Development of New Cancer Treatment Using Approved MRI Contrast Agent and Induction Heating Device

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Abstract

MRI contrast agents, Feridex and Resovist have superparamagnetic substance as an active ingredients. Feridex does not show temperature rise under AC magnetic field. In contrast Resovist shows temperature rise under the same condition. We simulated the optimum frequency on Resovist using phantom and found it is 140 kHz. However treatable cancer volume was limited to 9cm^3. We tried a fractionation of Resovist. One of the fractions was found to be effective by more than 6 times compared to the drug by itself. This result suggests that the hyperthermia in combination with the fraction and induction heating device is a promising treatment for cancer.

1. Introduction

Ferromagnetic substances have been applied to induction heating hyperthermia [1-2]. However, no ferromagnetic substance has been approved by the authorities, for example, the Ministry of Health, Labour and Welfare in Japan and FDA in USA. This is because that these substances are considered as parenteral drug. Therefore it is essential to conduct a sufficient number of pharmaceutical and toxicological tests, for example, pre-clinical toxicity tests such as acute, subacute and chronic toxicity tests in addition to ADME, stability test, etc. Clinical studies are also essential, which are known as Phase I, Phase II and Phase III studies. Usually a new drug development requires a huge amount of expense and an extremely long time. Until now the induction heating hyperthermia has not been spread widely. Recently superparamagnetic substances known as magnetic fluids have been applied to the above mentioned hyperthermia because it is easy to be injected into various tumors, for example, solid tumors such as liver cancer, osteosarcoma, peritoneal dissemination of tumor in abdominal cavity and/or pleural dissemination of tumor in thorax cavity. One of the superparamagnetic substances, Ferucarbotran, is uptaken into various tumor cells [3-4]. This characteristic is an advantage for tumor treatment especially by induction heating hyperthermia. Superparamagnetic substances have been developed as MRI contrast agents. If these drugs are introduced in the hyperthermia, the risk of the new drug development may be reduced significantly.

2. Material and Experimental Method

1.Approved MRI contrast agents and their high magnetism fraction

Feridex made by Advanced Magnetic Co. and Resovist made by Bayel Pharma Co. were used. High magnetism fraction was obtained when using a magnetic separator, superMACS II made by Miltany Biotech Co.

2. Induction heating device

A device developed by Kanazawa University was used (Fig.1).

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Table 1. Specification of induction heating device

Size	W750 x H1730 x D830 mm
Output frequency	100-378 kHz
Coil	5 turns, 8.9 μH
Q value	460
Magnetic field intensity	Max. 18 mT at 1cm from the surface of a pancake coil

Fig.1: Picture of Induction heating device

3. In-vitro induction heating

The heating characteristics of superparamagnetic substance are expressed in Eq. (1) in our previous study [3], where *m* is a constant value of 3.14×10^{-3} [W/ Hz/ (mg/Fe/cc)/ T^2/ cc], *f* is the frequency [kHz], D is the concentration of the superpparamagnetic substance [mgFe/ cc], and B is the intensity of the applied AC magnetic field [T].

$$Q = \mathrm{m}\cdot f\cdot D\cdot B^2 \qquad [\mathrm{W/cc}] \qquad (1)$$

Temperature rise of superparamagnetic substance correlates to *f*, so we selected the frequency of 378 kHz which is almost the maximum frequency output by the induction heating device for in-vitro experiment.

4. Animal experiments

4-1. Pig experiment

A normal young adult pig is used under anesthesia. MRI contrast agent was injected into trachea then the pig was set under an AC magnetic field at 378 kHz.

4-2. Rabbit experiment

The experimental tumor, VX-2, were inoculated into fifteen young adult rabbits under anesthesia. When the inoculated VX-2 tumor became about 2cm in diameter, the tumor-bearing rabbits were used to test the anti-tumor effect. The drug was injected into tumors of the fifteen rabbits in a dose of 5mg/cm^3 as Fe. One hour after the injection, seven rabbits were treated under an AC magnetic field at 140 kHz and 18 mT. The tumor site was kept at 45 degrees for 20min by a temperature control. The VX-2 tumors in the fifteen rabbits were observed for 30days after this hyperthermic treatment or sham treatment.

3. Results

One of the approved MRI contrast agents, Feridex, does not show temperature rise under an AC magnetic field. Another approved MRI contrast agent, Resovist, diluted with saline and adjusted Fe concentration same as Feridex shows temperature rise as in Fig 2. In the pig experiment, temperature rise was observed on the neck area in addition with the Resovist injected area.

