating (SUH). From the data accumulated to date, it has been found that with SUH the tumour response is the result of an additive effect of the two heat treatments, whereas with SDH not only is there additional cell killing from the higher temperature, but significant sensitisation to the second heat treatment is also observed [38]. The effects of SDH and SUH on a combined heat and radiation treatment have been studied both in vitro and in tumours and normal tissues in vivo [31,43,44]. Examples of the in vivo effects are summarised in Fig. 4. In both tissues, SUH produced only a small increase in radiation response above that found with a single heat treatment. A slightly larger enhancement was obtained with SDH in skin, but the
Role of the Tumour Vasculature

Another factor that plays a critical role in influencing the tissue response to heat, and thus probably also has an important effect on thermal sensitisation, is blood flow. Blood flow is one of the major vehicles by which heat is dissipated. Thus, the vascular supply will influence the ability to heat the tissue. The relationship between blood flow and heating has been examined [45,46], and in general the lower the rate of blood flow the easier it is to heat the tissue. Blood flow is also important in determining the type of microenvironment that exists in tumours and thus sensitivity to heat; the compromised tumour blood flow results in the development of adverse microenvironmental conditions [14] and cells existing in such adverse conditions are more sensitive to hyperthermia [17–24]. There is now clear in vivo evidence that modifying tumour blood flow using physical clamping [47–49], physiological modifiers [50–52], or vascular disrupting agents (VDAs) [53,54], can enhance the tumour response to heat and that this involves both a better heating and increased sensitivity.

The vascular supply to a tumour can also play a role in the ability of heat to increase the effect of radiation. This is illustrated by the fact that larger tumours show a greater enhancement of radiation damage by heat than smaller tumours, although this is only when radiation and heat are given in a sequential schedule, not with a simultaneous treatment [37]; larger tumours are generally less well perfused than smaller tumours and as a result contain a higher proportion of cells that are radiation resistant, yet heat sensitive [14]. Thus, the increased thermal radiosensitivity seen in larger tumours is simply the result of an increase in heat cytotoxicity. Supportive data for this come from the finding that the greater the hypoxic fraction in tumours the greater the thermal enhancement [55], and that tumour sensitivity to heat alone also increases with size [56,57].

Another vascular-mediated effect that may play a role in thermoradiosensitisation is related not to any influence of the tumour vascular supply on heat, but rather to the effect of heat on the tumour vasculature. It is well known that heating can change tumour blood flow, but the effect depends on the thermal dose; at high thermal doses blood flow decreases and at low thermal doses it increases [58,59]. This will naturally affect tumour oxygenation status and several studies have investigated this issue in animal tumours and human tumour xenografts [60–62]. The consensus is that the heat-induced changes in tumour oxygenation parallel the effects on tumour blood flow, namely that at high thermal doses tumour oxygenation decreases and at low thermal doses it increases. However, the influence this has on the tumour radiation response is controversial. At high temperatures, the decrease in flow and associated reduced oxygenation are severe and maintained for periods that are long enough to induce substantial cell killing [63]. The cells most likely to die first are those that are already hypoxic and this may be an alternative and indirect method by which hyperthermic cytotoxicity can occur in vivo. With more mild hyperthermia treatments, any increase in tumour oxygenation will naturally decrease the radioresistant population and tumours will therefore become more radiation sensitive. As this effect occurs rapidly after starting to heat [62], it may explain some of the thermoradiosensitisation with a simultaneous treatment. The controversy comes with the duration of this improved effect, with some studies reporting a rapid return to normal oxygenation status in tumours when heating stops [62], whereas others suggest that the effect is maintained for up to 24 h [64]. If this latter is true, it could sensitisise tumours to subsequent fractionated radiation treatments. However, persistent improvements in oxygenation status after mild hyperthermia treatments are difficult to explain because the physiological changes that probably account for the enhanced tumour oxygenation by such heat treatments should return to normal at or soon after the cessation of heating.

The importance of the tumour vascular supply for thermal radiosensitisation suggests that modifying blood flow could be used to further improve the therapeutic potential. This has been shown with VDAs, many of which are currently in clinical testing [65]. When combining VDAs with thermoradiation, timing and sequencing of the drug, heat and radiation treatments will be critical to the response obtained. Additional studies have shown that when VDAs and radiation are combined, timing is not so important provided the VDA is given after irradiating [53]; giving the VDAs before radiation induces hypoxia that can actually reduce the efficacy of the subsequent radiation treatment. For the combination of VDAs with heat, the greatest enhancements are found when the heat is applied after drug injection, at the time when the drug-induced vascular collapse is maximal, which is typically 1–6 h depending on the VDA used [53,54]. This would argue for giving the VDAs in the middle of a sequential radiation and heat treatment, and in fact such a schedule has been used with a number of different VDAs [53,54]. Representative results for one tumour model and a normal tissue are shown in Fig. 5. In the tumour, hyperthermia alone only begins to enhance the radiation response at temperatures above 41.5°C, and this enhancement becomes larger as the temperature increases. With the VDAs there is an effect of the drugs alone on radiation, but when combined with thermoradiation the radiation response is enhanced at temperatures as low as 40.5°C. In fact, at this temperature the thermal enhancement is as good as one finds with 43°C alone. An even greater thermal enhancement occurs with the VDA and heat as the temperature increases, and it is interesting to speculate as to what enhancements could be achieved with temperatures above 41.5°C. Also shown in
Clinical Trials with Heat and Radiation

The large body of pre-clinical data clearly showing the benefit of combining radiation and hyperthermia has resulted in the translation of this approach into a number of clinical trials. A meta-analysis of all published trials, in which patients were randomised to radiation or radiation and heat, are summarised in Table 1. These results show locoregional control, which is the most relevant end point for locally applied treatments, and show significant heat-induced improvements in a number of distinct sites, including chest wall, cervix, rectum, bladder, melanoma, and head and neck. When all these clinical results were combined (1861 patients from 23 trials), a highly significant improvement was obtained ($P < 0.0001$), confirming the beneficial effect of combining hyperthermia with radiation. This positive result was seen despite the fact that the radiation and heat treatments were highly variable among the various tumour types.

