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Effect of hyperthermia by magnetite cement on tumor-induced bone destruction

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Abstract Our study focuses on the antineoplasmic action of hyperthermia. In this study, use of a heat-generating cement was exploited for the management of pathological and impending fractures in malignancies. The cement contains magnetic powder in ceramic particles and generates well-regulated heat when a magnetic field is applied externally. Eighteen rabbits were inoculated with blocks of VX_2 tumor into one of their tibia. One week after the procedure, 9 rabbits were exposed to a magnetic field (HT group) while the remaining 9 rabbits were not (non-HT group). In rabbits killed between 20 and 42 days after the VX_2 inoculation, the circumference of the operated leg was 7.9 ± 0.3 cm and 10.2 ± 1.0 cm (mean ± SE) in HT and non-HT groups, respectively ($P < 0.05$). Histological findings revealed the regressive change in tumor tissue of the HT group. By radiographs, pathological fractures and cortical bone destruction were seen in 5 and 8 rabbits in the non-HT group, respectively, but in the HT group these effects were absent in all the rabbits except 1 in which a definite diagnosis has not been made. Our findings demonstrate that controlled hyperthermia therapy using a newly developed bone cement suppresses tumor growth and prevents local bone destruction caused by VX_2 tumors.

Key words: Hyperthermia · Magnetite · Bone · Cement · Tumor

Introduction

In the multimodal approach to malignant tumors, hyperthermia has not been widely exploited compared to other therapies. The mainstays are surgical resection, chemotherapy, and radiation therapy, although the antineoplasmic action of hyperthermia is well known.[2] However, recent developments in technology, particularly in the field of material science, have renewed enthusiasm for recognizing hyperthermia as a promising treatment for patients with malignant diseases.[3,9]

We have developed a bone cement made of glass ceramic that is partly replaced by magnetite, which generates heat in a regulated magnetic field. In a previous report,[14] we showed that the temperature of animal bone was increased and controlled by the interaction of the cement and a magnetic field. We now report the results of applying this cement to a lesion of the distal tibia inoculated with VX_2 tumor in rabbits.

Materials and methods

Preparation of bone cement

Specially designed bone cement was made by Nippon Electric Glass (Ohtsu, Japan).[8] The main components of the cement are filler and resin. The filler, which occupies 90% by weight of the cement, comprises a fine mixture of two types of powder. One is magnetite powder, which consists of 13-μm-diameter particles, and the rest is silica glass powder consisting of 3-μm-diameter SiO_2 particles. The structural strength of the cement comes from the bis-*a*-glycidymethacrylate-based resin component, which consists of a mixture of bis-*a*-glycidymethacrylate and triethyleneglycol dimethacrylate. When the cement is molded and solidified, it generates heat via a polymerization reaction in the resin.

The magnetic field in this study was produced by an AC magnetic field generator (Sumitomo, Tokyo, Japan). The amount of heat generated is determined by the volume of the magnetite in the cement and by the intensity of the applied magnetic field. In this experiment, an alternating magnetic field of 100 kHz was used. The intensity was adjusted to obtain around 43°C in the tissue. The tissue temperature was monitored by a fine sensor. Studies with limbs of rabbits

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and human cadavers have shown that the temperature of the cemented bone can be controlled and that the cement has adequate mechanical strength.[14]

Experimental protocol

Eighteen Japanese white rabbits, 8 weeks old and weighing 2.0–2.5 kg, were used for the experiment. The protocol was reviewed and approved by the Animal Study Committee of Mie University. Animals were anesthetized generally with 25 mg/kg intravenous pentobarbital sodium solution and anesthetized locally in the soft tissue surrounding one tibia with 0.5% lidocaine hydrochloride. A 2-cm skin incision was made over the patellar ligament, which was then transected and inverted. The medullary canal of the tibia was drilled to give a hole approximately 2 mm in diameter and 10 mm in depth. Two cubic blocks, each 2 mm long, of VX_2 tumor preparation were implanted into the hole. The hole was then covered with bone wax, the patellar ligament was reconstructed, and the skin was sutured. Seven days after the procedure, the wound was opened again under general anesthesia. Most of the VX_2 tumor was curetted out and the defect was filled with the cement.

The rabbits were randomized. Nine rabbits were exposed to a magnetic field for 50 min to receive hyperthermic therapy (HT group). This hyperthermic therapy was given only once to each rabbit. The remaining 9 animals were not exposed to the magnetic field (non-HT group).

Rabbits were killed by intravenous administration of an overdose of pentobarbital sodium solution at intervals from 20 to 42 days after inoculation with VX_2 tumors. No animal died spontaneously during this period.

