Biological Effects of Heat

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Abstract

The biological effects of heat appear to be favorable for its use to treat cancer. Heat kills cells in a predictable and repeatable way. The age response function complements X-rays in that S-phase cells are most sensitive, and at the same time cells that are at low pH or are nutritionally deprived are also more sensitive. This offers the possibility that cycling tumor cells and quiescent cells that have resorted to hypoxia may be more sensitive to heat than are the slowly turning over cells of the normal tissues responsible for late effects. Thermotolerance, in general, represents a problem and a complication in clinical practice but may be exploited to advantage. The interaction of heat with ionizing radiation has been studied extensively and is complex; in general, heat inhibits the repair of both sublethal and potentially lethal X-ray damage, but it is not obvious how to exploit this to advantage. By contrast, the potentiation by heat of the action of chemotherapy agents has been relatively neglected. This is a promising area, since local hyperthermia can "target" drug action in a way not otherwise possible. Heat is a weak mutagen and has not been shown to be a carcinogen; this is a most desirable property at a time of increasing concern for the oncogenic potential of agents used to treat cancer.

If you ask a European to look ahead to the future, it is inevitable that he will begin by looking to the past. History has a habit of repeating itself, at least in general terms, although seldom in detail. Sir Winston Churchill once said: "If you do not learn the lessons of history, you are doomed to repeat them." He was not thinking of hyperthermia when he said this. On the contrary, the subject was hypothermia, since he was reflecting on the fact that Hitler was caught in the cold of a Russian winter by repeating the mistakes of Napoleon.

Hyperthermia is a relatively new modality for the clinical treatment of cancer (excluding the early induction of fevers). What lessons can we learn from the past and from the development of more conventional modalities?

1. If a treatment works, it doesn't matter that you don't know why. Understanding mechanisms at the molecular level is interesting and intellectually satisfying but, from a clinical point of view, not essential. Cancer patients were cured by X-rays for over 50 years before we knew of the existence of DNA, much less suspected it as the primary target for X-ray damage.

2. A differential effect on tumors relative to normal tissues is the basis of any antineoplastic agent, but the differential need only be small. Claims that a given agent kills only cancer cells, with no effect on normal tissues, is usually an indication of an early stage in the development of a field (hyperthermia went through this phase years ago). When more is known, the differential is usually very small indeed. This is certainly true of X-rays and the commonly used chemotherapy agents.

In preparing the overview for the International Hyperthermia Conference in Fort Collins in 1980, we summarized the situation in the slogan: "The Biology is with us" (18). This is still a true and accurate assessment. The basic biological effects of heat are favorable for its use as a cancer treatment modality. There are 7 specific points to be considered.

1. Heat kills cells in a predictable and repeatable way, as do radiation and chemotherapy agents (Chart 1). This fact alone justifies its use experimentally in the treatment of cancer. In addition, heat interacts with radiation and drugs, 2 of the most important current clinical modalities (15, 17).

2. The age response function for heat complements that for X-rays (Chart 2). The relatively radioresistant S-phase cells are selectively killed and radiosensitized by heat. On this basis, cycling tumor cells should be killed selectively by hyperthermia compared with the slowly turning over normal tissues responsible for late effects.

3. Cells that are nutrient deficient and/or at low pH are more sensitive to killing by heat as shown in Chart 3. These are likely to be hypoxic tumor cells, which may well be out of cell cycle. It might be possible to amplify this effect in tumors in vivo by glucose infusion (31).

The combination of these 2 properties of heat constitute a basic rationale for a selective effect on the tumor, both on rapidly cycling cells and on slowly cycling or quiescent cells that may be hypoxic (14).

4. Cells can become thermotolerant (a term used to describe the development of a resistance to subsequent heat by prior heating). This has been shown by many investigators (2, 6, 20). An early example is shown in Chart 4. Acquired resistance is recognized as a difficulty associated with drug therapy but is not a problem in radiotherapy. The phenomenon of thermotolerance is a nuisance and a complication in the clinical use of hyperthermia. At lower temperatures of around 42°, thermotolerance is induced during the heating period after an exposure of about 2 or 3 hr. By contrast, at higher temperatures of around 45°, thermotolerance cannot be produced during the heating, and it is delayed by 8 hr or so after the heating period. There is some evidence from the work of Field and Law and their colleagues at Hammersmith (5, 6) that, in normal tissue systems such as gut, skin, and cartilage, the appearance of thermotolerance may not reach a maximum until 20 hr after heating. Thermotolerance is a substantial effect; the D0 of a survival curve may be increased by a factor of 4 to 10, which translates into a difference in cell kill from 10^-6 in sensitive cells down to only 10^-1 in thermotolerant cells. The time taken for cells that have become thermotolerant to revert to their normal sensitivity, i.e., the decay of thermotolerance, may take as much as 100 hr. The greater the degree of
Overgaard\textsuperscript{2} has shown that there is much thermotolerance that can be induced in transplantable mouse tumors and that this thermotolerance decays very slowly, requiring something of the order of 120 hr before the decay is complete.
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There are at least 2 factors concerning the induction and decay of thermotolerance that may have important implications concerning a differential between tumors and normal tissues: (a) a reduction in pH during, and especially between, heating periods greatly reduces the magnitude of the thermotolerance produced (Chart 5). While reduced, it is not eliminated until such low pH values that are physiologically unlikely to occur in vivo. This has been shown by Gerweck and also by Golden and Leeper (12). There is no clear-cut answer to the question as to whether a low pH alters the decay of thermotolerance; (b) it appears that the decay of thermotolerance occurs faster in cells that are cycling than in those that are not cycling. This is illustrated in Chart 6. Both of these factors, lowered pH and cycling cells, might form a rationale for supposing that a given heat treatment may produce more thermotolerance in the slowly cycling cells of the normal tissues responsible for late effects than in the tumor cells which may either be rapidly cycling or at low pH. However, basing a strategy on this differential would appear to be somewhat hazardous until much more detailed information is obtained.

