Clinical trials of magnetic induction hyperthermia for treatment of tumours

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Abstract

Introduction

Magnetic induction hyperthermia uses a magnetic medium such as thermoseed and magnetic nanoparticles in a specific area of the organ where the tumour is located and heats it moderately. The unique feature includes short heating time, even distribution, specificity and safe application. Clinical trials of thermoseed are under investigation for malignant glioma, prostatic cancer, oral cancer, cholangiocarcinoma, oesophageal cancer and other malignant tumours. On the other side, magnetic nanoparticles are mainly under clinical trial for prostatic cancer, malignant glioma, metastatic bone tumours and some other malignant tumours. The aim of this critical review was to discuss clinical trials of magnetic induction hyperthermia for treatment of tumours.

Conclusion

All pre-clinical studies are completed for magnetic fluid hyperthermia with magnetic nanoparticles as treatment media; the current clinical trial of nanohyperthermia has only been conducted in Germany. China is expected to become the world’s second country after Germany in the application of cancer nanotechnology in clinical research treatment, and is expected to gain new progress in medical innovation technology.

Introduction

Unlike conventional thermotherapy, a fundamental idea of magnetic induction hyperthermia technology is to change the situations of traditional extensiveness and middle or low temperature for heating treatment, which increases the specificity and the temperature-targeted efficient treatment. In this method, heat can be concentrated at the tumour site, avoiding the normal tissues from damage. This method has the characteristics of good security, short heating time, well-distributed heat and minimally invasive treatment. At present, some widely fundamental research studies abroad have been carried out and some have entered into clinical trials¹⁻⁴. Many fundamental research studies have been conducted in China⁵⁻⁷, and clinical research is being carried out⁸. The magnetic thermal medium of magnetic induction thermotherapy for animal experiments in cancer and clinical trials is mainly ferromagnetic thermoseeds and magnetic nanoparticles. Thermoseed material is a special alloy consisting of non-magnetic material (such as antimagnet, paramagnet) and magnetic metals (such as iron magnet). Due to its automatic temperature control feature at Curie point, thermoseeds can reduce the requirements for invasive temperature measurement and avoid the charring and carbonisation of tissues to improve the safety of the treatment. The implantation of thermoseeds can be conducted under the direction of computed tomography (CT), magnetic resonance imaging (MRI) and other diagnostic technologies of iconography, so that open surgery can be avoided to achieve minimally invasive treatment. The thermoseeds have a good histocompatibility, can remain in the body for a long time and is easy to repeat the heating. The induction hyperthermia therapy with thermoseeds has been shown to have good prospect in animal experiments⁹⁻¹¹ and clinical trials research¹¹ has achieved a better remission rate, and is safe and reliable. This critical review discusses clinical trials of magnetic induction hyperthermia during treatment of tumours.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies. Animal care was also in accordance with the institution guidelines.

Magnetic induction hyperthermia of thermoseeds for treatment of malignant tumours

Magnetic induction hyperthermia of thermoseeds for treatment of brain glioma

Thermoseed magnetic induction hyperthermia for treatment of brain tumours was first reported by Kida et al.¹² in 1990. A length of 15⁻20 mm, diameter of 1.8 mm and Curie point of 68⁻69°C Fe-Pt alloy thermoseed was used for seven cases of metastatic brain tumour research studies including six cases of combined...
radiation therapy, with the treatment time of 30–60 min, 2–3 times a week. The treatment temperature of tumour tissues can reach 44°C–46°C during the treatment. Two cases of complete response (CR) and one case of partial response (PR) were confirmed in efficacy evaluation after the treatment. Then, a wider range of clinical trials was conducted by Kobayashi et al., thermoseed with Curie point of 68°C was used for treatment of 23 cases of brain tumour patients. Evaluation of the effects of this new treatment is still preliminary and overall response rate was 34.8%. Stea et al., have carried out a tissue hyperthermia of implanted thermoseeds and radiotherapy (external beam radiotherapy and/or an interstitial implant with Ir-192) in 28 patients with glioma, in which the treatment temperature in the alternating magnetic field was above 42°C, and the median survival of this group was 20.6 months. Stea et al., subsequently combined the treatment with radiation therapy, and compared the efficacy with interstitial brachytherapy alone. Twenty-five glioma patients have been treated with magnetic induction hyperthermia combined with radiotherapy (external beam radiotherapy and the interstitial brachytherapy) and were compared with 37 glioma patients treated with the interstitial brachytherapy alone and the results indicated that about half of the combined treatment group showed the effective treatment. However, fewer intracranial tumour therapy trials have been reported recently, the reason is probably that the intracranial implantation of thermoseeds has some difficulties; it needs penetration of the skull, which can result in a large trauma. It is also difficult to make thermoseed to reach the tumour site through the normal brain tissues, which may be damaged. Moreover, the biological boundaries of gliomas are unclear, and it is difficult to locate the tumour tissues exactly according to their shapes. These factors limit further applications of thermoseeds hyperthermia in the treatment of intracranial tumours, but the treatment of implanted thermoseeds is noninvasive, which is very effective for the treatment of some highly recurrent intracranial tumours such as glioma, and is also extremely meaningful as a palliative remedial treatment in surgery.