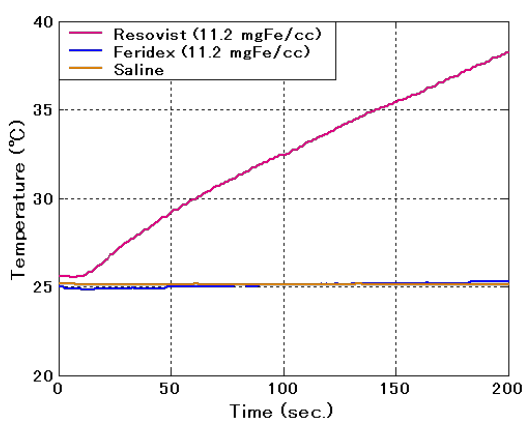

Fig. 2: Temperature rise at 378KHz

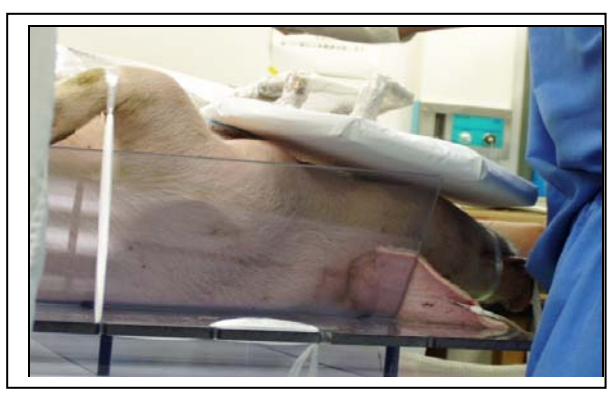

Fig.3: Pig experiment as a model of human size body

The temperature rise at the neck area was an unexpected result, and it may cause burn in the clinical use. We simulated the optimum frequency of Resovist as a human treatment. The temperature rise was considered to be caused by eddy current loss in normal tissues. Therefore by using an EM simulator, Faraday V6.1 (Integrated Engineering Software Co.), the eddy current loss in the pig tissues were examined under the condition of the coil diameter of 300mm and the phantom size of W120 x H80 x D300. As a result of the simulation, high temperature area was observed near the border of coil for the case of 380 kHz (Fig. 4). In contrast, high temperature area was not observed for the case of 140 kHz (Fig. 5). Therefore, we selected the frequency of 140 kHz for later studies, to avoid an excess heating of the normal tissues.

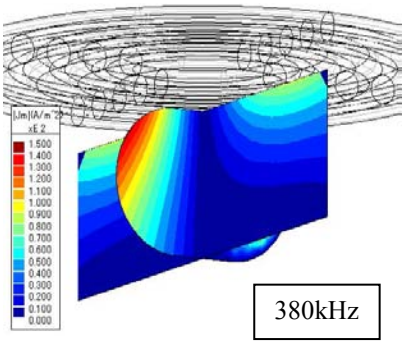

Fig. 4: Eddy current loss at 380 kHz

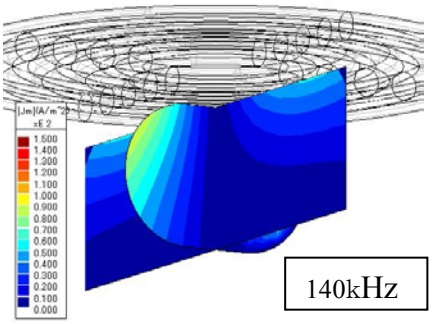

Fig. 5: Eddy current loss at 140 kHz

The results of the rabbit experiments are shown in Figs. 6 and 7. The suppression of the growth of the tumors observed in the treated group (7 rabbits) was significantly greater than that in the control group (8 rabbits). In particular there are three rabbits with complete regression of the tumor in the treated group. This result strongly suggests the effectiveness and the applicability of the induction heating method for the cancer treatment.

