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Hyperthermia in Cancer Therapy

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Many malignant cell lines exhibit a therapeutic response to supernormal temperatures. Selective destruction of tumor cells has been observed following moderate hyperthermia (42° to 43°C) in vivo, and tumor eradication by heat has been achieved without normal tissue morbidity. Thermal cell killing appears to be independent of oxygen tension, and the sensitivity of S-phase cells to thermal damage is complementary to that for cellular radiation response. Hyperthermia is therefore a promising adjunct to radiotherapy. At the Claire Zellerbach Saroni Tumor Institute, Mount Zion Hospital and Medical Center, San Francisco, the differential thermal sensitivity of malignant cells is being studied to achieve improved tumor control in patients refractory to more conventional treatments. Preliminary results of a two-year clinical trial indicated increased local objective responses when hyperthermia and radiation were used in combination.

THE THERAPEUTIC EFFECTS of hyperthermia on various types of cancer have been recognized for more than 100 years.[1] In 1893 Coley[2] reviewed the cases of 38 patients with advanced cancer in whom high fevers developed consequent to accidental or deliberate infection of erysipelas; in 12 patients there was complete regression of tumors and the conditions of 19 others improved. Strauss[3,4] used hyperthermia and surgical procedures to achieve improved responses in 250 patients with carcinoma of the colon and rectum. Hot baths were used with good results by Westermark[5] for inoperable cervical cancer and by Goetze[6] for carcinoma of the penis. Hall and co-workers[7] treated 32 patients with carcinoma of the urinary bladder by perfusing the organ with hyperthermic solutions ranging in temperature from 41.5° to 45°C; in 26 patients there was substantial tumor regression and in four patients complete regression of tumors was achieved. Other early reports described a therapeutic action of heat on sarcoma[2,8] and uterine carcinomas.[9]

Hyperthermia has also been used to augment the effects of other cancer therapies. Stehlin and co-workers[10,11] have treated melanoma of the extremities by perfusing the area with blood combined with melphalan. When the perfusate was hyperthermic, a five-year survival of 76.7 percent of the patients was obtained, compared with a five-year survival of 22.2 percent of those without

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hyperthermia therapy. Cavaliere and colleagues[12] used hyperthermic perfusion alone and in combination with surgical procedures or chemotherapy to treat 111 patients with tumors in the limbs; encouraging results were obtained with osteogenic sarcoma and melanoma. These researchers showed that heat can cause tumor regression, and suggested that hyperthermia stimulates an antitumor immune response for immunogenic tumors.

Interest has developed regarding the use of hyperthermia as an adjuvant to radiotherapy. In 1910 Müller[13,14] reported the cases of 100 patients with histologically confirmed advanced cancer who were treated with combinations of diathermy and x-ray irradiation. Of these patients, there was complete regression of the treated lesions in 32 and rapid but temporary improvement in 36. Warren[15] used various combinations of induced fever and roentgen therapy to achieve significant improvement and palliation in 29 of 32 patients with cancer whose conditions were considered "hopeless." In 1948 Korb[16] reported his results using an internal control to compare the response of tumors to x-rays alone and to a combination of x-rays and heat. He treated two separate basal cell carcinomatous lesions of the skin in the same patient with the same radiation dose, but used hyperthermia as an adjuvant to the treatment of one lesion. The tumor which received x-ray irradiation alone showed no response while the tumor treated with both hyperthermia and x-rays regressed completely.

Recently, Brenner and Yerushalmi[17] used hot air jets and microwave diathermy to achieve local tumor hyperthermia before and during x-ray irradiation of six patients in whom there had been no response to conventional therapies. The results were impressive with three complete regressions and two partial improvements. Kim and co-workers[18] treated 36 patients with an assortment of malignant cutaneous lesions, including melanoma, Kaposi sarcoma, mycosis fungoides and two types of lymphoma. These investigators concluded that radiation followed by hyperthermia was more effective than either modality alone and that prolonged benefits were much greater for the combined modality relative to radiation therapy alone.

Thermal Cell Killing

In the early 1900's several investigators showed that fragments of experimental tumors lost the ability to produce tumors in host animals if they were heated to temperatures of 42° to 47°C for short periods.[19-22] In 1903 Jensen postulated that tumor cells are more sensitive to heat than normal cells,[21] and in 1927 Westermark[23] carried out a comprehensive study using the Jensen sarcoma and the Flexner-Jobling carcinoma in rats. Using diathermy, he was able to heat tumors to 44°C in vivo and obtain complete tumor regression without damaging surrounding skin and normal tissue. Crile destroyed S91 melanoma and sarcoma 180 tumors implanted in the feet of mice with thermal treatments that left the foot intact;[24] he was able to obtain similar therapeutic results with several other experimental and spontaneous tumors.[25]