A number of these clinical studies reported on the potential of combining radiation and hyperthermia to improve overall survival [66–71]. In two trials in head and neck cancer [66,67] and one involving tumours of the pelvic region [70], significant improvements in survival were observed in the radiation and heat-treated patients compared with radiation alone. For the head and neck trials, tumour stage may have been an important factor influencing the response, as in one study a survival benefit of adding heat was only seen in the stage III and IV patients [66], whereas in the other study where a clear benefit was seen, the patients were all stage IV [67]. Tumour type may also be an important factor determining outcome, as the study investigating the effect of heat on the radiation response in tumours of the pelvic region [70] reported that the benefit seen in the patients was primarily influenced by the large enhancement in the cervix group; in rectum and bladder no significant improvements were seen. For the remaining trials, no survival benefit was found for radiation and heat compared with radiation alone [68,69,71]. In one of those studies, using a variety of recurrent or persistent tumours [68], there was also no significant improvement in local control by adding heat to the radiation treatment.

![Figure 5](image_url)

**Table 1** — Meta-analysis of all clinical trials in which patients were randomised to receive radiation alone or radiation with hyperthermia*

<table>
<thead>
<tr>
<th>Tumour site</th>
<th>No. of trials</th>
<th>No. of patients/lesions</th>
<th>Radiation alone (%)</th>
<th>Radiation + hyperthermia (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced breast</td>
<td>2</td>
<td>143</td>
<td>67</td>
<td>68</td>
<td>1.06 (0.52–2.14)</td>
</tr>
<tr>
<td>Chest wall</td>
<td>4</td>
<td>276</td>
<td>38</td>
<td>59</td>
<td>2.37 (1.46–3.86)</td>
</tr>
<tr>
<td>Cervix</td>
<td>4</td>
<td>248</td>
<td>52</td>
<td>77</td>
<td>3.05 (1.77–5.27)</td>
</tr>
<tr>
<td>Rectum</td>
<td>2</td>
<td>258</td>
<td>9</td>
<td>19</td>
<td>2.27 (1.08–4.76)</td>
</tr>
<tr>
<td>Bladder</td>
<td>1</td>
<td>101</td>
<td>51</td>
<td>73</td>
<td>2.61 (1.14–5.98)</td>
</tr>
<tr>
<td>Prostate</td>
<td>1</td>
<td>49</td>
<td>79</td>
<td>81</td>
<td>1.16 (0.28–4.77)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1</td>
<td>70/128</td>
<td>31</td>
<td>56</td>
<td>2.81 (1.36–5.80)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>5</td>
<td>274</td>
<td>33</td>
<td>51</td>
<td>2.08 (1.28–3.39)</td>
</tr>
<tr>
<td>Mixed</td>
<td>3</td>
<td>442</td>
<td>34</td>
<td>39</td>
<td>1.24 (0.84–1.82)</td>
</tr>
<tr>
<td>All trials</td>
<td>23</td>
<td>1861</td>
<td>38</td>
<td>52</td>
<td>1.80 (1.50–2.16)</td>
</tr>
</tbody>
</table>

CI, confidence interval. *All results are for locoregional control.
This lack of benefit in both local control and survival was probably because of the 88 patients who received heat only one actually received an adequate hyperthermia session. Another study in rectal carcinoma [71] did report an increase in survival, but this was not significant, which may simply have reflected the low patient number (20 patients in each arm). The most surprising negative result was that from the large breast cancer study that reported results from five randomised trials, and had shown a clear benefit of hyperthermia on local control [69]. However, the lack of any improvement in overall survival was attributed to the finding that many of the patients had a history of metastatic disease outside the treatment area at the time of randomisation. Furthermore, most of the patients also showed progression outside the treatment area during follow-up, which would clearly affect survival.

Overall, the randomised clinical trials clearly showed significant improvements in local tumour control by combining heat with radiation, and in certain tumour types these effects could be translated into enhanced overall survival. Such benefits are only relevant provided there are also no significant increases in morbidity. A number of these clinical studies did investigate the possible influence of heat on early and late adverse reactions induced by radiation. None of the studies found any significant increase in acute toxicity [66–72], and although one study did report a slight increase in late damage [67], no increase in late reactions was seen in any of the other studies [66,68–72].

Conclusions and Future Perspectives

Despite the extensive pre-clinical studies establishing the rationale for combining heat with radiation, and the large number of randomised clinical trials showing a significant benefit of adding heat treatments to radiation therapy to improve outcome, the use of this combined therapy approach has not been adopted in routine clinical practice. This can probably be attributed to the difficulties in adequately heating tumours in patients. The consensus was generally that all one required to effectively enhance the radiation response was a few good heatings. This is probably still true today, although there are suggestions that mild hyperthermia treatments can also be effective. However, the role of mild hyperthermia in improving the radiation response is still not proven. If it were true then one would probably have expected many more trials to be successful. Those trials that did successfully combine heat and radiation were those in which a few good heatings were obtained, and to achieve that one clearly needs good equipment and dedicated personnel.

So, how can we change the current thinking about the application of hyperthermia and radiation? Clearly, with so many randomised trials showing obvious benefits it is unlikely that carrying out additional trials would be the answer. What is needed are improvements in the physics and biology so that preferential tumour heating becomes easier. From a biological standpoint, there are numerous studies demonstrating that the application of clinically relevant vascular modifying drugs not only improve tumour heating, but can also enhance the efficacy of heat; this latter effect will make an easily obtainable mild hyperthermia treatment equivalent to a more difficult to achieve, yet more effective, higher temperature. Advances in heating technology are another area where improvements in heating can be achieved, and there is certainly considerable interest and effort being made in improving current approaches and developing new methods. Obviously, the more we do the better it will become. However, whatever the outcome we should always remember that despite the scepticism often shown by certain groups in the scientific community, hyperthermia is a very effective sensitiser of radiation and clinically it works, which is probably the most important issue that concerns cancer patients.