Magnetic induction hyperthermia of thermoseeds for treatment of prostate cancer

Prostate cancer is another malignant tumour with more of research studies. In 2002, Tucker et al. implanted the cobalt–palladium thermoseed, with a diameter of 1 mm, length 14 mm, in accordance with the arrangement of end to end and 1 cm of space into four patients with T1–T2 prostate cancer. After implantation of thermoseed, heating was conducted in the exchange magnetic field, with 60 min of heating time. The patients underwent radical prostatectomy 9–31 days after the last hyperthermia treatment, which found that three of four patients had no residual tumours after hyperthermia treatment. The intraoperative prostate tissues were cut during the pathological examination, and the results showed that if the arrangement spacing between thermoseeds was no more than 1 cm, and was end to end, a continuous tissue necrosis would occur. Deger et al. conducted a phase II clinical trial to evaluate the efficacy of thermoseed magnetic induction hyperthermia treatment combined with radiotherapy, and 41 patients with localised prostate cancer were conducted with the hyperthermia treatment by implanted cobalt–palladium thermoseed combined with three-dimensional conformal radiotherapy. The hyperthermia treatment was conducted once a week, and continued six times. During the hyperthermia treatment, the temperature within the prostate reached 42°C–46°C, while the radiation therapy was conducted at 1.8 Gy for each dose, and 68.4 Gy for total irradiation dose. After the treatment, the prostate volume was significantly reduced, and prostate-specific antigen (PSA) decreased significantly, with no serious side effects. Tucker thought that thermoseed with 70°C of the Curie point can achieve the effect of thermal removal, 55°C of the Curie point can destroy tumour tissues, increase the sensitivity of tumour tissue to radiation. Thirty patients were treated with the hyperthermia of thermoseed at 55°C of the Curie point, once a week, for 1 h each time, for a total of 6 weeks. The patients received three-dimensional conformal radiotherapy within 2 h after hyperthermia treatment, with a total dose of 68.4 Gy. The results showed that a slight complication occurred after treatment, PSA decreased significantly and continued for more than 1 year. Nineteen patients at T1–T2 phase and five recurrence patients after irradiation received hyperthermia removal treatment of 70°C thermoseed. The pre-treatment PSA value in 19 patients was 2.5–10.7 ng/mL, 79% of patients (15/19) had PSA <1.0 ng/mL after treatment. In five patients with recurrence, the PSA in 4/5 reduced to <0.2 ng/mL within four weeks after treatment, no acute complications occurred. Deger et al. conducted a retrospective analysis to compare the thermoseed hyperthermia treatment combined with radiation treatment with brachytherapy with Ir-192 in prostate cancer patients. Thirty-six patients were conducted with the paired comparison, hyperthermia radiation treatment and brachytherapy with Ir-192 and both had higher than 82 Gy. Patients with hyperthermia radiation treatment and Ir-192-high-dose rate brachytherapy had no significant difference in PSA decline and progression-free survival. In order to verify whether the hyperthermia removal treatment with 70°C Curie point of thermoseeds in...
patients with prostate cancer at T1–T2 phase is safe and effective, Tucker et al. treated 20 aged patients with prostate cancer, with 2.5–10.7 ng/mL of PSA values. The widest spacing for implanted thermoseeds was less than 1 cm with continuous implantation and a treatment time of 60 min. Rebiopsy was conducted after 1 year, five positive cases were confirmed, considering it was due to the lower density of thermoseed implantation in these patients. Eight patients showed erectile abnormality, no defecation incontinence and no other significant complications. Thermoseed hyperthermia removal treatment of T1-T2 prostate cancer is safe and tolerable. These clinical trials showed that the use of tissue hyperthermia treatment with automatic temperature-controlled thermoseeds for the treatment of prostate cancer is feasible and well tolerated by the patient during the treatment.

