Possible Benefits of Hyperthermia to Chemotherapy

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Abstract

The advantages of hyperthermia for chemotherapy are discussed in detail. These advantages are (a) synergy with chemotherapeutic drugs and also with ionizing radiation, (b) low host toxicity, (c) ease of control (heating precisions in the range of ±0.1°C and specific definable localized areas), and (d) low resistance (chemotherapeutic resistance and hyperthermic resistance). The potential for hyperthermia and chemotherapy in the treatment of specific human cancers, both disseminated and solid tumors, are discussed with respect to current therapy and the possible benefit of hyperthermia treatment.

Introduction

Many aspects of hyperthermia and its effects on cells have been discussed in other papers of this conference. In particular, these papers have examined the relationships between hyperthermia and chemotherapeutic drugs and the effects of both on tumors. In this presentation, we attempt to indicate ways that both hyperthermia and chemotherapeutic drugs may be used to maximal benefit for patients.

To do this, we may begin by asking what are the advantages of hyperthermia that other therapies do not have? What is it that hyperthermia offers chemotherapy that is of unique advantage? Several features may be pointed to in answer to these questions, including synergy, low toxicity, control, and prevention or reversal of drug resistance.

Synergy

The most obvious benefit of hyperthermia to chemotherapy is the fact that hyperthermia shows synergy with some drugs against cancer cells (6, 15, 18, 20, 37, 59). The drugs with which this synergy occurs have been described by Dr. Marmor and Dr. Hahn in this conference. Additionally, not only is there potentiation by hyperthermia with drugs but also by ionizing radiation (3, 17, 24, 26, 30, 39, 44, 47, 55, 57). There are few other instances of a treatment modality with this kind of relationship between drugs and radiation. An exception to this is the demonstration of increased radiosensitivity of cells treated with metronidazole and misonidazole (1, 2). The antitumor effects of the polypeptide antibiotic, amphotericin, and the nitroimidazole antibiotic, misonidazole, by themselves are not effective, but both are potentiated by hyperthermia (4, 19, 21, 53, 54). It is of importance that hyperthermia appears to potentiate not just one but several drugs belonging to more than just one class of chemotherapeutic agent.

Low Toxicity

Of critical importance to any therapeutic modality for a disease is the problem of specificity of treatment. The goal is to provide maximal therapy with minimal toxicity to the patient. In this regard, hyperthermia offers another advantage to chemotherapy, low host toxicity. Several studies have investigated the relationship between hyperthermia and its effects on normal tissue, in animals as well as humans. Although the topic has by no means been exhaustively studied, it appears that hyperthermia has more effect on tumor tissue than on normal tissue (9, 11, 26, 31, 32, 34, 36, 43, 45, 46, 55). This lack of significant host toxicity should allow for the inclusion of hyperthermia in chemotherapeutic regimens without significant additional detrimental effect to the patient.

To appreciate the desirability of being able to use one treatment vector with another without significant additional host toxicity, let us consider for a moment the combination of other modalities. When radiation therapy is added to chemotherapy, the result is usually increased host toxicity (29, 33). In many cases, this increased toxicity is immediate, but it may also be delayed, as is the case with doxorubicin (16, 28) or bleomycin (13). When we consider combining chemotherapy and immunotherapy, we find that many of the drugs, but not all, are immunosuppressive (7). Hyperthermia, however, is not generally known, at this time, to increase host toxicity to drugs but, rather, by combination, to improve the therapeutic efficacy against tumors.

In the case of hyperthermia and immunotherapy, the existing studies are conflicting and insufficient, with some reports indicating a decrease in immune function (23, 40, 49, 51, 52, 56) and with others indicating enhanced immune function (12, 52, 58). If, indeed, hyperthermia does suppress immune responsiveness, the effect may have more to do with the extent of delivery of hyperthermia than with any question of the utility of hyperthermia. For example, while it is entirely plausible to suppose that whole-body hyperthermia would suppress immune functions, we would find it difficult to suppose that local hyperthermia would lead to any significant decrease in immune response except in the area of treatment. It may be argued, however, that immunosuppression in the region of the tumor is a key part of host defenses against neoplasms. This argument, like the argument of increased antigenicity of residual tumor tissue following hyperthermia treatment, remains to be proved.

