Role of Whole-Body Hyperthermia in the Treatment of Neoplastic Disease: Its Current Status and Future Prospects

H. Ian Robins

Department of Human Oncology, Divisions of Clinical Oncology and Radiation Oncology, University of Wisconsin Medical School and the Wisconsin Clinical Cancer Center, Madison, Wisconsin 53792

Abstract

Modern cancer therapy has included surgery, radiotherapy, chemotherapy, and most recently, immunotherapy and hyperthermia. As neoplastic diseases are heterogeneous in regard to each cell subpopulation’s response to a given therapy, a multimodality treatment approach should enhance the chances of all subpopulations of cells being killed.

The potential of hyperthermia as a treatment modality for cancer was first predicted following observations that several types of cancer cells were more sensitive to temperatures in excess of 41°C than were their normal cell counterparts. Beyond these studies, there now is preclinical evidence as well as the clinical suggestion that hyperthermia potentiates radiation and/or drugs for the treatment of cancer. As most cancers refractory to conventional therapy are systemic diseases, the proposal that whole-body hyperthermia in combination with other therapies be used to treat metastatic disease is an inherently attractive approach. The basis and the practicality of this proposal is presented here with suggestions for its application to current preclinical and clinical research.

Introduction

Interestingly, when the anecdotal literature of Phase I studies of WBH is analyzed using cooperative group response criteria, the response rates are such that, had these been controlled Phase I drug trials, Phase II and III studies would surely be planned. Although research relating to WBH has continued over the past 10 years, many clinicians have shied away from the field because of equipment complexities, potential toxicities, and the lack of interest of industry in pursuing WBH as a goal (1–5). Private industry has been more interested in regional and local hyperthermia systems requiring “high-tech” electronics. Recently, the limitations and problems inherent in regional and local hyperthermia have become apparent to some clinicians. With regard to regional hyperthermia, problems include invasive thermometry requiring surgery, labor-intensive treatment procedures, toxicity, uneven heating, and the production of WBH when regional hyperthermia is attempted (6–9). With regard to local hyperthermia, problems continue to exist with thermometry, reproducibility of treatments, temperature gradients, and ability to reach target temperatures (6, 8, 10–15). Furthermore, the data recently reported by the University of Arizona group in both dogs (6) and humans (16) demonstrates the profound clinical significance of the fact that heating is not homogeneous (6). The studies of Oleson and Dewhirst (6) and of Oleson et al. (16) support the conclusion that in patient groups treated with specific equipment the lowest temperature achieved in a tumor mass is the best predictor of response. Beyond these considerations, as cancers refractory to conventional therapy tend to be systemic, local hyperthermia by its very nature may in many cases limit itself to a palliative goal.

As a field, hyperthermia has moved away from considering heat alone for the treatment of cancer patients (6, 8). In this regard, temperatures necessary for synergism between systemic hyperthermia, radiation, and/or drugs are obtainable in humans (17–45). Considering our greater awareness of the limitations and problems inherent in local and regional hyperthermia as well as research relating to combined modality approaches and to WBH technology, a more concentrated research effort in the area of systemic hyperthermia is warranted at this time. This paper presents arguments and data from both clinical and preclinical investigations supporting this contention.

Current Status

The Argument for Multimodality Therapy and Its Implication for WBH. It has become increasingly obvious that low-response rates as well as short-response durations limit hyperthermia as a single-treatment modality for spontaneous neoplasms (6, 46–49). The possible biological bases for these observations are discussed by Oleson and Dewhirst (6) in their insightful review of the field. Alternatively, the full potential of hyperthermia may be as an adjunct for other forms of therapy. The use of hyperthermia in combination with other modalities is biologically advantageous. Studies in tumor biology suggest cell heterogeneity of various cancers limits the effectiveness of any given treatment modality, whether it be radiation, chemotherapy, hyperthermia, or immunotherapy (50–54). In this context, the potential of WBH in combination with other modalities as a systemic approach to cancer is a biologically attractive concept.

