Hyperthermia in gynecologic cancers

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Summary

The opinion from most of the current data is that malignant tumors may be more heat sensitive than normal tissues. Hyperthermia has been tested in both randomized and non-randomized trials in gynecologic cancers, but has not found a place currently, as there is scarce data. As a consequence, adding this tool into the conventional methods of cervical cancer and ovarian cancer treatment has not been supported. Hyperthermia modifies the effects of not only ionizing radiation but also a number of chemotherapeutic agents. The use of hyperthermia in cervical cancer is of interest to the radiotherapist, not only because it sensitizes cells to the lethal effects of X-rays but even more because hypoxic cells which are most resistant to X-rays appear to be most sensitive to hyperthermia. Most of the data on the efficacy of intraperitoneal infusion with hyperthermia comes from experimental studies or some phase I/II investigations. Since intraperitoneal chemotherapy is potentiated by hyperthermia in areas which are at high risk for recurrence, further study maybe indicated. The current role for hyperthermia in ovarian cancer remains experimental. Additional trials to test the value of hyperthermia in patients treated with concurrent chemotherapy and radiation are imperative, and good news is expected from the ongoing studies.

Key words: Hyperthermia; Thermal effect; Gynecologic cancer; Therapy.

Introduction

Hyperthermia (HT) has been used for cancer therapy since the late 1800's. Busch in 1866 [1] first described the complete disappearance of a histologically proven sarcoma of the face. Subsequently, isolated reports of application of heat in cervical and endometrial cancers were reported [2, 3]. A combination of artificial fever and X-ray therapy was described by Warren in 1935 to be advantageous in hopeless cancers [4]. In 1960, Woodhall *et al.* [5] used combined high temperature of 42°C and alkylating agents for head and neck tumors.

Experimental studies have also been carried out on regression in tumor growth in animals and tumor lines in-vitro, and early studies suggested that tumor cells are more heat sensitive than normal cells [6-11]. Despite some encouraging and anecdotal results, data of earlier studies were not consistent enough to warrant a sustained effort in applying heat in cancer therapy. The clinical use of heat has been hampered by a lack of adequate equipment to effectively deliver and measure heat in deep-seated tumors.

The risks and complications encountered in these earlier series have been gradually overcome and more recent studies on the selective destructive effect of high temperature on neoplastic cells suggest the possibility of combining this treatment with a conventional method when feasible.

The rationale and the mechanism of heat effect

Hyperthermia and radiation

The rationale for the combined use of hyperthermia with radiotherapy is thermal enhancement of cellular radiosensitivity via increased cytotoxicity at S-phase in hypoxic cell fraction. Unfortunately, hyperthermia may cause vascular damage and thereby, increase the hypoxic cell fraction in the tumor.

There is increasing understanding of biophysical changes at the cellular level due to hyperthermia. Heat is an entropic disordering agent [12] and is expected to disrupt highly ordered structures and processes in cells [12, 13]. Heat theoretically destroys all areas in cells and adversely affects the cellular functioning responses.

Hyperthermia inhibits the repair of DNA lesions induced by ionizing radiation and increases the frequency of chromosomal aberrations [14]. Heat is capable of selectively killing and radiosensitizing S-phase cells, which are resistant to ionizing radiation. It has also been shown that hypoxic cells are more sensitive to heat than normal cells. However, more recent studies claim that not the hypoxia per se but the low pH associated with hypoxia is responsible for the increased thermo-sensitivity of cells. It has also been shown that cell death progresses when a tumor is left in situ after heating [15-17]. Such a progressive cell death has been attributed to either immunological or physiological mechanisms related to vascular damage [17] and the latter is thought to be of most importance in in vivo cell killing by heat [15].

The opinion from most of the current data is that malignant tumors may be more heat sensitive than normal tissues [18]. Chen and Heidelberger [19] and Levine and Robbins [20] similarly showed a differential in the thermosensitivity of malignant versus normal cells in culture.