Control

As a technique, hyperthermia has features that suggest the possibility of interfacing it with biological systems in such a way as to allow for specificity of treatment in several areas. It is in this ease of control and specificity that another advantage for chemotherapy exists.

One domain of this specificity is the control of the amount of heat delivered per unit of time. Several other papers of this conference have discussed the problems of instrumentation and dosimetry in hyperthermia. While there are many problems still to be resolved, we have the ability to heat all or part of the
body with precisions that are on the order of parts of a degree centigrade. Thus, we are able to control with precision the amount of heat as well as the duration of heat treatment. This should allow us to work, or heat tissue, within the limits of toxicity in the range that is most optimum for tumor cell kill for a given drug. Dr. Marmor and Dr. Hahn have discussed, for example, their data on the temperature threshold ranges that yield optimal tumor cell kill for bleomycin, 42–43°C, and bis-chloronitrosourea, 41–42°C. As more chemotherapeutic drugs are studied, we would expect further information as to the temperature thresholds at which hyperthermia and chemotherapy may combine for more effectiveness.

Another domain of specificity in the control of hyperthermia is that of localization. This domain also offers advantages for use with chemotherapy. By localization we refer to the ability of local hyperthermia, as exemplified by ultrasonic or radio-frequency techniques, to be applied to specific areas or volumes of the body. This may allow, for example, the treatment of specific nodes in lymphoproliferative disease, of particular bones giving pain from metastatic disease, or of a given segment of lung with unresectable tumor, to mention just a few. Unlike chemotherapy, such localizing capability avoids nontumor areas of the body that may be sensitive, such as bone marrow, liver, or brain. Nontumor toxicity would also be limited to that core of area defined by the transducer. When one considers the possibilities with focused systems, the nontumor toxicity should only further decrease. The capability for local hyperthermia would be more advantageous if we had a drug that was virtually inactive in the body at 37°C but quite tumor toxic at 42–43°C, as has been suggested by Dr. Hahn. Hyperthermia and chemotherapy might then combine to act in the tumor area only, while sparing other organs.

Resistance: Chemotherapeutic Resistance and Hyperthermic Resistance

Tumors are well known to often become clinically resistant or refractory to a given chemotherapeutic drug regimen. Too frequently, the development of tumor resistance to one drug will also lower the likelihood of obtaining a therapeutic response to other drugs. It is toward a solution of this problem that hyperthermia offers 2 more benefits to chemotherapy.

The first benefit is that hyperthermia may be helpful in either preventing or delaying the development of tumor resistance to a given chemotherapy drug or in reversing the acquired resistance of a tumor to a given chemotherapeutic drug. The former case has yet to be explored or studied. There is some work with respect to the latter case, reversal of acquired drug resistance (36). Help from hyperthermia in dealing with these problems would be tremendously important. Presently, aside from delimiting host toxicity, the major reason for clinical failure in the treatment of cancer patients may be ascribed, at least in great part, to either lack of tumor response or development of resistance after an initial response has been achieved.

The second benefit to chemotherapy is that hyperthermia in itself seems to have a low or absent tumor resistance. Obviously, as a treatment vector, it would be of limited value if, after a few treatments with a chemotherapeutic drug, hyperthermia were no longer effective. Thermal tolerance is known to occur, and this subject has been recently reviewed (14, 22, 25, 44). Will tumors become resistant to hyperthermia and chemotherapy in vivo? What are the conditions that will delay the development, if any, of thermal resistance to chemotherapy? Answers to these questions may result in clinically significant benefits.

Last in this section on the advantages of hyperthermia for chemotherapy, we wish to point out that hyperthermia gives us an additional dimension with which to view and to investigate the pharmacology of chemotherapeutic drugs. This need not necessarily be construed as an advantage, but we feel that it will allow us to expand our information about cells and chemotherapeutic drugs and to see how the drugs may be used most efficaciously.

Potential for Hyperthermia and Chemotherapy in the Treatment of Specific Human Cancers

In light of the advantages of hyperthermia discussed, how may we best combine hyperthermia and chemotherapy? The variables, such as local versus whole-body hyperthermia, the degree of heating, the sequence of hyperthermia and drug treatment, and so on, are many. Studies of hyperthermia with drugs in patients should be carefully designed to yield useful information and should be restricted initially to drug-hyperthermia combinations that have a firm experimental base. Obviously, it follows that we must carefully pick clinical situations that will provide the maximal information; otherwise, 5 or 10 years from now we will still be debating whether hyperthermia and chemotherapy used together are worthwhile.