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References


Part I. Clinical Hyperthermia

The Kadota Fund International Forum 2004 – Clinical group consensus*

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Abstract
The results from experimental studies indicate that hyperthermia is both an effective complementary treatment to, and a strong sensitisier of, radiotherapy and many cytotoxic drugs. Since the first international hyperthermia conference in 1975, Washington DC, techniques to increase tumour temperature have been developed and tested clinically. Hyperthermia can be applied by several methods: local hyperthermia by external or internal energy sources, perfusion hyperthermia of organs, limbs, or body cavities, and whole body hyperthermia. The clinical value of hyperthermia in combination with other treatment modalities has been shown by randomised trials. Significant improvement in clinical outcome has been demonstrated for tumours of the head and neck, breast, brain, bladder, cervix, rectum, lung, oesophagus, for melanoma and sarcoma. The addition of hyperthermia resulted in remarkably higher (complete) response rates, accompanied by improved local tumour control rates, better palliative effects, and/or better overall survival rates. Toxicity from hyperthermia cannot always be avoided, but is usually of limited clinical relevance. In spite of these good clinical results, hyperthermia has received little attention. Problems with acceptance concern the limited availability of equipment, the lack of awareness concerning clinical results, and the lack of financial resources. In this paper the most relevant literature describing the clinical effects of hyperthermia is reviewed and discussed, and means to overcome the lack of awareness and use of this modality is described.

Keywords: Hyperthermia, clinical results, level I evidence, review, acceptance of treatment

General introduction
Hyperthermia is the elevation of temperature above the physiological level with the objective to achieve therapeutic gain. Hyperthermia is generally defined as a modest elevation of temperature to a range of 39 to 45°C. Higher temperatures are used for thermal ablation. Only clinicians using classical hyperthermia participated in the Kadota meeting; therefore, this report is limited to the use of temperatures in the range of 39°C to 45°C.

The use of elevated temperatures for the treatment of cancer has been well documented for centuries [1]. The first international congress on hyperthermic oncology held in 1975 in Washington DC ignited worldwide interest in hyperthermia. As with most new treatment modalities, hyperthermia was initially met with ever increasing enthusiasm reflected by an exponential increase in the number of papers and participants at meetings. Interest in hyperthermia waned thereafter due to disappointing clinical results of the first randomised studies in the USA, accompanied by reluctant sponsoring authorities and hospital boards concerned over support of future research. However, more recent results of several randomised studies have shown great improvement.
<table>
<thead>
<tr>
<th>Ref no.</th>
<th>Tumour</th>
<th>Treatment</th>
<th>Patients (lesions)</th>
<th>endpoint</th>
<th>Effect with HT</th>
<th>Effect without HT</th>
</tr>
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<tbody>
<tr>
<td>13, 14</td>
<td>Lymphnodes of head &amp; neck tumours</td>
<td>RT +/- LHT</td>
<td>41 (44)</td>
<td>CR rate</td>
<td>83%</td>
<td>41%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-yr local control</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-yr survival</td>
<td>53%</td>
<td></td>
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<td>15</td>
<td>Melanoma</td>
<td>RT +/- LHT</td>
<td>70 (138)</td>
<td>CR rate</td>
<td>62%</td>
<td>35%</td>
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<td>2-yr local control</td>
<td>46%</td>
<td></td>
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<tr>
<td>16</td>
<td>Breast</td>
<td>RT +/- LHT</td>
<td>306</td>
<td>CR rate</td>
<td>59%</td>
<td>41%</td>
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<td>17</td>
<td>Glioblastoma multiforme</td>
<td>RT +/- LHT postoperative</td>
<td>68</td>
<td>Median survival</td>
<td>85 weeks</td>
<td>76 weeks</td>
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<td></td>
<td></td>
<td>2-yr survival</td>
<td>31%</td>
<td>15%</td>
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<tr>
<td>18</td>
<td>Bladder, cervix and rectum</td>
<td>RT +/- LHT</td>
<td>298</td>
<td>CR rate</td>
<td>55%</td>
<td>39%</td>
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<tr>
<td>18</td>
<td>Cervix</td>
<td>RT +/- LHT</td>
<td>114</td>
<td>3-yr survival</td>
<td>30%</td>
<td>24%</td>
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<td></td>
<td></td>
<td></td>
<td>3-yr survival</td>
<td>89%</td>
<td>57%</td>
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<tr>
<td>19</td>
<td>Rectum</td>
<td>RT +/- LHT preoperative</td>
<td>115</td>
<td>5-yr survival</td>
<td>36%</td>
<td>7%</td>
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<tr>
<td>20</td>
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<td>CR</td>
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</tr>
<tr>
<td>21</td>
<td>Various superficial</td>
<td>RT +/- LHT</td>
<td>92</td>
<td>Response</td>
<td>82%</td>
<td>63%</td>
</tr>
<tr>
<td>22</td>
<td>Cervix</td>
<td>RT +/- LHT</td>
<td>40</td>
<td>CR</td>
<td>85%</td>
<td>50%</td>
</tr>
<tr>
<td>23</td>
<td>Rectum</td>
<td>RT +/- LHT</td>
<td>14</td>
<td>Response</td>
<td>100%</td>
<td>20%</td>
</tr>
<tr>
<td>24</td>
<td>Bladder</td>
<td>RT +/- LHT preoperative</td>
<td>102</td>
<td>3-yr survival</td>
<td>94%</td>
<td>67%</td>
</tr>
<tr>
<td>25</td>
<td>Oesophagus</td>
<td>RT +/- LHT</td>
<td>125</td>
<td>3-yr survival</td>
<td>42%</td>
<td>24%</td>
</tr>
<tr>
<td>26</td>
<td>Rectum</td>
<td>RT +/- LHT preoperative</td>
<td>122</td>
<td>pCR</td>
<td>23%</td>
<td>5%</td>
</tr>
<tr>
<td>27</td>
<td>Bladder</td>
<td>CT +/- RHT preoperative</td>
<td>52</td>
<td>pCR</td>
<td>66%</td>
<td>22%</td>
</tr>
<tr>
<td>28</td>
<td>Bladder</td>
<td>CT +/- RHT postoperative</td>
<td></td>
<td>2-yr relapse free survival</td>
<td>~82%</td>
<td>~38%</td>
</tr>
<tr>
<td>29</td>
<td>Lung</td>
<td>CT +/- WBHT</td>
<td>44</td>
<td>Response</td>
<td>68%</td>
<td>36%</td>
</tr>
<tr>
<td>30</td>
<td>Soft tissue sarcoma</td>
<td>CT +/- LHT</td>
<td>341</td>
<td>Local relapse free survival</td>
<td>45.3 months</td>
<td>23.7 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Disease free survival</td>
<td>31.7 months</td>
<td>16.2 months</td>
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<tr>
<td>31</td>
<td>Oesophagus</td>
<td>RT + CT +/- LHT</td>
<td>66</td>
<td>CR</td>
<td>25%</td>
<td>6%</td>
</tr>
<tr>
<td>32</td>
<td>Oesophagus</td>
<td>RT + CT +/- LHT preoperative</td>
<td>53</td>
<td>Palliation</td>
<td>70%</td>
<td>8%</td>
</tr>
</tbody>
</table>
IMPACT OF HYPERThERMIA COMBINED WITH RADIOCHEMOTHERAPY IN LOCALLY ADVANCED PANCREATIC CANCER

