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Commentary

Hyperthermia and Chemotherapy: When Will They Be Used in the Clinical Treatment of Cancer?*

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INTRODUCTION

HYPERTHERMIA improves the ability of many drugs to kill tumor cells [1, 2]. Recent research has investigated the cytostatic interaction of heat and drugs against tumor cells in culture [3], and in general these studies have been confirmed by *in vivo* results in mice [4]. However, considering the potential improvement in drug action that heat offers the chemotherapist, it is unfortunate that few clinical trials have been initiated. The relative neglect of this area of cancer treatment is particularly difficult to understand in view of the rapid clinical application of local hyperthermia with ionizing radiation therapy. Why has the clinical development of thermochemotherapy been so slow? What are the barriers that prevent its acceptance by the chemotherapist? How can relevant data on the design of effective combination therapy be provided to the clinician? In this paper I will address these questions and offer suggestions intended to speed the clinical application of thermochemotherapy.

The rapid growth of ultrasonic, microwave and radiowave methods for the production of local and whole-body hyperthermia is clearly documented in recent publications [5] and symposia [6, 7]. Although these heating systems can be used equally well in conjunction with chemotherapy or radiation therapy, it is the latter that has seen the most rapid advance toward clinical trials. This situation may have developed because the radiation therapist is more comfortable using hyperthermia apparatus, while the chemotherapist doest not want to add the unknown complications of heat when he usually has the alternative of prescribing another active drug. It is certainly true that the concepts of focusing ultrasonic or microwave energy to a region of the body are most familiar to the radiation therapist, yet the expertise of the chemotherapist in applying combination therapy involving drugs, surgery and ionizing radiation is also well established. In fact, a few chemotherapists have already mastered the skills of clinical hyperthermia production [8–11]. Thus it is unclear why thermochemotherapy is not more widely used as a part of cancer treatment.

The current clinical application of local hyperthermia as an adjuvant to radiation therapy is based on a strong foundation of preclinical studies. This research is described in an explosion of research papers and it has been reviewed at recent international symposia [6, 7]. These studies have carefully examined many aspects of the interaction of heat with ionizing radiation, such as treatment temperature, duration and schedule; high and low energy radiations; dose rate; the induction of thermal tolerance; and the effects on normal tissues as well as tumors. Although the story is not yet complete, a concensus has emerged that allows the clinician to plan combined treatment protocols based on a large number of clinically relevant animal experiments. This foundation of information has not yet been provided concerning the interaction of heat with drugs, and the absence of these data is one of the primary reasons for the slow clinical acceptance of thermochemotherapy.

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ANALYSIS OF HEAT AND DRUG INTERACTIONS

The existence of a synergism in cell killing between heat and drugs has been established clearly for several drugs, but the second phase of relevant preclinical animal experiments has barely been initiated. A few of these studies [4, 12] have been undertaken; however, the complex effects of local or whole-body hyperthermia on drug pharmacokinetics, pharmacology and toxicity must be evaluated for each drug that has shown potential as a thermochemotherapy agent. These experiments will not be easy to design or execute because of the various ways the drug–animal interaction could be modified by heat. In some cases, because of the alteration of drug activity under hyperthermic conditions, we are in a sense studying the biological activity of a new anticancer agent. Rather than continuing to identify potential drugs for thermochemotherapy, future studies should focus on completing this second phase of preclinical experimentation.

Many drugs are known to have an increased anticancer activity at elevated temperatures. Recent reviews [1, 2, 13] list the drugs whose cell killing abilities at hyperthermic temperatures have been studied *in vitro* or *in vivo*. The drugs are divided into three groups: (i) those that show little interaction at hyperthermic temperatures; (ii) those that show synergism at temperatures less than 42°C; and (iii) those whose activity is enhanced only at temperatures greater than 42°C. This division at 42°C is due to the fact that whole-body hyperthermia cannot be sustained for long periods of time above 42°C [10, 14]. Thus in order for a drug to be considered for whole-body thermochemotherapy it must show an increased effectiveness at temperatures below 42°C. Local hyperthermia can be used in conjunction with drugs activated by temperatures greater than 42°C.

We need to answer basic questions concerning the interaction of heat with anticancer drugs. Under the conditions of whole-body hyperthermia the situation is very complex because of the gross physiological stress that it places on all the major organ systems. In brief, we must alter the balance between therapeutic and toxic drug effects under hyperthermic conditions to an extent that justifies the extra therapeutic apparatus and risk to the patient. The potential improvement in cytostatic drug effect that can be obtained by modifying the treatment temperature is enormous. Recent *in vitro* studies [15] illustrate that for some drugs raising the temperature of cells from 30 to 43°C results in an improved cell kill of 3–4 log units. Thus hyperthermia can provide a large improvement in selective drug sensitivity and cell killing under optimum conditions.