The interactions of hyperthermia with radiation, chemotherapy, or immunomodulators in vivo are probably due to hyperthermic effects other than its direct tumoricidal activity (discussed below). Thus, concepts developed in the study of heat killing of cells in vitro cannot be directly applied clinically to hyperthermia in combination with other modalities. For example, Mivechi and Hofer (55) have demonstrated that heat potentiation of radiation lethality and direct heat death are 2 distinct phenomena. The optimal temperatures for the potentiation of WBH with drugs may be considerably below tumoricidal temperatures for hyperthermia alone; thermal tolerance (56–62) may not be relevant to...
clinical multimodality studies. It is with this orientation that the current status and future potential of hyperthermia will be surveyed.

**WBH and Heating Time to Target Temperature.** As suggested above, the development of thermal tolerance may not be a factor in combination therapy. Parenthetically, one may question whether thermal tolerance is even relevant to WBH as a single modality. Studies claiming to report thermal tolerance in the setting of WBH have actually looked at the survival of animals (63, 64), which may be a gross physiological adaptation rather than a cellular phenomenon, as thermal tolerance is traditionally defined (56–62). In one murine WBH study in which change in tumor cell kill was the criteria for thermal tolerance, the phenomenon was not observed (65). The explanation for this may relate to the physiological changes which occur during systemic hyperthermia, e.g., decreased pH, hyperglycemia, and changes in carbohydrate and fatty acid metabolism as well as endocrine function (66). Hence, concerns relating to heating times and thermal tolerance may have been overemphasized. Further research specifically addressing WBH in combination with other modalities is clearly required to assure those concerned about thermal tolerance. From a clinical standpoint, addressing both patient and professional concerns (5) at least 2 systems for WBH have heating times (time to target temperature, ~41.8°C) of about 1 hr (31, 43, 67, 68).

**WBH and Toxicity, an Area for Optimism.** Robins and Neville (66) have recently reviewed the literature relating to the biology of WBH. They observed that many of the toxicities associated with WBH are related to the methodology used. Analysis of the correlations of toxicity and WBH methodology affords one the possibility of elucidating the basis for toxicity and potentially eliminating it (66). For example, neither Bull’s water suit technique nor Robins’ radiant heat system is associated with disseminated intravascular coagulation. This may relate to the use of sedation in their systems (66) as opposed to general anesthesia in other methods. For a given WBH system, the pig (~70 kg) as an animal model exhibits all the changes seen in humans during WBH (including heating profiles, hematological, biochemical, pharmacological, and cardiovascular parameters). This model provides an excellent means of studying the potential morbidity of WBH in combination therapies (69).

Utilizing the pig as a preclinical model and the data gained from earlier clinical studies, the University of Wisconsin group has recently begun clinical WBH trials with maximal temperatures of 41.8 to 42°C by means of a low-power density radiant heat device. So far (~70 treatments as of January 1984), none of the toxicities which have been associated with WBH (i.e., protracted nausea and vomiting, protracted diarrhea, confusion, pulmonary edema, myocardial infarction, hepatitis, seizures, arrhythmias, disseminated intravascular coagulation, electrolyte abnormalities, strokes, peripheral neuropathy, pressure sores, and burns) (66), have been observed with this method. The contention that the problem of toxicity of WBH is solvable (5) appears justified.

**Future Prospects.** The following discussions examine the potential for the combination of hyperthermia with other therapies in unique settings.

**Chemotherapy and WBH as Adjuvant Therapy, an Approach to Occult Disease.** In his monograph, Hahn (8) reviews many of the positive interactions between chemotherapeutic agents and hyperthermia from a therapeutic viewpoint. In this regard, Phase I (toxicity) and Phase II (disease-specific-therapeutic) studies combining WBH and chemotherapeutic agents have already demonstrated the feasibility of such an approach (22, 66). Although the use of WBH and chemotherapy in a metastatic setting may prove therapeutic, this combination may play its most significant role in an adjuvant setting. Here the term adjuvant refers to therapy directed at sterilizing micrometastases in patients who have been rendered free of gross or detectable disease by surgery but are at high risk for relapse. To avoid confusion, it is proposed that the term “adjunctive” be applied to situations in which hyperthermia is used to potentiate other forms of therapy, e.g., radiation, in the metastatic setting.