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Background:
Gemcitabine improved outcome of patients with locally advanced pancreatic cancer (LAPC) better than 5FU (Burris). Considering the synergistic cytotoxicity observed in vitro when Gemcitabine is combined with radiotherapy (Lawrence) and the hyperthermic enhancement reported by in vivo / in vitro studies (van Bree, Haveman), radiotherapy combined with Gemcitabine and hyperthermia (HT) could be a promising treatment in LAPC.

Methods:
From 2000 to 2006 57 patients were treated in our department by using chemoradiotherapy combined or not with HT. Eleven patients were lost at follow up. Of 46 evaluable patients, 25 were treated by using chemoradiotherapy or chemotherapy combined with hyperthermia (Group A). In 5 patients affected by distant metastases (M1), RT was excluded. In 21 cases, according to decision of patients, only chemoradiotherapy was performed (Group B). Chemotherapy consisted of Gemcitabine alone (54.3%) or Gemcitabine combined with 5Fu or cis/oxaplatin. Radiotherapy was delivered at mean dose of 54 Gy (range 51-56 Gy), with an HT session once a week.

All patients were affected by primary tumor but five patients in group A and five patients in group B with local recurrence.

Results:
All patients achieved an 1-year overall survival of 52.1%, with a mean survival of 15.4 months (median 13 months). At 12 months 17 patients (68%) were alive in the group A and 10 (47%) in the group B. At 24 months, 9 patients (36%) were alive in the group A, whereas only 4(19%) in the group B. Chemoradiotherapy was well tolerated, with no more toxicity in the group A.

Conclusions:
Hyperthermia is a promising therapeutic modality in the treatment of LAPC. HT doesn't increase acute or late toxicity of combined treatment, and seems to enhance the efficacy of radiochemotherapy and chemotherapy alone also in metastatic disease, seeing that 5 patients with distant metastases (M1) were included in group A (no metastatic disease was reported in group B). To statistically demonstrate the effectiveness of hyperthermia a larger randomized trial is needed.
Background:
The benefit of GEM when combined with either a platinum analog or capecitabine compared to GEM alone in pancreatic cancer became clear in our recent meta-analysis of fifteen randomised trials (JCO, 2007 Vol 25, No. 18S:4515). Based on the rationale of chemosensitization of CIS by RHT we performed a prospective single-center phase II trial with GEM+CIS combined with RHT under the guidance of ESHO (European Society of Hyperthermic Oncology).

Methods:
Overall 22 pts with metastatic (n=19) or locally advanced (n=3) pancreatic cancer with GEM-refractory (n=12), GEM-resistant (n=9) disease or after adjuvant GEM treatment (n=1) were eligible. Primary endpoint was progression free survival (TTP2, defined as time from start of 2nd-line therapy until progression of disease or death). As secondary endpoints we defined overall survival and best clinical response. Treatment consisted of GEM (1000mg/m2) day 1 and CIS (25mg/m2) combined with RHT (BSD systems) on days 2+4, biweekly. The complete treatment included two treatment blocs with 4 cycles each. According to published data we anticipated a target TTP2 > 4 months in one third of all pts., corresponding to a median TTP2 of > 2.3 mo.

Results:
Until 09/07 22 pts were enrolled with a median follow-up of 14.2 mo. Pt characteristics: male 55%, female 45%; median age 59 yrs; WHO-PS 1/2 (55%/45%). Except grade 3 anemia in 3 pts (14%) only grade 1 and 2 toxicities occured. Grade 2 toxicities included anemia (59%), leukopenia (32%), neutropenia (18%; with fever 9%), thrombocytopenia (5%), metabolic toxicity (9%) and nausea/vomiting (68%). Median TTP1 (defined as time from start first-line therapy until progression of disease) was 5.6 mo (CI: 3.6-8.8). The median TTP2 was 4.2 mo (CI: 2.1-7.7) and the OS 16.9 mo (CI: 11.8-22). Best clinical response was 45% (20/22 pts evaluable) with 1 CR, 1 PR and 8 SD.

Conclusions:
12/22 pts reached the target TTP2 of > 4 mo (54.6%). GEM+CIS plus RHT shows anti-tumor activity even in GEM-pre-treated pancreatic cancer with tolerable toxicity. Based upon these data a prospective randomized 1st-line phase III clinical trial has been initiated.
THE EFFECT OF THE COMBINATION THERAPY OF HYPERTHERMIA AND GEMCITABINE FOR THE TREATMENT OF ADVANCED INOPERABLE PANCREATIC CANCER

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Background:
Gemcitabine (GEM) has been shown to be a potent hyperthermic sensitizer in preclinical study. Moreover, we have shown that hyperthermia (HT) inhibits GEM-induced activation of NF-κB, resulting in the enhancement of the cytotoxicity of GEM. These studies suggest that the combination of GEM plus HT may improve survival in patients with pancreatic cancer. In the present study, we estimated clinical efficacy and toxicity of the combination of GEM plus HT in patients with unresectable pancreatic cancer.

Methods:
This study was a retrospective analysis of patients who were treated with the sequential combination of GEM plus HT between 2004 and 2007. Patients treated with GEM alone at our hospital between December 2003 and April 2005 were allocated as a control group (historical control). All patients who fulfilled the following requirements were selected for this analysis: (1) inoperable advanced pancreatic cancer; (2) no prior treatment for pancreatic cancer; (3) at least 2 courses of GEM and HT received; (4) ECOG performance status of 2 or less at the time of diagnosis. GEM was given intravenously over 30 minutes weekly for 3 weeks with 1 week rest until disease progression or unacceptable toxicity. HT was performed once a week 24 h after GEM. This schedule was based on an in vitro study which revealed that HT enhanced the cytotoxicity of GEM especially when HT was performed 24 h before or after the treatment of GEM. The response of target lesions was objectively evaluated according to RECIST guidelines.

