Sequencing of the Total Course of Hyperthermia and Irradiation

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Abstract

The effect of sequencing of the total course of hyperthermia and irradiation on local tumor control was studied on a murine tumor system (RIF). The results showed a 20% control rate for the treatment arms: (a) total course of irradiation followed by total course of hyperthermia; or (b) total course of hyperthermia followed by total course of irradiation.

A superior (70%) control rate was achieved when irradiation and heat were given close to each other on each session. The detailed results are presented.

Introduction

There have been a few reports of local tumor control by heat alone (8, 11); in most studies of utilization of hyperthermia as cancer therapy, heat in the clinical range of 41-43°C has caused regression but not complete cure unless it was combined with radiation. Moreover, the combined use of heat and radiation has been shown to be more effective than either modality alone (8, 11) (Table 1).

The rationale for combining heat and radiation is based on 2 distinctly different effects of heat on tumors: (a) the direct cytotoxicity of hyperthermia; and (b) heat sensitization of cells to the effects of radiation. Regardless of the target of thermal tumor cell killing, there is a definite agreement in the type of cells most affected; they are nutritionally deficient, hypoxic, and low in pH, in sharp contrast to the oxic, well-nourished, and higher-pH cells which are more sensitive to radiation (4). In addition, heat profoundly affects the stroma and environment of the tumor (3); some authors believe that this is one of the mechanisms of the cytotoxicity of heat.

In the combined use of radiation and hyperthermia, the sequence of and interval between the 2 treatment modalities is of significant importance (10, 14). Based on experimental data, it has been suggested that the administration of heat after radiation may result in higher therapeutic gain (10, 14). The majority of these experiments, however, used a single treatment schedule. The rationale for fractionated scheduling of hyperthermia has not been adequately addressed. In this context, 2 questions must be answered: (a) can one deliver the entire course of one modality, then the entire course of the second modality with equal therapeutic gain as if the 2 modalities are used in close proximity to each other in every session; and (b) if so, what is the best sequence? To answer these questions, we have carried out a series of experiments on a murine tumor model system at the Division of Radiation Oncology, Mallinckrodt Institute of Radiology. The technique and methodology have been described in detail elsewhere (9).

Materials and Methods

C3H mice and the murine fibrosarcoma (RIF-1) tumor system were used throughout the experiments. The radiation was delivered via a 220-kVp orthovoltage X-ray generator specially designed for small-animal tumor irradiation. We used a specially designed radiofrequency system for the hyperthermia treatments. The details of this hyperthermia system have been described elsewhere (9). Temperature was controlled by a feedback thermistor which was positioned along with the monitor thermistors to provide temperature readout at the base of each tumor. Nine to 12 animals were used in each treatment group.

The 2 modalities were delivered as follows. The course of irradiation chosen for these experiments was 4000 rads in 8 fractions with each session separated by 72 hr. The course of hyperthermia was given in 4 sessions (45° for 15 min), with each session separated by 72 hr.

The irradiation and hyperthermia schedules are chosen as such in order to be as close as possible to currently used clinical protocols.

Experimental Group. Group 1, control (no treatment); Group 2, radiation control (these animals received radiation alone as described above); Group 3, hyperthermia control (these animals received hyperthermia alone as described above); Group 4, sequential heat followed by radiation (the entire course of hyperthermia was followed by the entire course of radiation); Group 5, sequential radiation followed by heat (the entire course of radiation was followed by the entire course of hyperthermia); Group 6, simultaneous (sessions of hyperthermia and radiation given together). Hyperthermia was given with either the first 4 or the last 4 radiation fractions. In each session, radiation preceded hyperthermia.

Throughout the course of therapy and subsequently, the animals were observed twice a week, and their tumors were measured. All animals have been followed for a minimum of 120 days or until death.

Results

There were no cures in any of the control arms, indicating that these tumors are resistant to radiotherapy alone and hyperthermia alone as administered in these experiments (Table 2). The sequential courses of therapy (Groups 4 and 5) yielded a 20% cure rate, and there was no difference whether the total course of hyperthermia preceded or followed the total course of radiation. In the simultaneous thermal-radiotherapy group (Group 6), there was a 70% tumor cure rate. There was no difference in cure rate between mice receiving hyperthermia in the first 4 sessions and those receiving it in the last 4 sessions.

Discussion

Experimental data, supported by clinical observation (Table 1), reveal that the combination of hyperthermia and radiation is more effective in tumor eradication than is either modality alone. However, there is no agreement on which sequence of these 2 modalities is best. Although biological data (10) suggest that the sequence of radiation followed by hyperthermia yields the best therapeutic ratio, the clinical results are not as convincing. Treat-
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Table 1
Response of superficial tumors to heat, irradiation, or irradiation plus heat

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of patients</th>
<th>Irradiation alone</th>
<th>Heat alone</th>
<th>Hyperthermia + irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al. (5)</td>
<td>54</td>
<td>26</td>
<td>7</td>
<td>78</td>
</tr>
<tr>
<td>Marmor et al. (7)</td>
<td>15</td>
<td>7</td>
<td>12</td>
<td>43</td>
</tr>
<tr>
<td>Marmor et al. (8)</td>
<td>21</td>
<td></td>
<td>12</td>
<td>43</td>
</tr>
<tr>
<td>Arcangeli et al. (1)</td>
<td>15</td>
<td>46</td>
<td></td>
<td>85</td>
</tr>
<tr>
<td>Raymond et al. (13)</td>
<td>7</td>
<td>14</td>
<td></td>
<td>86</td>
</tr>
</tbody>
</table>

Table 2
Results

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>% cured</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Control (no treatment)</td>
<td>0</td>
</tr>
<tr>
<td>2. Heat alone</td>
<td>0</td>
</tr>
<tr>
<td>3. Irradiation alone</td>
<td>0</td>
</tr>
<tr>
<td>4. Total course of irradiation + total course of hyperthermia</td>
<td>20</td>
</tr>
<tr>
<td>5. Total course of hyperthermia + total course of irradiation</td>
<td>20</td>
</tr>
<tr>
<td>6. Irradiation combined with heat for 4 treatments, then 4 additional irradiations or 4 irradiations, then irradiation combined with heat for 4 treatments</td>
<td>70</td>
</tr>
</tbody>
</table>

The results of superficial human tumors with radiation followed by heat (12) has yielded tumor control rates similar to those achieved with the opposite sequence (2). The separation of the 2 modalities, i.e., the use of a total fractionated course of hyperthermia as an independent modality, is attractive not only from a scientific but also from a logistic point of view, since patient scheduling for hyperthermia sessions in a busy radiotherapy department is an enormously complicated procedure. Moreover, if it could be established that hyperthermia, as an independent modality, is effective against cancer, establishment of an independent hyperthermia clinic would also be attractive to some. Our data clearly indicate that, in the animal system used in these experiments, hyperthermia or radiation alone did not cure any tumors. When the 2 modalities were used in sequence (Groups 4 and 5), there was a modest therapeutic yield manifested by a 20% tumor cure rate. However, a significantly greater cure rate can be achieved when these 2 modalities are used simultaneously (within 1 hr of each other). Finally, the idea of an independent hyperthermia clinic is not supported by the results of these experiments.

References

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