Tumor control and cell damage in vivo can occur with thermal doses which would leave a large proportion of viable cells if heating was carried out in vitro.[25-30] In fact, thermal cell killing in tissue culture is not invariably enhanced for malignant cells.[31-34] One differential thermal response that is consistently observed in cancer cells in vitro is the inhibition of oxidative metabolism by moderate hyperthermia (41.5° to 43°C).[35,36] For example, Cavaliere and associates[37] found that irreversible inhibition of oxygen consumption by Novikoff hepatoma cells occurred after two hours at 42°C, whereas this temperature produced no effect on respiration in normal and regenerating rat liver cells. Dickson and coworkers have observed irreversible inhibition of oxidative metabolism in several malignant cell lines by 42°C hyperthermia, and they have correlated this inhibition with inability to produce tumor implants in hosts.[38-42] The specific characteristics of malignant cells responsible for this differential heat response have not been identified, but the presence of a relatively heat-labile function in the mitochondrial membrane of cancer cells has been suggested.[43-45]

Using light or electron microscopy, Overgaard and Overgaard[46,47] and Muckle and Dickson[10] have studied the histopathology of experimental tumors treated with moderate hyperthermia in vivo. An outstanding feature of in vivo tumor cell response to temperatures of approximately 42°C is a rapid reaction involving cell pyknosis, destruction and lysis. The reaction occurs selectively in tumor cells and appears to result from stimulated lysosomal activity. Overgaard[30] has hypothesized that inhibition of oxidative metabolism without a corresponding decrease in anaerobic glycolysis causes increased production of lactic

acid and consequent acidification of the intracellular and extracellular compartments; this acidification stimulates the acid reaction of lysosomal enzymes and increases lysosomal digestion. Because thermal inhibition of respiration is enhanced specifically in malignant cells, their destruction is selectively increased. It is noteworthy that the lysosomes of Novikoff hepatoma cells have been found to be more labile than those in normal cells.[48]

Environmental factors probably enhance selective in vivo thermal destruction of cancer cells. Decreasing the pH concentration[49,50] or nutrient levels[51,52] of the extracellular fluid can increase thermal cell killing by several orders of magnitude. Malignant tissue shows relatively elevated production of lactic acid under oxygenation[53,54] and hypoxia increases the rate of lactic acid production by a factor of 2 or 3.[55] The interstitial fluid of tumors presents decreased glucose levels and increased levels of hydrogen ion, carbon dioxide and lactate relative to subcutaneous interstitial fluid and blood serum, and these features become more pronounced with increasing hypoxia.[56-60] As might be expected, induction of additional tissue hypoxia by clamping a tumor-bearing limb before heating enhances tumor destruction.[24,61-63] Environmental influences on in vivo thermal response are difficult to evaluate for obvious reasons, not the least of which is the fact that conditions are not homogeneous within a tumor volume and probably fluctuate in complex ways during thermal treatment.

Thermal stimulation of antitumor immune response may also influence tumor regression in vivo. Experimental tumor systems have been used to show that heating a primary tumor can inhibit the growth of metastases[64,65] and contralateral tumors[66] distant from the site of treatment. Based on clinical observations Cavaliere and colleagues[12] and Stehlin and co-workers[11] have suggested that tumor response to hyperthermia may be improved secondary to stimulation of an antitumor immune response. Stehlin[11] reported increased in vitro cytotoxicity of patient lymphocytes toward their own tumor cells following hyperthermic perfusion for melanoma, and suggested that destruction of melanoma by perfusion liberates antigenic material. Mondavi and associates[67] found that the immunogenicity of heat-killed Ehrlich ascites tumor cells was increased relative to those killed by x-ray. Sugaar and LeVeen[68] conducted histopathologic studies on lung tumors heated with radiofrequency diathermy and observed extensive degeneration of tumor vasculature followed by massive infiltration of round cells and lymphocytes; they noted the similarity of this phenomenon with that of acute allograft rejection and suggested its role in tumor regression.

Obviously, in vivo thermal response is a complex function of several factors, and the relative importance of each is difficult to estimate. Fortunately, enough is known of the selective destructive effect of moderate hyperthermia on cancer tissue to enable a therapeutic gain using carefully planned thermal treatments. Continuing improvements in technology are making selective heating of malignant tissue more feasible. This is particularly encouraging to radiotherapists because hyperthermia is a potent radiosensitizer.

Hyperthermia as Adjunct to Radiotherapy

Radiotherapy involves the destruction of malignant cells by various types of ionizing radiation. Treatment by radiation alone may be effective in achieving control of disease; however, several obstacles to local cure often develop. The radiation dose which may be used in a clinic to control cancer is limited by the radiation tolerance of normal tissue within the field of treatment. Occasionally, tumors recur in areas where normal tissue tolerance has been severely compromised by previous irradiation; in these cases, the allowable radiation dose may be so low that tumor control by radiotherapy is unlikely or inconceivable.