Results:
The disease control rate (CR+PR+SD) was 57.1% for patients treated with GEM plus HT and 14.3% for patients treated GEM alone (historical control). The 1-year overall survivals for GEM alone and GEM plus HT were 30% and 49%, respectively, and the results were significantly better in GEM plus HT group. Median survival time was 182 days for patients treated with GEM alone and 326 days for patients with GEM plus hyperthermia. Combination therapy with GEM plus HT improves OS compared with GEM therapy alone (p=0.024).

Conclusions:
These results indicate that this combination therapy could be a potential first-line treatment for patients with advanced pancreas cancer.
EFFECT OF PRE-HYPERTHERMIA COMBINED WITH GEMCITABINE ON THE APOPTOTIC CELL DEATH IN CULTURED HUMAN PANCREATIC CELL LINES

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Kyoto Prefectural University of Medicine, Japan, Telephone: +81752515508, E-mail: sadachi@koto.kpu-m.ac.jp

Background:
It is reported that NF-κB is further activated by chemotherapy in some cancer cell lines and NF-κB activation is one of mechanisms by which tumors are induced to become resistant to chemotherapy. Therefore, the blocking of NF-κB activity may be associated with the suppression of angiogenesis, and induction of apoptosis. In this study, we examined the relevance of NF-κB in the resistance of pancreatic carcinoma cell lines against for gemcitabine, (Gem). We and other groups reported that hyperthermia-induced Hsp70 could inhibit IKK, resulting in the inhibition of NF-κB activation. Therefore, we speculated that the activated NF-κB in pancreatic cell line might be inhibited by hyperthermia, resulting in the enhancement of Gem-induced cytotoxicity.

Methods:
Cultured human pancreatic cancer cells, AsPC-1 and MIAPaCa-2 were treated with various concentrations (0-30uM) of Gem for 24h. Hyperthermia (43 degrees Celsius 1h) was combined with Gem at the various timing. The effect of Gem and hyperthermia on cell survival was determined by WST-8 assay. The status of NF-κB in cells exposed to Gem was investigated by EMSA. We analyzed cell death in cells by flow cytometry. Furthermore the several protein expression levels, Hsp70, VEGF, cyclin D1 and survivin, Bcl-xL was measured by Western Blotting. The activity of caspasa-3 was evaluated by Western Blotting and ELISA.

Results:
A significant cytotoxicity was observed with Gem. Gem activated NF-κB binding activity in both cell lines. Hyperthermia inhibited the Gem-induced activation of NF-κB and enhanced the apoptotic cell death especially when hyperthermia was performed 24h before the treatment of Gem. The level of Hsp70 was increased by hyperthermia. On the other hand, Gem did not affect the protein level of Hsp70. The levels of anti-apoptosis proteins, survivin and Bcl-xL, in MIA PaCa-2 were decreased by hyperthermia combined with Gem. Caspase-3 was activated by the treatment of hyperthermia combined with Gem.

Conclusions:
Hyperthermia inhibited Gem-induced activation of NF-κB and decreased the expression of anti-apoptosis proteins, resulting in the enhancement of the cytotoxicity of Gem.
Synopsis und Therapieschema

Randomisierte Phase III Studie zur Behandlung des lokal fortgeschrittenen, inoperablen Pankreascarcinoms mit Gemcitabin versus Gemcitabin und regionaler Elektrohyperthermie (Celsius TCS)

Patientenzahl:
70 Patienten in einer 1:1 Randomisation; zentrumsbezogen.

Studienziele

Primäres Studienziel:
- Gesamtüberleben (OAS) im Vergleich zwischen der Behandlung mit Gemcitabin und Gemcitabin plus regionaler Elektrohyperthermie beim inoperablen, lokal fortgeschrittenen und / oder metastasierten Pankreascarcinom.

Sekundäre Studienziele:
- Vergleich des progressionsfreien Überlebens (PFS) zwischen den zwei Behandlungsarmen.
- Gesamtansprechraten (ORR) im Vergleich der beiden Therapiearme gemäß RECIST-Kriterien.
- Vergleich der Rate an Fällen mit kontrollierter Erkrankung (disease control rate; DCR) als Summe aus CR, PR und SD Raten gemäß RECIST-Kriterien.
- Vergleich der Veränderungen im ECOG-Performance-Status / Karnofsky-Index zwischen den Behandlungsarmen.
- Erfassung der Lebensqualität gemäß EORTC QLQ-C30 Evaluationsbogen.
Studiendesign und Behandlungsplan

Dies ist eine randomisierte, multizentrische Phase-III-Studie bei Patienten mit inoperablem, lokalkomplex fortgeschrittenem Pankreascarcinom. Die Patienten erhalten in Arm A Gemcitabin 1000 mg/m² Körperoberfläche intravenös (30 Minuten) an den Tagen 1, 8, 15 sowie eine regionale Elektro-Tiefenhyperthermie (Celsius TCS; 25 cm Elektrode; je 1 Std. Behandlungsdauer; Leistungsmaximum mindestens 80 Watt) auf den Tumorbereich an den Tagen 1, 3, 8, 10, 15, 17, 22, 24. Die Wiederholung des gesamten Zyklus erfolgt am Tag 29. Die Patienten im Arm B erhalten Gemcitabin 1000 mg/m² Körperoberfläche intravenös (30 Minuten) an den Tagen 1, 8, 15; Wiederholung am Tag 29. Die Therapie wird bis zum Eintreten eines Progresses, maximal aber über 6 Zyklen entsprechend 6 Monate durchgeführt.

Kontrolle der Vitalparameter, körperliche Untersuchung, klinische Laboranalysen, Überprüfung des Performancestatus sowie Kontrolle der Tumorausbreitung mittels Röntgen, CT oder MRT erfolgen nach festgelegtem Zeitschema.