Analyses

After death, skin and subcutaneous tissue of the operated leg of each animal was removed for macroscopic and radiographic examination. The maximum circumference of the skinned leg was measured to record tumor growth or local inflammatory responses quantitatively. Then, radiographic films were taken of each leg. All the radiographic films were gathered and evaluated for pathological fracture and cortical bone destruction by two senior orthopaedic surgeons familiar with tumor care, who were blinded to the experimental protocol including the group allocation. The microscopic samples were fixed by formalin and stained by hematoxylin and eosin.

Statistical analyses for the maximum circumference of the operated legs was performed on a general linear model with univariate procedures using SPSS 9.0 software (SPSS, Chicago, IL, USA). In this model, the dependent variable was the circumference of the limb. Covariates were days from the VX_2 inoculation and group. With regard to radiographic findings, the number of animals that showed pathological fracture was compared between HT and non-HT group by the chi-square test. Cortical bone destruction was evaluated in the same manner.

Results

The maximum circumference of the operated leg was 7.9 ± 0.3 cm (mean ± SE) and 10.2 ± 1.0 cm (mean ± SE) in the HT and non-HT groups, respectively ($P < 0.05$), possibly reflecting the difference in tumor growth and inflammatory response of the surrounding soft tissue. The leg circumference did not vary significantly with time after VX_2 inoculation (Fig. 1). The histological section from the non-HT group showed rapid tumor growth, whereas the section from the HT group revealed a marked regressive change of tumor tissue (Fig. 2). Figure 3 shows the radiographs of the pathological fracture and cortical bone destruction in a non-HT rabbit. Pathological fracture was seen in 5 of 9 rabbits in the non-HT group. It was absent in all the rabbits in the HT group except 1, in which the final diagnosis has not been made because the diagnosis by the two senior orthopaedic surgeons conflicted ($P < 0.05$). Cortical bone destruction was observed in 8 rabbits in the non-HT group. It was absent in all the rabbits in the HT group except 1 in which the final diagnosis has not been made, again because the

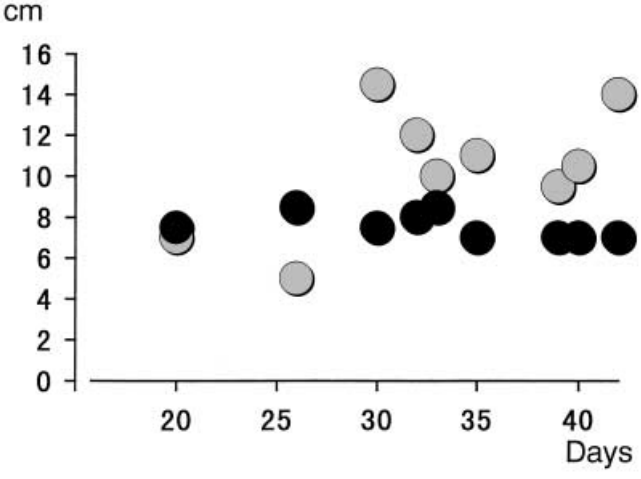

Fig. 1. Maximum circumference of the skinned leg as a function of time after inoculation of VX_2 tumor in hypothermic therapy (HT) group (*black circles*) and non-HT group (*gray circles*). A significant difference is shown between groups ($P < 0.05$) but not with time

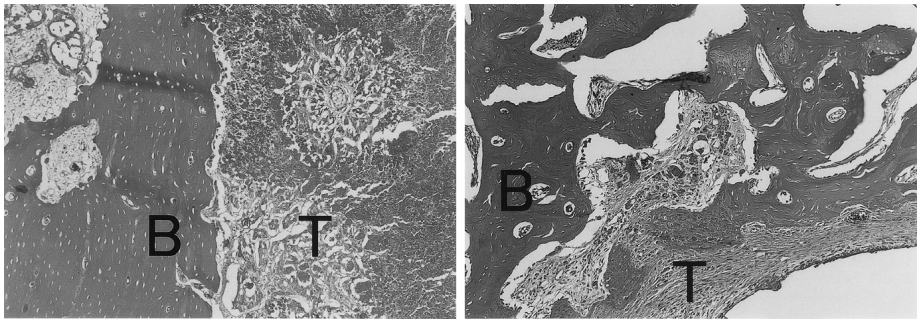

Fig. 2. Histological feature of VX_2 tumor appearance in non-HT group (*left*) and HT group (*right*). *B*, bone tissue; *T*, VX_2 tumor tissue. Note the growing appearance of tumor tissue in non-HT group (*left*) and its regressive change in HT group. hematoxylin and Eosin. ×110