This differential response might be the result of decreased integrity of anatomical and physiological properties of tumors due to distorted circulation and diminished nutrient intake, oxygen transfer and pH buffering control. Hyperthermia would therefore be expected to be selectively toxic to intramural regions of solid tumors that are

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resistant to radiation. It can be hypothesized that hypoxic cells in the core of the tumor are vulnerable to heat whereas the peripheral tissue is more sensitive to irradiation but thermoresistant, and thus the premise supports the use of combined irradiation and heat.

Normal tissue exerts a temperature-dependent increase in blood flow at temperatures of up to 46°C. In contrast, blood flow through neoplastic tissue increases to a smaller extent. There may be two fundamental mechanisms; first is direct cytotoxic effects and second is vascular stasis, by which supranormal temperatures can be selectively toxic to neoplastic cells. If vascular stasis occurs, hyperthermia would also favor deeper penetration of drugs into the tumor. However, this evidence strongly indicates that patients with minimal gross residue are most likely to derive a therapeutic benefit from this approach.

Low extracellular pH is probably the most important factor for the thermo-sensitivity of mammalian cells. Acidic conditions not only enhance the heat killing but also inhibit the repair of thermal damage and the development of thermo-tolerance [21, 22].

Hyperthermia and chemotherapy

Although, less is known about heat-drug interactions and the mechanisms of enhancement, heat may enhance or inhibit drug transport or increase membrane permeability, increase the rate of reaction between the drug and its target molecules, inhibit the repair of drug-induced lesions, or a combination of all aforesaid mechanisms. Hyperthermia modifies the effects of not only ionizing radiation but also a number of chemotherapeutic agents. As an example of this synergism, a phase I/II clinical trial of surgical cytoreduction combined with intraperitoneal hyperthermic chemotherapy for patients with disseminated peritoneal carcinoma can be given. In this study by Loggie et al, intraoperative two-hour, heated abdominopelvic perfusion with mitomycin administration to 15 patients with positive peritoneal cytology resulted in conversion to negative cytology [23]. Another recent study of intraperitoneal hyperthermic chemoperfusion was carried out with mitomycin in gastrointestinal malignancies and with cisplatin in a case of ovarian cancer with malignant ascites. A remarkable improvement in quality of life was observed in patients who responded to therapy. Ascites disappeared in 16 out of 19 patients; tumor markers that were elevated postoperatively in 16 patients returned to normal values in ten patients and dropped more than 50% in three others [24]. The combination of hyperthermia plus adriamycin has been shown to act synergistically as well [25, 26].

Applications in gynecologic oncology

Methods of hyperthermia

There are several sources that have been employed to heat tumor tissue. Electromagnetic fields at radiofrequencies (most commonly 13.56 and 27.17 MHz) and ultrasound are two distinct approaches [27].

Interstitial hyperthermia can be delivered through the same catheter used for interstitial brachytherapy immediately before insertion or after the removal of the radioactive sources [28]. Interstitial hyperthermia may be produced through the use of coaxial microwave antennas inserted in Teflon catheters implanted in the tissue. Intracavitary microwave antennas are also used to deliver hyperthermia to tumor sites in cavities. Temperatures of 42°C can be achieved for lengths of about 5 cm with effective penetration of 0.5 cm around the applicator. Interstitial heating with radiofrequency is essentially resistive heating in which needle arrays are used.

1. *In the Hot source technique*, the tissue is heated by thermal redistribution within the implanted arrays. Unlike the aforementioned sources, no power deposition is directed to tissue.

2. *Ferro-magnetic seeds* is a technique in which the tissue is heated by thermal conduction and convection (via blood perfusion) of heat, radially away from the seeds already implanted in any desired length without having any external connection.

Dosage or unit to be standardized

A minimum tumor temperature of 43°C appears optimal, and heating sessions of 30-90 minutes are employed in most trials. However, temperature monitoring in a patient is extremely difficult because of the need for multiple indwelling catheters at various depths and numerous temperature measurements (thermal mapping) along the track of each catheter throughout every treatment session [29].