Treatment is further complicated by the presence of radioresistant cell subpopulations within malignant lesions. Cells under hypoxic conditions are approximately three times more resistant to radiation than oxygenated cells, and the relative abundance of hypoxic cells within a tumor is a major factor determining the radiation dose necessary for tumor control. Hypoxia provides no protection from thermal killing in vitro[50,69] and sensitizes cells in vivo.[62,63] Thermal sensitivity of cells varies during the cell cycle and contrasts with the variation in radiosensitivity; the S phase is, at once, the most radioresistant and thermosensitive position in the growth cycle.[70-72] Hyperthermia may also sensitize hypoxic cells and S phase cells to radiation.[33,36,62,70,73,74] This remarkable complementary relationship between hyperthermia and radiation allows tumor control with reduced doses of radiation thus decreasing the possibility of unacceptable normal tissue morbidity. Improved rates of tumor control and cure have been re-

ported consistently by investigators using hyperthermia as an adjunct to radiation therapy.*

It must be stressed that improved tumor response to the combined treatment modality is not due solely to the effects of supernormal temperatures on radioresistant cell subpopulations. Hyperthermia has a general effect on mammalian cells of potentiating radiation damage.[33,70,74,80,81] When mammalian cells are irradiated they suffer cumulative damage before being lethally affected. Cells which are not lethally damaged are able to recover by repairing various lesions caused by the treatment. Hyperthermia inhibits cellular repair processes and reduces the capacity to recover from radiation damage.[33,73,82] The net effect is that cell killing by radiation increases with temperature, even for temperatures which produce insignificant thermal killing.[73]

Local Tumor Hyperthermia and Radiotherapy

Thermal cell killing and radiosensitization increase with temperature. Although in vivo thermal cell killing is enhanced in malignant tissue, hyperthermia augments radiation damage in all mammalian cell types. Therefore, it is desirable to achieve fairly selective, differential heating of lesions to be irradiated. Tumor morphology can make this goal attainable. Heat deposited in tissue is dissipated by the flow of relatively cool blood.[83] As blood flow per volume of tissue decreases, so too does this cooling effect.[83,84] Owing to a relatively decreased blood flow, differential heating of tumor tissue relative to surrounding normal tissue is possible.[68] The authors have observed temperature differences of several degrees centigrade between normal tissue at the periphery of a tumor and tissue at the core in spontaneous animal tumors; the magnitude of the heat gradient which can be attained appears to increase with tumor size.

Methods used to induce local tumor hyperthermia in humans must meet several requirements. Generally, it is necessary to deposit energy at depth. A qualitative approximation developed from in vitro and in vivo data is that a 1°C rise in temperature doubles the thermal destruction effect.[25,72] Because small differences in temperature can cause such large differences in response, it is desirable to achieve a homogeneous temperature distribution throughout the tumor volume. Normal tissue must not be heated excessively, and preferential absorption of energy by normal tissue in the treatment area should be avoided. The heating techniques which are most widely used and show the most promise include inductive heating by electromagnetic radiation, heating by ultrasound and capacitive heating using pairs of electrodes. Each of these methods has characteristic advantages and disadvantages.

Radiofrequency inductive heating[85,86] allows induction of hyperthermia at depth with minimal heating of skin and fat. Focusing of energy into a tissue volume is not possible, and differential tumor heating relies on decreased tumor blood flow relative to surrounding normal tissue. As frequency increases to the microwave range, localization of heating improves, but penetration is compromised. Preferential absorption of energy by skin or fat does not occur, but reflection and standing-wave phenomena become important, and burns can result. Microwave diathermy is useful currently for superficial lesions, but special applicator designs will soon allow invasive tumor heating and heating of cavities such as the bladder, rectum and esophagus. Thermal dosimetry is a major problem associated with these heating methods. Metal temperature probes perturb electric fields and distort the heating patterns they would normally produce. Continuous accurate monitoring of temperature is difficult because spurious readings and inhomogeneous heating result from the interaction of the electric field with the probes and their conductive leads. Nonperturbing temperature probes and a technique of noninvasive thermometry are currently being researched and may resolve these problems in the future.

Ultrasound[87] can be applied with single or multiple transducers to obtain varying degrees of focus. Good penetration may be achieved with the correct choice of frequency, and fat is not heated preferentially. However, preferential absorption by bone precludes the use of ultrasound in many cases. Furthermore, ultrasound is not transmitted adequately through air pockets and much reflection occurs at air-tissue and muscle-bone interfaces. Thermometry with conventional probes is feasible. The volume of heating obtainable by ultrasound may occasionally be too limited for therapy.