In this section, we consider the opportunities and problems with certain human neoplasms that may be considered for these trials. These are acute lymphatic leukemia, acute myelocytic leukemia, lymphoma, melanoma, cancer of the head and neck, and 3 major tumors, breast cancer, lung cancer, and gastrointestinal cancer. Obviously, other tumors may offer unique opportunities for investigation, but these will serve as examples of the problems and opportunities.

Acute Lymphatic Leukemia. This disease by definition is systemic and is effectively treated, especially in children, by combinations of drugs that usually include vincristine and prednisone, with or without asparaginase, for induction; intrathecal methotrexate with whole-brain irradiation; and additional “maintenance” chemotherapy with 6-mercaptopurine and methotrexate (27). Adriamycin and cyclophosphamide have been added in certain regimens in an attempt to increase the number of long-term survivors. The opportunity for hyperthermia to contribute to the management of this disease would appear to be minimal, since (a) whole-body hyperthermia would need to be used and (b) the key drugs used have not been studied extensively with reference to interaction with hyperthermia. On the other hand, human lymphoblasts may be highly sensitive to moderate hyperthermia (42, 50), and despite the lack of demonstrated synergy with the drugs used, heat treatment may give additive antitumor effects. More information is required regarding heat sensitivity and chemotherapy potentiation with human lymphoblasts in culture. Human experimentation should probably be limited initially to patients in relapse. Should antileukemic effects be demonstrated in this circumstance, hyperthermia treatments could be incorporated into maintenance drug regimens.

Acute Myelocytic Leukemia. Although chemotherapy is now effective in producing high remission rates in this disease, long-term remissions are on the order of only 10%. The effective programs for remission induction involve the use of anthra-
cyclines, rubidomycin, or Adriamycin, in combination with 1-β-o-arabino-furanosylcytosine (5), with 6-thioguanine and methotrexate used in some regimens. Since a fair amount of data exist on Adriamycin-hyperthermia interactions, the use of whole-body hyperthermia in this disease, with and without chemotherapy, would be a worthwhile pursuit, since an additional effective treatment modality could lead to a marked increase in long-term survivors. However, in view of the improved remission induction obtained with combination chemotherapy, initial trials should be done with patients in relapse. Some human lines are available for study that have the characteristics of acute myelocytic leukemia and could be useful models (10, 35).

**Lymphoma.** Lymphomas are generally radiosensitive, and Stage I and II disease is usually adequately treated with radiation therapy. Therefore, the value of local hyperthermia together with radiation therapy as the primary treatment would be limited. However, local hyperthermia with systemic chemotherapy to test advanced disease may be a worthwhile approach, since hyperthermia would have the possible advantage of not compromising marrow function, and this allows maximal doses of chemotherapy to be given concomitantly. Since the 5-year, disease-free survival rate, even in advanced Hodgkin’s disease, is good (about 50 to 70%), trials of hyperthermia, with or without drugs, may be relegated to patients who relapse on current regimens. Another problem here, as well as with the acute leukemias, is the use of drug combinations, thus making evaluation of drug-hyperthermia interactions difficult.

Since nodular, poorly differentiated lymphocytic lymphoma appears to be palliated effectively with single-agent therapy (chlorambucil or cyclophosphamide), as with the 3-drug CVP regimen (cyclophosphamide, prednisone, and vincristine), the opportunity exists here as well as in patients with chronic lymphocytic leukemia to study hyperthermia and alkylating agent interaction carefully in previously untreated patients. Use of hyperthermia could be either localized to areas of bulk disease or whole body, since in most cases this disease is disseminated at the time of presentation, often with marrow involvement.

**Melanoma.** Melanoma is generally poorly responsive to drug treatment. However, dissemination often results in multiple skin lesions, and this accessibility provides an excellent opportunity for the study of hyperthermia-drug effects. Some data are already available on the effect of hyperthermia on this tumor. Melanoma patients could provide an opportunity to study synergy of single agents and hyperthermia, even with drugs that alone are not effective, since response rates (even with 5-(3,3-dimethyl-1- triazeno)-imidazole-4-carboxamide (DTIC), the most effective single agent) are only on the order of 20 to 30%.