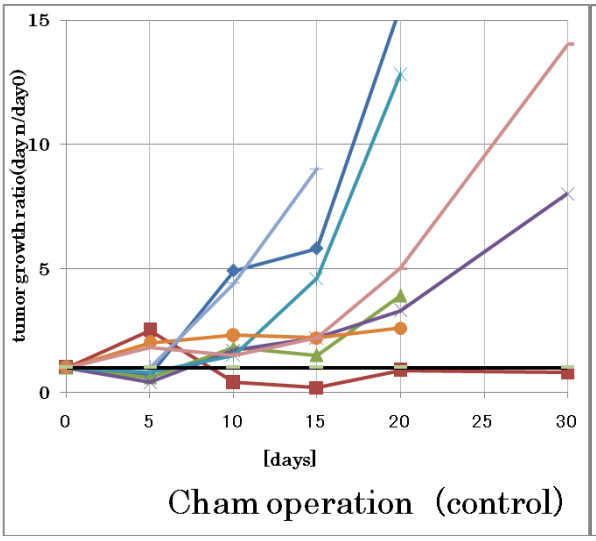

Fig 6: VX-2 tumor growth and mortality in untreated rabbits

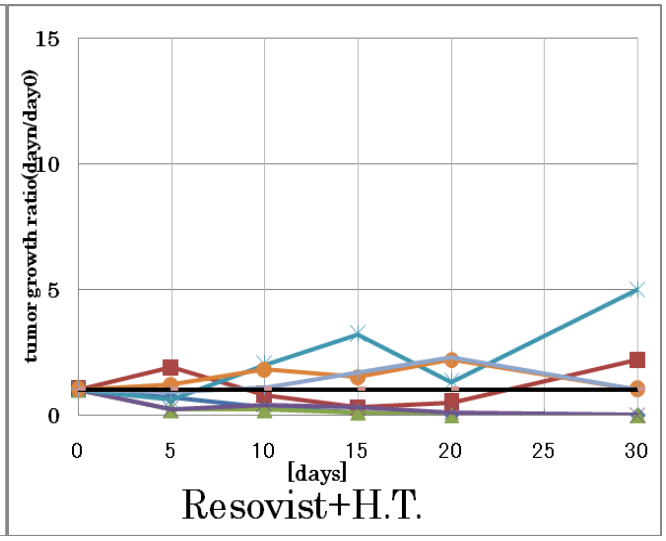

Fig 7: VX-2 tumor growth and mortality in treated rabbits. Suppression and complete regression of XV-2 were observed. No rabbits died as a result of hyperthermia.

Iron is a one way substance. Injected iron is not excreted easily from human body. Although we confirmed anti-tumor effect by original Resovist, a dose of Resovist contains Fe of 5mg/cm^3. Acceptable amount of Fe is 44mg/human when used as an MRI contrast agent. Therefore the tumor size which can be treated by the drug by

itself is limited to only 9 cm^3 (=44/5). In order to obtain approval by authorities we have to find a more effective substance which is not harmful to the human body, because we cannot use the high-frequency AC magnetic field such as 380 kHz by using original Resovist. So we tried to obtain a more effective superparamagnetic substance using a magnetic separator.

High magnetic fraction was obtained by the aforementioned method. The fraction exhibited significant temperature rise. The effectiveness of the temperature rise is more than 6 times in comparison with the drug by itself (Fig. 8). The TEM microscopic picture showed that the size of the fraction was about 20 nm (Fig. 9). This fraction is a component an approved drug. Therefore the safety of the fraction must be in the allowable range.

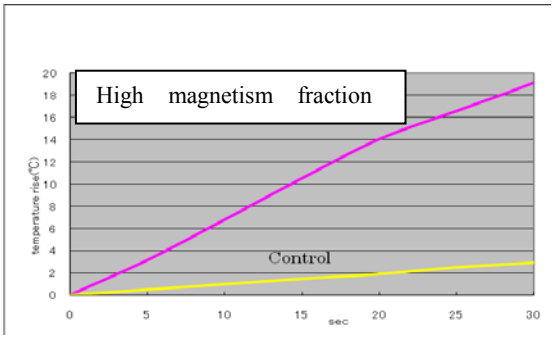

Fig. 8: Temperature rise of high magnetism fraction

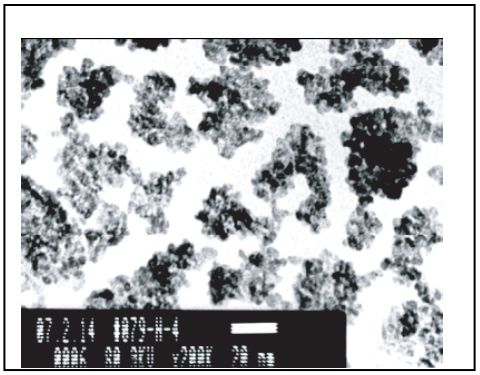

Fig. 9: TEM-microscopic picture of high magnetism fraction

4. Conclusion

We have investigated the feasibility of using the approval drugs containing the superparamagnetic subustance in hyperthermia treatment of cancer by using an induction heating device. Resovist showed the temperature rise under an intense AC magnetic field of 4.4mT at 140 kHz. High magnetism fraction of Resovist showed the effectiveness by more than 6 times compared with the drug by itself. These results suggest that the possibility to obtain approval by authority is promising. In summary, we are sure that the induction hyperthermia combined with Resovist is a very beneficial and promising approach to treat deep seated cancer.

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