Radiofrequency capacitive heating[88] is obtained with pairs of electrodes positioned on either side of the volume to be heated. This intervening tissue acts as a resistor and heating occurs as local cur-

*References 17,18,25,46,62,63,75-80.

rents are generated in it. Electrodes can be shaped to specific requirements and the use of multiple electrodes can allow increased localization and depth of energy deposition. Unfortunately, skin and fat are heated preferentially because of their high resistivities. Cooling the electrodes protects the skin, but the amount of intervening fatty tissue limits the power which may be applied. Consequently, this method often is unsuitable for treating persons who are obese. Inhomogeneous resistivity of the volume of tissue being heated may make it difficult to predict thermal distributions; however, conventional thermistors can accurately measure the temperature in the immediate vicinity of the probe.

A few other methods of heating show promise. Hyperthermic perfusion has achieved impressive results with melanoma and osteogenic sarcoma.[10-12] Whole-body hyperthermia can achieve and maintain accurate uniform thermal distribution, but physiological considerations limit the treatment temperature to a maximum of 41.8°C, and, therefore, prolong the duration of hyperthermia required to produce the desired thermal destruction.[89,90] Treatment by either of these methods is relatively complicated, and careful medical supervision of patients for prolonged periods is required. However, both methods have unique advantages and potentials which guarantee their place in the growing arsenal of therapeutic procedures.

Clinical Experience at Mount Zion Hospital, San Francisco

At the Claire Zellerbach Saroni Tumor Institute in San Francisco, hyperthermia as a treatment modality for advanced cancer is being investigated. For several reasons, we have concentrated our efforts on patients with superficial lesions refractory to other therapy. Superficial tumors may be easily observed and they are well suited to quantitative dimensional measurement. Thermometry is simplified by the ease and accuracy with which thermistor probes may be positioned. Heating may be achieved by microwave diathermy, thus reducing the possibility of involving critical tissues in an undesirable thermal response. The location of superficial human tumors facilitates a careful study on the thermal response of spontaneously arising malignant tissues.

Over two years we have used microwave diathermy apparatus operating at 915 and 2,450 MHz to administer 49 courses of local tumor hyperthermia. Of these, 38 courses were combined with radiotherapy; in these cases, hyperthermia was administered immediately after the ionizing radiation. A typical course of hyperthermia (with or without radiotherapy) consisted of six or nine one-hour fractions, delivered on alternate days, three times per week. Thus, six or nine hours of tumor hyperthermia were delivered over two or three weeks. Photographs and caliper measurements of all treated lesions were taken immediately before each treatment.

All of the patients treated were suffering from recurrent or metastatic disease which was not responsive to conventional treatment. The prognosis for survival of these patients was generally poor, so the effectiveness of treatment was judged by local tumor regression. A complete objective response was represented by complete tumor regression. If regression was not complete, but the tumor decreased in volume by more than 50 percent, it was considered a partial objective response. No response was represented by regression of less than 50 percent.

Several conclusions were reached in the study. In agreement with Crile's early report,[14] complete tumor regression was much more probable when radiation was combined with hyperthermia. The complete objective response rate was 42.1 percent for the combined modality compared with 18.2 percent for hyperthermia alone. Hyperthermia produced an objective response in 36.4 percent of the patients whereas a 78.9 percent objective response rate was obtained with the addition of radiotherapy. Hyperthermia enhanced tumor radiation response and complete regression was obtained with radiation doses which would have been subcurative without this adjuvant therapy. It should be emphasized that radiation was almost invariably administered in low doses due to the past treatment histories of most of our patients.

A considerable number of treatments were given for recurrent adenocarcinomas; 30 courses of combined low-dose radiotherapy and hyperthermia were administered to patients with this diagnosis, and 23 objective responses were obtained for a response rate of 76.7 percent. Squamous cell carcinomas also appear to be responsive to combined treatment; in three out of four patients treated there was complete tumor regression. The limited number of treatments administered for other diagnoses prohibits any conclusions

regarding the relative sensitivity of various cancers to these treatments.

Complications occasionally result from hyperthermic treatment by microwave. These are usually minor and consist of erythema and slight blistering. Rarely, rapid tumor necrosis and regression leave an open sore which requires cleansing and dressing. Such complications show the need for careful medical and technical supervision of patients during and after treatment.

Our investigation has shown that hyperthermia can be useful in cancer therapy, particularly in the management of patients with recurrent tumors in areas subjected to previous irradiation.

Conclusion

Cells in central hypoxic regions of tumors resist radiation damage and may be relatively inaccessible to chemotherapeutic agents. The potent action of hyperthermia on cells of this type is one indication of its potential as an adjuvant therapy. Hyperthermia can be useful in the treatment of patients refractory to conventional therapy. If techniques can be developed which selectively sensitize cancer cells to heat (such as tumor acidification) or which increase the relative absorption of electromagnetic energy by tumor tissues relative to surrounding normal tissues, then hyperthermia may become a primary mode of treatment.

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