**Cancer of the Head and Neck.** Treatment of this solid tumor offers one of the most promising clinical opportunities to study drug-hyperthermia interactions. These tumors are usually accessible to controlled heating, have been shown to be responsive to hyperthermia (41), and in the advanced state are not curable in most cases by surgery and/or X-ray therapy despite the lack of distant metastasis in the majority of patients. Furthermore, there is no established advantage of combination chemotherapy over single-agent use, and the drugs that we use, which are temporarily effective, are methotrexate, bleomycin, and cis-diaminedichloroplatinumdecyl pthalate, drugs which have been studied in conjunction with hyperthermia in experimental tumors. Thus, the potential benefit of drug-hyperthermia treatment, the effect of hyperthermia on prevention or delay of drug resistance, and eventually the effect of combined radiation-hyperthermia-chemotherapy treatment may be studied. These tumors are also easily accessible for biopsy, allowing biochemical and morphological concomitants of treatment to be assessed. Should hyperthermia be of value in advanced disease, it could be evaluated as part of adjunctive programs with chemotherapy preceding or following surgical resection or radiation therapy.

**Breast Cancer.** Disseminated breast cancer, while effectively palliated in the majority of cases by hormone therapy when estrogen receptors are positive or by combination chemotherapy, remains essentially an incurable disease at this stage. Thus, both local and systemic hyperthermia are worthy of study in an attempt to improve this dismal long-term outlook. The problems that arise with breast cancer dissemination, however, are that lung, liver, bone, and brain are often involved, and techniques to heat these sites are in the developmental stage. Therefore, in the near future, attempts to treat advanced or recurrent breast cancer will probably be concerned mainly with the treatment of local soft tissue recurrence. If hyperthermia is shown to be of benefit with or without chemotherapy, the possibility of using whole-body hyperthermia in the adjunctive mode could be an important extension.

**Gastrointestinal Cancer.** Treatment of advanced, Duke’s C, or recurrent gastrointestinal cancer remains unsatisfactory. Except possibly for gastric cancer, where drug combinations have been reported to produce 40 to 50% remission rates (8), no clear benefit from drug combinations has been established for pancreatic and colon adenocarcinoma. The nitrosoureas, especially methyl-1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea and 5-fluorouracil, are effective agents, but only benefit 20 to 30% of the patients. Presumably, local hyperthermia, if effective, would play only a palliative role in the management of this disease unless new effective agents and combinations are developed that can eradicate all but bulky disease in circumstances where the primary tumor has been removed.

**Lung Cancer.** The situation for oat cell carcinoma, the most chemotherapeutically responsive of the 4 major types of lung cancer, is in a sense analogous to that for breast cancer. Effective chemotherapy exists; combination therapy is required; and the patterns of spread are to liver, marrow, brain, and bone. Encouraging results have been reported, especially for disease limited to the thorax, when treated with X-ray therapy together with combination chemotherapy. If hyperthermia is shown to be of value against these cells, either local or whole-body hyperthermia could contribute to potentially curative adjuvant regimens for this tumor.

The non oat cell varieties of lung cancer are only poorly responsive to chemotherapy, and combination programs have only marginal advantage over single-agent treatment. If the technology for using hyperthermia for lung disease is perfected, the opportunity would be present for studying hyperthermia-single drug interaction or combinations of X-ray, hyperthermia, and chemotherapy.

**Human Tumor Model Systems**

If we could be further guided in these efforts by experimental models using representative human tumors growing in tissue...
culture and in the immunodepressed mouse, this would be an important step forward. Sufficient variability to heat responsiveness or chemotherapy responsiveness exists even within one human type of tumor that, if we base clinical trials on effects of a drug and hyperthermia on a Chinese hamster cell, for example, the clinical situation may be different. Clearly, mechanism studies and detailed biochemical studies are best done on these well-characterized model systems, but there should be another intermediate step before these data are extrapolated to humans. Finally, if we could measure the effects of hyperthermia on the proliferation of normal and neoplastic stem cells in vitro, this would also be a step further, since we are interested primarily in this fraction of tumor cells. Some progress has been made in recent years (48), and this may be possible for some human cancers even now.

References

6. Braun, J., and Hahn, G. M. Enhanced cell killing by bleomycin and 43° C. D. Kowal and J. R. Bertins
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