Einschlusskriterien

Histologisch/zytologisch nachgewiesenes lokal fortgeschrittenes, inoperables Adenocarcinom des Pankreas, in der Bildgebung (CT, MRT) zweidimensional messbare Raumforderung, Alter über 18 Jahre, keine Vorbehandlung, Karnofsky-Performance-Status > 60%, adäquate Knochenmarksreserve sowie unterschriebene Einwilligungserklärung des Patienten.

Ausschlusskriterien

Vorliegen einer Schwangerschaft oder Stillzeit, aktive Infektion, inadäquate Organfunktion oder Zweittumorerkrankung.

Statistik

Power 90% für eine mediane Überlebenszeitverlängerung von 1 Monat. Zwischenauswertung nach 35 Todesfällen.

Studienleitung

PD Dr. med. Hartmut Kirchner
Klinikum Region Hannover GmbH
Roesebeckstr. 15, 30449 Hannover
Tel.: 0511/ 927 28 05
Fax.: 0511/ 927 28 10
Prospective phase II trial for recurrent high-grade gliomas with low radiofrequency (LRF) hyperthermia

Abstract: ASCO 2008, # 2047

Author Block: E. D. Hager, H. Sahinbas, D.H. Groenemeyer, F. Migeod; BioMed-Hospital, Bad Bergzabern, Germany & University Witten-Herdecke, Bochum, Germany;

Background: In spite of many new approaches the treatment of malignant gliomas is still disappointing. Concomitant radiotherapy with temozolomide could improve in a RCT median survival of pts with glioblastoma multiforme from 12.1 to 14.6 months (EORTC 26981-22981; NCIC,3; ASCO 2004). About 20% of pts with gliomas benefit from therapy depending on genomic mutations. Deep Hyperthermia with low-radiofrequency coupled-electrodes (LRF-DHT) with 13.56 MHz is feasible in treating pts with brain tumors (Hager ED et al., ASCO 2003,#470). 4/5 of the effective RF-energy can induce selectively apoptosis in cancer cells instead of heat. Heat alone would be contraindicated for the treatment of tumors in the brain. Therefore, electro-hyperthermia (EHT) is also referred to this technique.

Methods: N=179 pts with highly-malignant gliomas (WHO grade III/IV at 1st diagnosis) where treated with LRF-DHT after recurrence of the disease after surgery, radiotherapy and/or chemotherapy. N= 53 Pts in the astrocytoma WHO grade III group) and N=126 pts in the WHO grade IV group (glioblastoma multiforme), KI >50%, where analysed in an intention-to-treat observational study. Recruitment time was from 02/2000 to 04/2007.

Results: Complete data where collected from all pts and considered for evaluation if at least 1 cycle of LRF-DHT could be performed. The median overall survival times (MST) are listed in table 1. Longstanding complete and partial remissions could be achieved after recurrence in both groups.

Conclusions: LRF-DHT is feasible in treating pts with highly malignant gliomas without any severe side effects. Hyperthermia may increase overall median survival time (MST) by about 6 months after recurrence. Quality of life and survival could be improved by this method. Further trials are urgently warranted.

1) MST of patients with WHO° III & IV gliomas (Kaplan-Meier-Estimation)

<table>
<thead>
<tr>
<th>MST from</th>
<th>AA ; N = 53 pts months±se [95%CI]</th>
<th>GM; N = 126 pts months±se [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed</td>
<td>38.2±3.5 [31.3;45.0]</td>
<td>20.3±1.7 [17.0;23.6]</td>
</tr>
<tr>
<td>1. LRF-DHT</td>
<td>10.6±2.0 [6.7;14.4]</td>
<td>7.6±0.9 [5.9;9.3]</td>
</tr>
<tr>
<td>Events/Censored N (%)</td>
<td>39/14 (26.4%)</td>
<td>101/25 (19.8%)</td>
</tr>
</tbody>
</table>

2) Survival probability (Kaplan-Meier-Estimation)

<table>
<thead>
<tr>
<th>From newly diagnosed</th>
<th>1 yr</th>
<th>2 yrs</th>
<th>3 yrs</th>
<th>4 yrs</th>
<th>5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA WHO° III; N=53</td>
<td>96</td>
<td>72</td>
<td>53</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>GM WHO° IV; N=126</td>
<td>82</td>
<td>41</td>
<td>23</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>
Prospective phase II trial for recurrent high-grade malignant gliomas with capacitive coupled low radiofrequency (LRF) deep hyperthermia

ED Hager, H Sahinbas, DH Groenemeyer, F Migeod; Biomed-Hospital & University Witten-Herdecke, Germany  
ASCO 2008, 2047

Treatment
- Deep hyperthermia was biweekly performed with 13.56 MHz capacitive coupled electrodes (Oncotherm®)
- Power: Increasing from 20 to max. 100 Watts
- Treatment time: 60 minutes
- Treatment including RTx, CTx, and Boswellia cerali (6x 400 mg/die), a selective inhibitor of leukotrienes

CASE REPORT
Anaplastic Astrocytoma (WHO* III)

06/01 sub. 1 rec. 14/01 sub. 2 rec. 14/01, sub. 3 rec. 14/01
05/01 sub. DHT+ B. +Thal.+ELP
01/06/02 sub. 4 rec. 17/03/03, 7xTemodal)

STATISTICS
- Prospective open-label, single-arm observational study
- Mono-centred phase II trial
- AIMS
  1. Median overall survival-time and survival rate
  2. Response rate
  3. Quality of life

Inclusion criteria
- Recurrent after surgery, RTx and/or CTx
- Progression after RTx and/or CTx in subtotally resected or incompletely cases
- Age > 15 years
- Karnofsky Performance Score ≥ 50

Exclusion criteria
- Uncontrolled epileptic seizures
- Tetraplegia
- KPS < 50%

RESULTS
Complete data were collected from all pts. and considered for evaluation if at least 1 cycle of LRF-DHT could be performed. The median follow-up time was for AA: 39 and GM 34 months. Median age: 43.9 yrs. (AA:40; GBM:49)

The median overall survival times (MST) with confidential intervals are listed in table 1 and the survival probabilities in table 2. Complete and partial remissions could be achieved in both group by LRF-DHT alone.