DIRECTION OF FUTURE THERMOCHEMOTHERAPY RESEARCH

First, to make the most use of current knowledge we should select a few of the most promising drugs and subject them to further study. Table 1 contains a list of drugs and references to hyperthermia studies that show enhanced antitumor activity in animals and humans. Based on this information, bleomycin and *cis*-platinum appear to be good candidates for local thermochemotherapy at temperatures greater than 42°C, and one of the nitrosoureas looks promising for whole-body hyperthermia at temperatures less than 42°C. In addition to showing an increase in tumor growth delay, it is also necessary to consider the principal sites of drug toxicity in these studies [16]. Hyperthermia could alter the toxic dose or primary site of toxicity from that seen in normothermic animals [17]. Fortunately, hyperthermia has a relatively low toxicity compared with conventional anticancer modalities, and this fact simplifies the study of drug toxicity under hyperthermic conditions.

Table 1. Anticancer drugs that show enhanced antitumor activity in animals and humans when combined with hyperthermia

Drug	References	
	Animal	Clinical
Alkylating agents		
Melphalan	[28]	[33–35]
Cyclophosphamide	[22]	[34]
Nitromin	[23]	
DTIC		[36]
Antibiotics		
Adriamycin	[19, 21, 26]	[32]
Bleomycin*	[25–27, 30, 31]	[32]
Actinomycin D	[24]	
Nitrosoureas		
BCNU	[4, 29]	[8]
CCNU	[4, 28]	
Methyl-CCNU	[4]	
Miscellaneous		
cis-Platinum*	[4, 20, 31]	[8]

*These drugs exhibit a threshold for heat-induced drug potentiation near 42°C.

We should proceed with specific studies that consider the effects of combination thermochemotherapy in more detail on both the tumor and its animal host. With regard to the tumor, clear answers to the following questions should be defined. What is the mechanism of the cell killing interaction between heat and drug? Does

it result from an increase in drug uptake by the tumor, an increased drug reactivity at elevated temperatures or an inhibition of the repair of drug induced cell damage? Some of this information can be obtained from cell culture studies, but animal experiments are necessary to establish the proposed mechanisms *in vivo*. Does the drug interaction appear in many types of tumors or just a few? Is the effect seen in both solid and ascitic tumors? Does it depend on the rate of tumor growth or the tumor's size at the time of treatment? Must both heat and drug be administered simultaneously? How long a time period can exist between the two treatments before the interaction disappears? Is the sequence of treatments important? How many treatments are necessary to achieve the best results? Do multiple treatments produce tolerance to subsequent heat or drug action?

In the case of the animal host, again many questions remain to be answered. The pharmacology and toxicity of only a few drugs have been studied under hyperthermic conditions [18, 19]. Does heat alter the primary site of drug toxicity or the dose at which it occurs? Does the time course or route of drug administration affect the development of toxicity? How is the organ distribution of the drug changed under the conditions of hyperthermia? What is the effect of drug on normal tissues surrounding the tumor that may also be heated? Does drug toxicity interact with the type of anesthesia given to the animals during the hyperthermic treatment? Does heat alter the known pattern of drug metabolism? It should be clear from these questions that many things need to be determined before we completely understand the interaction of heat with anticancer drugs.

We should not, however, become discouraged at the difficulty of completely understanding thermochemotherapy, but rather keep in mind the benefits that this new form of adjuvant therapy can provide. First, the moderate hyperthermic temperatures needed to show drug synergism are easy to produce and are not substantially harmful to the patient. Second, it may not be necessary to administer the two treatments simultaneously. This is the case for radiation therapy. A 1- or 2-hr gap would greatly simplify the scheduling of thermochemotherapy in the clinic. Third, based on preliminary studies, the magnitude of increased cell killing to be obtained is substantial, being an extra 3–4 log cell kill. Thus the potential exists for greatly improving the therapeutic activity of known anticancer drugs. If we can establish the range of therapeutic effectiveness of one or more drugs as outlined above, then we will be able to more confidently predict the performance of this combination therapy in humans. With this knowledge, clinical protocols could be rationally planned to test the effects of the combination of hyperthermia and chemotherapy in the treatment of cancer.

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