Cervical cancer

Earlier clinical trials using radiation therapy with hyperthermia have demonstrated an improvement in overall response rate, local control and median survival for the combined approach [30-32]. However, five-year survival was not improved [32]. Local hyperthermia was not associated with significant short- or long-term toxicity. The rapid tumor shrinkage in the combined approach of radiotherapy with hyperthermia before beginning brachytherapy seems to improve the results in cure of advanced cancer of the uterine cervix [33, 34].

Current state of hyperthermia and radiation in cervical cancer

Different sequencing schedules, fractionation and number of hyperthermia treatments have been studied. In two studies [35, 36], no significant impact on clinical response with various parameters of treatments was found. However, the tumor control seemed to be enhanced via increasing the heat and the size of radiation dose fractions.

The randomized Radiation Therapy Oncology Group (RTOG) trial 81-04 showed no impact of number of hyperthermia treatment sessions on complete response rate in patients with superficial tumors treated with radiation alone versus radiation and hyperthermia [37]. However, in a recent, prospective, randomized study for locally advanced tumors of the bladder, cervix and rectum, despite the disappointing results with bladder and rectum cancer, complete response and duration of local control rates were significantly improved in cervical cancer patients with the addition of hyperthermia to radiotherapy. Complete response rate with radiotherapy plus hyperthermia was 83% compared with 57% after radiotherapy alone ($p = 0.003$). Three-year overall survival was 27% in the radiotherapy group and 51% in the radiotherapy plus hyperthermia group [38].

Hornback *et al.* [39] reported on a non-randomized study in which the combination of microwave hyperthermia and irradiation resulted in improved pelvic tumor control and survival in a group of 79 patients in comparison with previously irradiated historic controls. The use of afterloading interstitial implants provides an opportunity to use interstitial radiotherapy and hyperthermia together. Recently, Bloss *et al.* [40] compared tumor response and complications of 16 patients receiving a combination of external and interstitial radiotherapy with nine patients receiving the same treatment plus interstitial hyperthermia (Stages II/IIIB). No difference was detected in tumor response rate and disease-free survival.

In the RTOG trial 81-04 [37, 41], which included breast, head and neck, extremity tumors, radiation alone vs radiation plus hyperthermia was compared. According to Emami *et al.* [42], the addition of one or two satisfactory hyperthermia treatment sessions to irradiation (compared to no satisfactory hyperthermia session), does have a significant impact on local control. But in terms of complete response rate, one vs two sessions does not differ. In non-randomized trials of thermoradiotherapy with cervical cancer patients, an average of 70% of improved pelvic control and complete response rates compared to that of 50% in controls of irradiation alone have been reported [39, 43, 44]. As an example of interstitial hyperthermia, the RTOG 84-19 trial [45], found no significant difference in tumor control inbetween thermoradiotherapy and radiation alone.

Downsides and variables

Wide variations in the number of daily treatments, the number of treatment days per week, the dose per fraction, the total radiation dose, the hyperthermia technique, the equipment used, the sequencing of radiation and hyperthermia, tumor temperature goals, the hyperthermia treatment durations and the fraction have been known to interfere with all previously published studies. However, achieving, controlling and maintaining the degree and homogeneous distribution of temperature with current equipment still remain difficult. Besides tumor and normal tissue blood flow intracellular and extracellular pH, thermotolerance and the absolute and differential temperature exposure are the other variables still a challenge to randomize ideally.

Complications and side-effects

The most frequent complaints are local pain and discomfort. Systemic stress and anxiety can be seen in some patients. Cardiac symptoms can be encountered occasionally . Incomplete heating can be considered as a side-effect.