As an example, adjuvant chemotherapy has both delayed disease recurrence, and increased the survival of women with Stage II breast cancer (auxiliary node involvement) (70–73). In spite of this achievement, at least 33% of patients will relapse in 5 years with some manifestation of systemic disease (72, 73). Relapse after adjuvant chemotherapy suggests drug resistance. Surprisingly, patients who have received adjuvant chemotherapy and who subsequently develop metastatic disease will respond to the same drugs given in the adjuvant setting (73, 74).

One explanation for these results, i.e., kinetic resistance, may relate to an inadequate microvasculature leading to a failure of drug penetration at time of adjuvant therapy. Ironically, this comes at a time when tumor burden is minimal and multidrug therapy should have its major impact. It is argued that hyperthermia, specifically WBH, may be of value in this setting by increasing drug sensitivity, i.e., overcoming kinetic resistance (as opposed to biochemical resistance), e.g., by increasing membrane permeability or by altering cellular metabolism. This theoretical proposal, i.e., that WBH and chemotherapy in the adjuvant setting may be most efficacious against microscopic disease is testable in both transplantable and spontaneous animal models.

When one proposes adding WBH to adjuvant chemotherapy, the question of clinical feasibility of WBH is raised. Our experience at the Wisconsin Clinical Cancer Center has demonstrated that WBH can be accomplished with our radiant heat system in a range from 39.5 to 41.8°C, for up to 150 min. Treated patients with no underlying problems require only 12 to 24 hr of hospitalization posthyperthermia.

Another innovative area relates to chemotherapeutic drugs which have activity as single agents, are nonmyelosuppressive, and are both radiation and hyperthermia sensitizers. LONIDAMINE is an example of such a drug (75–79). Having completed Phase I (drug alone) studies, Memorial Sloan-Kettering Cancer Center is currently engaged in radiation-drug studies. A WBH-lonidamine study will be initiated at the Wisconsin Clinical Cancer Center in conjunction with Memorial Sloan-Kettering. The ultimate goal is to combine all 3 modalities; Kubota et al. (80) have recently reported such a trimodality approach in the treatment of bladder cancer.

**WBH and WBI.** Preclinical work has demonstrated the utility of combining WBH and WBI. Our group using the AKR leukemia model (81), which is nonimmunogenic (82) and can be quantitated using spleen colony methods (83, 84), has shown a supraadditivity by combining WBI and WBH (85). Table 1 summarizes the results obtained after treating 7- to 8-week-old AKR mice on
Days 5, 6, 7, and 8 after transplantation of 10^6 syngeneic leukemia cells. Treatments consisted of WBI, 100 cGy/day (Cesatron Model E irradiator; Atomic Energy of Canada, Ltd.) and ~41.0° WBH, 1 hr/day (attained by using a radiant heat box) (86) (Enteromics, Inc., Brookfield, WI) used singly and together. The spleen weight, spleen colony assay, and the days of post-splenectomy survival support the conclusion that the effect of combining WBI and WBH is supraadditive (survival data not shown).

WBI has already been shown to be therapeutically useful in the treatment of both chronic lymphocytic leukemia and nodular poorly differentiated lymphocytic lymphoma (87–92). Rubin et al. (91) in reviewing the Eastern Cooperative Oncology Group experience with WBI have suggested that protocols were needed to capitalize on the known effectiveness of radiation to induce responses. The AKR model presented above illustrates one possibility and led to the design of a clinical trial. In this regard, 2 patients have been entered on a WBI-WBH protocol at the Wisconsin Clinical Cancer Center. Preliminary results from this study have thus far been encouraging in both toxicity and response.

Along with the use of (low-dose) therapeutic WBI in combination with WBH, there is a potential for combining (high-dose) ablative WBI in bone marrow transplantation programs for the treatment of acute leukemia. This proposal is discussed in detail elsewhere (109) as well as in the next section. Inherent in this proposed use of WBH is the preferential hyperthermic killing of leukemic cells (93) as well as the theoretical potentiation of chemotherapy and ablative WBI.