Table 1: MST of patients with WHO III & IV gliomas (Kaplan-Meier-Estimation)

<table>
<thead>
<tr>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
</tr>
<tr>
<td>AA: N=53</td>
</tr>
<tr>
<td>GM: N=126</td>
</tr>
</tbody>
</table>

Table 2: Survival probability (Kaplan-Meier-Estimation)

<table>
<thead>
<tr>
<th>Interval</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
<th>4 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA: N=53</td>
<td>55%</td>
<td>47%</td>
<td>35%</td>
<td>27%</td>
<td>11%</td>
</tr>
<tr>
<td>GM: N=126</td>
<td>60%</td>
<td>53%</td>
<td>38%</td>
<td>26%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Adverse effects:
- A) Short-term (2h) anaphylaxis after treatment (8-10%)
- B) Local redness (rash) of the skin (8%)
- C) Edema of (fresh) scars (1-2%)
- D) Complications:
  - Subcutaneous fibrosis of fat tissue (1%)
  - Burning blisters stage II (2%)
  - Headache, fatigue & nausea (1-2 days) (12%)

Summary & Conclusions
- DHT with capacitive coupled electrodes with low radiofrequency (13.56 MHz) is feasible without any severe side effects, and even pts. at advanced stages of disease could be treated.
- Complete and long duration partial remissions or stable disease is possible.
- A significant prolongation of survival after relapse and progression after 1st line therapy could be demonstrated.
- Further randomized trials are warranted.

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MULTICENTRE, OPEN-LABEL, PHASE II TRIAL TO EVALUATE THE
EFFICACY AND SAFETY OF LOW-RADIOFREQUENCY DEEP
HYPERTHERMIA WITH CAPACITIVE COUPLED ELECTRODES
(LRF-DHT) IN TREATING PATIENTS WITH RECURRENT
HIGH-GRADE MALIGNANT GLIOMAS

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Background:
Recurrent or progressive high-malignant gliomas hardly respond to chemotherapy after primary surgery, radiation and/or chemotherapy. Targeted therapies and vaccination strategies are new approaches with some effect. Hager et al. could demonstrate that LRF-DHT with capacitive coupled electrodes at 13.56 MHz (LRF-DHT) is feasible in treating patients with brain tumors and may have some beneficial effect on quality of life and overall survival (Proc. ASCO 2003 #470). It could be demonstrated that 4/5 of the LRF-energy at 13.56 MHz can induce apoptosis and only 1/5 is due to heat. Therefore, LRF-DHT can be used to treat brain tumors.

Methods:
N=217 patients with anaplastic astrocytoma (incl. oligoastrocytoma and ependymoma) WHO-grade III (N=65) and glioblastoma multiforme WHO-grade IV (N=152) were treated with LRF-DHT. Recruitment time was from 09/1997-04/2007. Concomitant and/or intermittent radio- or chemotherapy was allowed. Study design: multicentre, open-label, phase II observational study with intention-to-treat analysis. Primary endpoints: median overall survival time (MST) and response rates. Patients were considered for evaluation if at least one cycle of LRF-DHT could be performed. Written informed-consent of the pts about treatment and analysis were given.

Results:
Median follow-up time 70 and 52 months, respectively. The MST from 1st diagnosis of disease could be determined by Kaplan-Meier-estimation for gliomas WHO-grade III as 39.0±3.7 months [95%-CI:30.8-47.2] (censored 30.8%) and for WHO-grade IV as 19.0±1.6 months [95%-CI:16.2,21.8] (censored 17.2%); from 1st LRF-DHT as 13.0±1.9 months [95%-CI:8.1,17.9] & 7.0±0.8 months [95%-CI:5.3,8.7], respectively. Complete and partial remissions could be achieved in both groups, preferable in astrocytoma.

Conclusions:
LRF-DHT is feasible in treating patients with brain tumors without any severe side effects. It may induce complete and partial remissions. MST could be increased by 13 and 7 months, resp. from 1st LRF-DHT after progression or recurrence following primary therapy. Quality of life could be improved without any side effects. With this larger trial previous results could be confirmed. Further randomized trials should be prompted.
Retrospective clinical study for advanced brain-gliomas by elektro-hyperthermia treatment

Sahinbas H., Grönenmeyer D.H.W., J.E. Baier, Uni. Witten/Herdecke, Germany

Introduction

Introduction: Treatment of high-grade malignant glioma contrary of numerous new approaches is still disappointing. The median survival time (MST) after surgery, radiotherapy and chemotherapy is 10-12 months, the prognosis of the disease is still poor. The high grade gliomas are not radiosensitive, and chemotherapy has only a marginal effect on survival. Only 20-30% of the patients with gliomas grade III and less than 15% of the patients with gliomas grade IV have benefit from a mono- or polychemotherapy in addition to surgery and radiation. Median survival in palliative care is 2-4 months, and 4-6, 8-10, 10-12 months after radiation, after surgery and radiation and after combined surgery, radiation and chemotherapy, respectively.

Objectives

Primary aim of this study was to present the therapy tolerance for patients of electro-hyperthermia (EHY) for advanced malignant gliomas and as main intention to show the increase of the median survival time (MST).

Methods

Our study was performed between February 2000 and April 2007. Patients with inoperable, subtotaly resected or recurrent astrocytoma and gliomas (WHO grade II to IV) or metatases with progression after radio- and/or chemotherapy and a Karnofsky Performance Score of >= 30-40% were included inoperable, subtotally resected or recurrent astrocytome and gliomas (WHO grade III and less than 15% of the patients with gliomas grade IV). Only 20-30% of the patients with gliomas grade III and less than 15% of the patients with gliomas grade IV have benefit from a mono- or polychemotherapy in addition to surgery and radiation. The high grade gliomas are not radiosensitive, and chemotherapy has only a marginal effect on survival. The statistics of the treated patients were treated with hyperthermia in combination with chemo/radiation. The median ages of patients were 43.9.