Recommendations for future studies

The role of hyperthermia in cervical cancer is yet to be fully identified. Its use is of interest to the radiotherapist, not only because it sensitizes cells to the lethal effects of X-rays but even more because hypoxic cells which are most resistant to X-rays appear to be most sensitive to hyperthermia. The current use of hyperthermia in cervical cancer remains in clinical trials. Some combination of hyperthermia, radiotherapy and cytotoxic chemotherapy may be useful in the future.

Ovarian cancer

Intraperitoneal chemotherapy and hyperthermia

Hyperthermia besides having its own antineoplastic effect, due to increased thermosensitivity of neoplastic cells compared to healthy cells, may increase the cytotoxic potential of anticancer drugs by increasing cell membrane permeability and drug transport [46, 47].

Increased temperature is able to potentiate the cytotoxic effects of antineoplastic drugs in a synergistic manner [48-50].

The selective lethal effect of supranormal temperatures on neoplastic cells and the additive or synergistic effect of combining hyperthermia with chemotherapy have been well established in laboratory models [51-53] and have provided the rationale for numerous clinical trials using whole body hyperthermia combined with systemic chemotherapy for treatment of advanced malignancies [54-57].

Pharmacokinetic study

Drug stability testing is done at the temperature already determined. Blood samples for drug assays are collected during infusion and after infusion in certain intervals. Peritoneal samples are also taken at the same times. Drug concentrations of peritoneal fluid and blood are plotted against the time on the chart and area under curve for each is calculated for further calculations. (AUC 0-24) Maximum concentrations (Cmax) in time (Tmax) are usually noted. The ratio between AUC in plasma and peritoneal fluid is calculated and adopted as an index of drug absorbability.

Morbidity

The potential role of hyperthermic intraperitoneal chemotherapy has to be carefully weighed against the hazards of the procedure. The overall morbidity is related to four distinct factors:

- peritoneal instillation of chemotherapeutic drugs;
- local hyperthermia;
- extent of cytoreductive surgery;
- general hyperthermia.

Hyperthermia and chemotherapy trials

In vitro experiments on cisplatin have shown that hyperthermia not only enhances its effectiveness particularly in drug-resistant lines [58] but also increases cisplatin-DNA adduct formation in tumor cells when compared with that of buccal cells [59]. In addition to this, in rats bearing peritoneal tumors regional hyperthermia increases cisplatin uptake of both tumoral tissues and normal tissues [60]. In clinical trials [61, 62], favorable clinical responses have been achieved by means of survival and CA-125. Clinical effectiveness of intraperitoneal hyperthermic chemotherapy (IPHC) has also been documented for other antineoplastic drugs and other forms of disseminated carcinomas.

Recently, Steller *et al.* [63] published a pilot phase I trial of hyperthermic therapy combined with high-dose carboplatin as primary treatment of patients with small-volume residual ovarian cancer. They concluded that patients with advanced-stage epithelial ovarian cancer are most likely to benefit from this therapy immediately following optimal surgical debulking with minimal gross disease and before resistant clones of tumors have been selected by surviving systemic chemotherapy. Similarly Nicoletto *et al.* [64] used mitoxantrone as intraperitoneal hyperthermic infusion in ovarian cancer and concluded that IP mitoxantrone administered under hyperthermia to advanced ovarian cancer patients can induce a response in about 30% of cases and is well tolerated. Their analysis of pharmokinetic data suggested that peritoneal and plasma drug disposition may be affected by IPHP and previous therapy cycles. Another phase I study applied hyperthermic intraperitoneal intraoperative chemotherapy using doxorubicin and cisplatin, after completion of cytoreductive surgery in patients with peritoneal carcinomatosis and sarcomatosis, and found encouraging results for local disease control, especially in terms of the perfusate/plasma area under the curve ratios for both drugs [65].

Conclusion

Most of the data on the efficacy of intraperitoneal infusion with hyperthermia comes from experimental studies or some phase I/II investigations. Since intraperitoneal chemotherapy is potentiated by hyperthermia in areas which are at high risk for recurrence, further study maybe indicated. The current role for hyperthermia in ovarian cancer remains experimental.

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