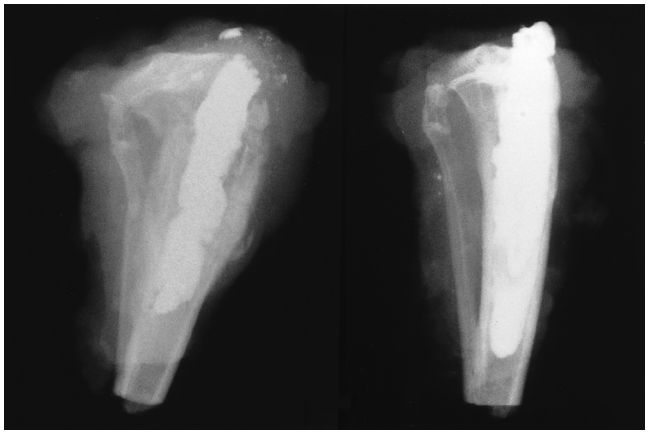

Fig. 3. Radiographs of VX_2-inoculated leg of one of the non-HT rabbits showing pathological fracture and cortical bone destruction (*left*). Neither pathological fracture nor cortical bone destruction was seen in any of the HT group (*right*) except one

diagnosis by the two senior orthopaedic surgeons conflicted ($P < 0.001$).

Discussion

One of the most difficult problems in the management of bone tumors, particularly secondary to metastatic cancer, is the treatment of pathological and impending fractures. Fractured limbs are usually treated by internal fixation, often supplemented by methylmethacrylate, or sometimes by replacement arthroplasty, which is cemented in place, particularly in the case of the proximal femur. However, progressive growth of the tumor leads to further osteolysis and loosening and failure of the implant. It is very important to control this process, not only to prolong life but also to maintain its quality. Our study is particularly related to this kind of difficulty in cancer patients.

Chemotherapy or adjuvant endocrine therapy is sometimes used in an attempt to control tumor growth. However, these treatments are mainly used for systemic control of malignancies and are insufficient for locoregional control of bone destruction in many cases.

Use of bone cement containing an anticancer drug is another possible adjunct to the surgical management of pathological fractures caused by bone tumors. Wang et al. reported that methotrexate-embedded acrylic cement partially prevented local bone destruction in rabbits inoculated with VX_2 tumor.[15] However, it is uncertain whether a sufficient amount of drug is released locally even when a large amount is mixed into the cement.

In contrast to this local therapy, hyperthermia has a tumoricidal action over a practical temperature range. Recent progress in cell biology reveals that mild hyperthermia, variously reported between 40° and 45°C, triggers tumor cell death by apoptosis although the exact temperature differs in the individual condition.[4,11] It is now known that hyperthermia-induced apoptosis is characterized by the occurrence of internucleosomal DNA cleavage.[12] Thus, new knowledge concerning cell death suggests the use of mild hyperthemia for patients with malignancies, similar to the classic anecdotal observation of the tumoricidal action of hyperthermia in patients who have an infection with high fever.[1]

Hyperthermia has been used successfully to treat expanding local tumors such as recurrent rectal cancer.[10] Compared with other cancers of alimentary tract origin, rectal cancer spreads easily within the pelvis because there is no serosal layer covering the tumor under the peritoneal reflection of serosa above the anus. The same is true of the rapid local growth of metastatic bone cancer.

Hyperthermic therapy for metastatic bone cancer has been tested experimentally using the polymerization heat of polymethylmetharcylate bone cement.[7,13] However, this heat is only generated when the cement is molded and solidifies. The heat is unreliable, therefore; it is difficult to control and may not be sufficient to reduce tumor growth.

In contrast, the heat in our model is generated by the interaction between the ferromagnetic substance and

the magnetic field.[5] It is very important that in our system the amount of heat generated is determined by the content of magnetite and the intensity of the magnetic field applied. Thus, the heat is continuously and stably supplied with the magnetic field applied from outside the limb. In addition, there is the advantage that hyperthermic therapy can be applied repeatedly.

Although this type of hyperthermia therapy using magnetite has already been reported for breast cancer,[6] we believe it is particularly promising in the treatment of patients with primary bone tumor and secondary metastatic bone cancer. In a previous report, we have shown that the hyperthermia was confined to the surface of the cement and affected bone, implying that damage to surrounding normal tissue was minimal.[14] In this report, we demonstrate a dramatic effect of hyperthermia on local bone destruction by the VX_2 tumor implanted in the hindleg of the rabbit.

This hyperthermia therapy using a magnetic bone cement has advantages even if it is compared to chemotherapy or radiotherapy in terms of its local selective tumoricidal action, its lack of serious adverse effects, and its simultaneous mechanical support for pathological fractures. This therapy does not exclude the additional benefit of hyperthermia combined with radiotherapy or chemotherapy. The effect of these combined therapies is to be evaluated using our method.

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