**WBH and Immunology.** Greater immunogenicity of in vitro-heated (human) transformed lymphocytes in comparison to normal heated lymphocytes has been demonstrated (94). If this result is extrapolatable to human leukemic cells given hyperthermia, then addition of WBH to pretransplant conditioning regimens may have a distinct advantage. WBI may decrease residual leukemic cells, thereby decreasing the chance for leukemic relapse after bone marrow transplant. In addition, WBH is immunosuppressive itself (95) and may decrease the chance of host versus graft (rejection) reactions (109). Finally, WBH may promote persistent antigenicity of residual leukemic cells, thereby stimulating an effective graft versus leukemia reaction and decreasing the chance of leukemic relapse. All of these postulates are testable in animal models and lend themselves to incorporation into ongoing trials of human bone marrow transplantation for leukemia.

Beyond the proposals outlined above, the potential positive interaction between interferon and hyperthermia presents another area of interest (96–99). At least 3 clinical studies address-

### Table 1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Spleen wt (g)</th>
<th>Leukemic CFU (×10^5)</th>
<th>Leukemic cell kill factor</th>
<th>NormalCFU (×10^5)</th>
<th>Normal cell kill factor</th>
<th>Ratio of kill factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0.49 ± 0.02</td>
<td>22.0</td>
<td>=1</td>
<td>4.6</td>
<td>=1</td>
<td>1.2</td>
</tr>
<tr>
<td>WBI</td>
<td>0.39 ± 0.03</td>
<td>18.0</td>
<td>1.2</td>
<td>6.4</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>WBH</td>
<td>0.20 ± 0.01</td>
<td>6.8</td>
<td>3.2</td>
<td>4.3</td>
<td>1.1</td>
<td>3.0</td>
</tr>
<tr>
<td>WBI + WBH</td>
<td>0.09 ± 0.02</td>
<td>1.2</td>
<td>18.3</td>
<td>2.4</td>
<td>1.8</td>
<td>10.2</td>
</tr>
</tbody>
</table>

*a CFU, colony-forming units.

*b Normal CFU were taken as CFU per spleen (irradiated recipients) minus CFU per spleen (nonirradiated).

c Mean ± S.E.

### Table 2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Leukemic cell kill</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0.0 (20)</td>
</tr>
<tr>
<td>WBI (alone) (40–40.5°)</td>
<td>7.19 (20)</td>
</tr>
<tr>
<td>WBI (alone) (41–41.8°)</td>
<td>25.0 (20)</td>
</tr>
<tr>
<td>IFN (alone)</td>
<td>20.7 (20)</td>
</tr>
<tr>
<td>IFN 2 hr pre-WBH (40–40.5°)</td>
<td>49.5 (20)</td>
</tr>
<tr>
<td>IFN 2 hr pre-WBH (41–41.5°)</td>
<td>38.5 (10)</td>
</tr>
<tr>
<td>IFN 2 hr post-WBH (40–40.5°)</td>
<td>47.5 (10)</td>
</tr>
</tbody>
</table>

*a IFN, mouse interferon.

*b Spleen colony method (63, 64).

*c Numbers in parentheses, number of mice in each group.

*d 1 hr/day for 4 days.

*e 10^6 units/day for 4 days.

The combined use of WBH and interferon are being undertaken (at the University of Texas, by Bull and coworkers, at the University of Wisconsin, by Robins and coworkers, and at Rankin General Hospital, by Parks and coworkers). Table 2 presents preliminary data on interferon and WBH gathered using the AKR leukemia methodology described earlier. These data illustrate the point that the optimum temperature for interferon hyperthermia interaction is not necessarily 41.8° but may be lower. Such issues as these could never be answered in the context of clinical trials, and again illustrates the need for preclinical research in the area of WBH.

**WBH and Labilizers.** Labilizers have been defined as drugs that have no activity against neoplastic cells at normothermic temperatures but promote antineoplastic activity in the setting of hyperthermia. Anesthetic agents represent one class of drugs in this category (100–106). (Other classes are currently under investigation.) It is significant that in animal models such drugs can be administered in doses which demonstrate antineoplastic activity in the setting of hyperthermia in a range that is safe for humans.