Results

Discussion

Capacitively coupled low-frequency (13.56 MHz) deep-hyperthermia is feasible for brain tumor treatments. Partial remission and/or significant retardation of tumor growth were shown in advanced cases. The applied hyperthermia-treatment was well tolerated (also pediatric cases) by the patients even in advanced tumor stages: The curve show the Survival from first diagnoses. The relevant statistical data:

References

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Chemo-radiation with RF Hyperthermia – A Novel Trimodality Option for Advanced Head and Neck Cancer

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Abstract:
Chemo-radiation is the current standard of care in most of head and neck cancers. It has improved disease free survival, functional integrity and marginally the survival. Hyperthermia has been shown to improve survival when combined with radiation. There is a level I evidence for the same. Hyperthermia can also enhance the effects of chemotherapy by increasing tumour perfusion, altering cell membrane characteristics on inhibiting repair. Hence, combination of all the three modalities should in principle add to the response and overall survival. Importantly hyperthermia has non-overlapping targets along with chemo-radiation.

Materials and Methods:
Patients with non-resectable advanced head and neck cancers were treated with trimodality treatment. Nasopharyngeal cancers were not included in this prospective non-randomized study of cancer. All patients were scoped and imaged before obtaining histological confirmation. Twenty-three patients received radiation with conventional fractionation to a total dose of 70 Gy. Patients also received either 60mgs of paclitaxel or cisplatin 50 mg per week. Patients were evaluated periodically during and after the treatment. Initial response and toxicities were scored during and at the end of treatment. Initial response and toxicities were scored during and at the end of treatment.

Conclusion:
Trimodality treatment was well-tolerated ten patients showed a complete response and thirteen-showed PR. A randomized trial to assess the role of HT will be the next step.
The purpose of this study was to evaluate the activity and toxicity of electro-hyperthermia (ET) on relapsed malignant glioma patients. Twelve patients with histologically diagnosed malignant glioma entered the study. Eight patients had glioblastoma multiforme, two had anaplastic astrocytoma grade III and two had anaplastic oligodendroglioma. All patients were pre-treated with temozolomide-based chemotherapy and radiotherapy. Hyperthermia with short radiofrequency waves of 13.56 MHz was applied using a capacitive coupling technique keeping the skin surface at 20 degrees C. The applied power ranged between 40-150 Watts and the calculated average equivalent temperature in the tumours was above 40 degrees C for more than 90% of the treatment duration. One complete remission and 2 partial remission were achieved, with a response rate of 25%. The median duration of response was 10 months (range 4-32). The median survival of the entire patient population was 9 months, with 25% survival rate at 1 year. ET appears to have some effectiveness in adults with relapsed malignant glioma.
The State of Hyperthermic Treatment  
And its Clinical Evaluation in Japan

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To analyze the state of clinical hyperthermia (HT) used in Japan, a nation-wide survey was run by the health insurance control committee of ISHO. Data were obtained with questionnaires distributed in the main medical centers. A total of 25 institutes registered for this study, where 23 capacitive heating equipments of Thermotron-RF8 were used. The number of patients treated per institute ranged from 5 to 205 patients per year (average 41.3, median 18) and the number of HT sessions per patient from 1.3 through 13.8 sessions (average 10.4±9.5). The treatment period per patient ranged from less than one month to more than 6 months (average 2.1± 1.2) with about half the patients treated for less than one month with a HT session of 4.0±2.2 times.

The abdomen was the area most frequently heated with HT (37.3%), followed by the pelvic region (30.6%), thorax (19.7%), head & neck (7.3%) and bone & soft tissue (5.1%). Chemotherapy (CT), radiotherapy (RT) and chemo-radiotherapy (CT-RT) were applied in combination with HT, where CT was the most frequent modality (33.9%) followed by RT (25.4%), CT-RT (23.0%) and HT alone (17.6%).

The local response was analyzed for grouping of combination therapy of CT and/or RT. The best clinical effects were obtained with HT combined with RT (response rate =49.6%) followed by CT-RT(37.7%), CT (15.0%) and HT alone (7.5%). Based on the presented here, we now know that treatment is available for the following malignancies:
(1) locally advances carcinoma and/or postoperative recurrent tumors of the breast, lung, rectum and soft tissue sarcoma in RT-HT, and
(2) carcinoma of the oesophagus, pancreas and extrahepatic biliary system in CT-RT-HT.
These data might be useful to resolve some problems concerning financial balance in each hospital in Japan for the clinical application.

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THE PAST AND PRESENT STATUS OF HYPERTHERMIC ONCOLOGY IN JAPAN

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Background:
Clinical research in hyperthermic oncology was started by the Japanese Hyperthermic Study Group in 1978, and six years later, the first annual meeting of the Japanese Society of Hyperthermic Oncology (JSHO) was held in Kyoto. In order to analyse and evaluate the present status of clinical hyperthermia, the health insurance control committee of JSHO conducted a survey on the clinical applications of hyperthermia in Japan.

Methods:
The questionnaire form were mailed to the main institutes, in which hyperthermic equipment using an electromagnetic field was installed and had been applied for the treatment of cancer patients. Data were obtained from January, 2003 through December, 2004. The local response was analyzed for grouping of combination therapy of chemotherapy and/or radiotherapy. The data were obtained from subjective impressions of physicians in which 'excellent' meant that nearly all tumors and symptoms had disappeared including discomfort and pain, 'good' meant partial regression of the tumors or clinical symptoms, and 'no response' meant non or minimal regression nor any substantial changes.

Results:
A total of 25 institutes were registered for this study. The hyperthermic equipment consisted of 23 units of Thermontron-RF8, one of Thermontron pro-eight, and one of Thermax 500, all of which were radiofrequency (RF) capacitive heating equipment. A total of 1,151 patients had been treated with hyperthermia each year in these 25 institutes. The average number of patients treated per institute per year and sessions per patient was 41.3 and 10.4±9.5, respectively. The abdomen was the area most frequently treated with hyperthermia (37.3%) followed by the pelvic region (30.6%), thorax (19.7%), head & neck (7.3%) and bone & soft tissue (5.1%)

Conclusions:
The best effects were obtained with hyperthermia combined with radiotherapy in 134 out of 270 cases (49.6%) followed by chemo-radiotherapy in 92 out of 244 cases (37.7%), chemotherapy in 54 out of 360 cases (15.0%) and hyperthermia alone in 14 out of 187 cases (7.5%). Data obtained with questionnaires have shown the present state of hyperthermic treatment in the main hospitals in Japan.

100 Summaries and closing
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