5. The interaction between heat and ionizing radiations is complex and has been the subject of many investigations (3, 22, 23, 30). Heat inhibits the repair of radiation-induced single-strand breaks and radiation-induced chromosome aberrations (1, 4, 21, 26, 29). This inability to repair molecular damage translates into the inability to repair both SLD and PLD produced by radiation (Table 1).

Heat prior to a first dose of X-rays inhibits the repair of SLD, even if cells are at 37° between the first and second X-ray doses (Sequence A in Table 1 and Chart 7). Repair of SLD does not occur if hyperthermia is applied during the interval between the 2 doses of X-rays (Sequence B in Table 1). However, the effect is reversible; if cells are returned to 37° following the first X-ray dose and the heat treatment, but before the second X-ray dose, repair can take place (Sequence C in Table 1). Heat can reduce

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**Table 1**

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Δ - 10 min at 37° - x - t 37° - x</td>
<td>No SLD repair</td>
</tr>
<tr>
<td>B. x - Δ - x</td>
<td>No SLD repair</td>
</tr>
<tr>
<td>C. x - Δ - t 37° - x</td>
<td>Repair SLD</td>
</tr>
<tr>
<td>D. Δ - x</td>
<td>PLD repair</td>
</tr>
<tr>
<td>E. x - Δ</td>
<td>No PLD repair</td>
</tr>
</tbody>
</table>

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The abbreviations used are: SLD, sublethal damage; PLD, potentially lethal damage.

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Heat can reduce the heat damage to transit normal tissue relative to a deep-seated tumor. In this way, it might well be possible to reduce the heat damage to transit normal tissue relative to a deep-seated tumor. It would be technically much too difficult to achieve any such differential effect in the normal tissues that are more intimately associated with the tumor, but it would be possible to achieve this strategy for overlying transit normal tissues.
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The repair of X-ray induced PLD, but the sequence is of critical importance. Heat before irradiation does not inhibit PLD (Sequence D in Table 1 and Chart 8A), whereas heat afterwards does (Sequence E in Table 1 and Chart 8B).

6. The cell-killing potential of some but not all chemotherapy agents is enhanced substantially by a temperature elevation of even a few degrees (13, 15-17). This is illustrated for cisplatinum in Chart 9. The addition of local hyperthermia to a chemotherapy schedule would have the advantage of "targeting" and localizing the principal effect of the drug, allowing greater tumor cell kill for a given systemic toxicity. This would help to overcome one of the principal problems and limitations of chemotherapy. It is surprising that more has not been done in this area in view of the substantial potential benefits.

7. Hyperthermia has never been shown to be carcinogenic and is only weakly mutagenic. Several studies using in vitro oncogenic transformation assay systems have demonstrated no increase in the incidence of transformants over background levels for temperatures between 40 and 45°. There is less agreement concerning the combination of heat and X-rays (25). Harlslads et al. (19) showed that 2 hr of modest hyperthermia (42°) either before or after irradiation reduced the incidence of oncogenic transformation produced by 2 or 4 Gy of X-rays. By contrast, Raaphorst and Azzam (27) reported that heat increased the incidence of X-ray-induced transformation when there was a prolonged interval between irradiation and heating. These differences aside, there is general agreement that heat itself is not

The repair of radiation SLD, indicated by the increase of survival between split radiation doses. Seven min of heat (45.5°) prior to irradiation removes the shoulder from the survival curve and suppresses the return of the shoulder for 2 hr as seen in the center. Bottom, 7 min of heat administered 10 min prior to irradiation. Radiation was administered as a single or as split doses separated by various times [Garweck et al. (11)].

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Chart 7. Top, repair of radiation SLD, indicated by the increase of survival between split radiation doses. Seven min of heat (45.5°) prior to irradiation removes the shoulder from the survival curve and suppresses the return of the shoulder for 2 hr as seen in the center. Bottom, 7 min of heat administered 10 min prior to irradiation. Radiation was administered as a single or as split doses separated by various times [Garweck et al. (11)].

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Chart 8. A. Preheating at 43° did not inhibit repair of PLD. The 3 curves refer to progressively longer heating times (15, 30, and 45 min) followed by 1600 rads of X-rays and a repair interval at 37°. B. Postheating at 43° inhibits X-ray PLD repair. Curve e, repair of PLD after 1600 rads of X-rays with no heat. Curves b to e, effect of progressively longer periods of postheating for 15, 30, 45, or 60 min, respectively. From Li et al. (24).
This experimental rationale is supported by early clinical data for favor of a differential effect on tumors relative to normal tissues.

**Conclusion**

There is a strong biological rationale for the use of hyperthermia in cancer therapy. A number of biological principles argue in favor of a differential effect on tumors relative to normal tissues. This experimental rationale is supported by early clinical data for superficial tumors which can be heated adequately. In fact, one could go as far as to say that, if hyperthermia and X-rays were compared only on the basis of biological data, with no considerations of the physics of application and without the benefit of the 80 years of accumulated clinical experience for X-rays, then hyperthermia would appear to be a more likely modality than X-rays. To be specific, there are more diverse reasons to expect a differential effect between tumors and normal tissues for hyperthermia than for ionizing radiations. We see no reason to change the summary statement offered several years ago at the International Hyperthermia Conference in Colorado that, "The Biology is with us." The challenge is to design and make equipment to produce regional hyperthermia that can begin to equal the sophistication of dose distributions obtainable with super-voltage X-ray machines.

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