To illustrate, the drugs lidocaine and thiopental have been carefully screened for safety preclinically in both murine and porcine systems in terms of normal cell toxicity in the WBH temperature range of 41 to 42°C. These same drugs can potentially provide antineoplastic cell activity in this temperature range (103). In the context of our clinical WBH trials at the Wisconsin Clinical Cancer Center, these drugs are given in combination during WBH to provide sedation (107) and for seizure and arrhythmia prophylaxis, as well as for their potential antineoplastic activity (103).
above). As suggested by others, hyperthermia pharmacology is an important area for research if one is to optimize WBH as a treatment modality (108).

A Proposal for the Future

The purpose of this paper has been to advocate an increased exploration of systemic hyperthermia for the treatment of cancer. To foster this goal, the following proposal is presented.

To evaluate the efficacy of WBH as an adjunct to other cancer modalities, i.e., radiation, drugs and/or surgery, there is a need for prospective, multinational randomized studies. These studies should compare standard therapy (e.g., radiation or chemotherapy) to the standard therapy in combination with WBH. These studies should be designed to answer definitively the question of whether or not WBH has a place in the treatment of neoplastic diseases.

In order to implement such studies, there would be a need for a mechanism, such as a study group, to agree on and share protocols. This forum should further agree on a standardized system for thermometry. Each member institution would share a common system for WBH so that toxicity could be properly evaluated and compared.

The system selected for WBH should have the following characteristics: (a) a WBH system which offers the promise of being cost effective in the treatment of cancer; (b) heating time profiles should be reproducible in the given patient; and (c) the inherent toxicity related to WBH alone should be minimal.

Funds for the study group should provide for the following: (a) data management as well as protocol compliance audits; (b) thermometry quality assurance; (c) defrayal of costs regarding equipment (equipment leasing?); and (d) costs of study group meetings.

As a prelude to initiating the above investigation, a conference of existing WBH users (to include research workers and industry representatives), cancer experts, and the Food and Drug Administration and National Cancer Institute staffs should be convened. At such a conference, definitions of the state-of-the-art as well as potential problems could be identified. Estimates as to the potential of WBH for the treatment of cancer could be approximated by reviewing the protocols as well as the results of current preclinical and clinical research. Priorities with regard to the problems identified, e.g., thermometry, could be set. A plan for the evaluation of WBH technologies could be outlined. Inherent in this plan would be the development of criteria for comparing methodologies (this would include time-temperature profiles, the results of physiological monitoring, temperature gradients, etc.). Estimates of needs for training programs, the cost of multiinstitutional studies, and the personnel needs for each system of hyperthermia could be made.

The report from such a conference should provide the basis for the selection of a system for WBH which would lend itself to multimodality group trials. The role of an Oncology Study Group for WBH Trials and the funding mechanisms most appropriate for solving the major problems of WBH should be addressed by such a conference.

Acknowledgments

I am indebted to Patricia A. Martin, Alan J. Neville, and Warren H. Dennis for their many thoughtful suggestions regarding the preparation of this manuscript.

References

36. Reinhold, H. S., van der Zee, J., Faithfull, N. S., van Rhoon, G., and Wike-
46. Kim, J. H., Hahn, E. W., and Tokita, N. Combination hyperthermia and
42. Herman, T. S., Zuboski, C. F., Anderson, R. M., Mutter, J. J., Blitt, C. D.,
41. Herman, T. S., Zukoski, C. S., and Anderson, R. M. Review of the current

35. Ostro, S., Van Echo, D., Whitacre, M., Aisner, J., Simon, R., and Wiemik, P.
31. Parks, L. C., Minaberry, D., Smith, D. P., and Neeley, W. A. Treatment of far-
30. Barlogie, B., Corry, P. M., Yip, E., Lippman, L, Johnston, D. A., Khalil, K.,
51. Leith, J. T., DeWyngaert, J. K., Dexter, D. L, Calabresi, P., and Glicksman,
429,1982.


OCTOBER 1984

Future Prospects of Systemic Hyperthermia


Role of Whole-Body Hyperthermia in the Treatment of Neoplastic Disease: Its Current Status and Future Prospects

H. Ian Robins

Cancer Res 1984;44:4878s-4883s.

Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/44/10_Supplement/4878s

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.