**Thermoseed magnetic induction hyperthermia treatment for other malignant tumours** Mack et al. conducted magnetic induction hyperthermia combined with 1r-192 brachytherapy on 44 patients with advanced primary or recurrent extra-cranial solid malignancies who were enrolled in this study, using nickel–strontium thermoseed with 50°C–80°C of Curie point, 80–100 kHz of the frequency of the alternating magnetic field, 1.5–2.0 kA/m of the intensity, 43.7°C of the tumour maximum temperature. Forty-one out of 44 patients had entered into the assessment, 61% (25/41) of CR, 32% (13/41) of PR. The treatment achieved 93% efficiency, which was greatly encouraging for further treatment studies. The results from Tohnai et al. were interesting, they conducted the tissue hyperthermia treatment by implantation of iron–platinum thermoseeds with 68°C of Curie point in eight patients with oral cancer; heating once about 45 min per week, 3–6 times simultaneously, combined with the superficial temporal artery chemotherapy, and implemented the tumour resection at the end of hyperthermia and chemotherapy. Seven out of eight patients were CR and one PR. No residual tumour was found for the tumour histopathology examination after resection in all patients, showing that the tissue hyperthermia in combination with chemotherapy for oral cancer is an effective method of treatment.

**Alloy stent induction hyperthermia for treatment of malignant tumours** For the unresectable locally advanced bile duct cancer with poor prognosis, the survival is approximately six months to one year. In order to improve the treatment effects of locally advanced cholangiocarcinoma, Kamisawa et al. adopted a new technology of local magnetic induction hyperthermia combined with chemotherapy for the treatment of malignant biliary strictures. Eight patients with locally advanced extrahepatic bile duct cancer and obstructive jaundice were placed into the alloy stent to conduct the magnetic induction hyperthermia combined with radiotherapy and chemotherapy after percutaneous hepatic and biliary drainage, hyperthermia temperature of 42°C, with a treatment time of 40 min. The efficacy after repeated hyperthermia treatment in combination with radiotherapy and chemotherapy was evaluated in three cases of CR, two cases of PR and three cases of NC, with a survival rate of 13.2 ± 10.8 months in four cases of over 20 months. Akiyama et al. reported that iron–platinum alloy stents were used for magnetic induction hyperthermia treatment in 18 aphagosis patients with advanced H$_2$–IV$_8$ oesophageal cancer; treatment temperature of 50°C, treatment time of 10 min, with the treatment for once a week. Eighteen patients were conducted 52 times of hyperthermia, five cases of combined radiotherapy and chemotherapy and 13 cases of combined chemotherapy. Five patients can be further conducted with surgical treatment after the hyperthermia treatment. Seventeen patients entered into the clinical evaluation after treatment, including one case of CR and 12 cases of PR, 76% (13/17) of the efficiency. Patients who received above three times of hyperthermia included one case of CR and seven cases of PR, 89% (8/9) of the efficiency. Thus, the built-in magnetic induction hyperthermia treatment with alloy stents can inhibit local tumour growth, further increasing the therapeutic effect of advanced oesophageal cancer, improving the quality of life of patients.

**Magnetic fluid hyperthermia and magnetic induction hyperthermia treatments for malignant tumours** Magnetic fluid hyperthermia (MFH) is the magnetic fluid modified by encapsulation or adding a certain antibody that reaches the inside of the tumour by the arteriovenous route or direct injection. Then, this antibody is swallowed by tumour cells or deposited between cells, heated in the cross-varying magnetic field through Nair relaxation and Brownian relaxation mechanism, thereby killing the tumour cells, whereas the increase in temperature of surrounding normal tissues is not obvious, thus having a high degree of targeting. Extensive cellular and animal experiments have been conducted for an MFH, whereas clinical trials have only conducted some preliminary studies in prostate cancer and brain tumours, the treatment for other tumours is embarking.

**Magnetic fluid hyperthermia and magnetic induction hyperthermia treatment for prostate cancer** Johanssen et al. first reported using an MFH (R) 300F-type magnetic induction hyperthermia instrument to conduct the first example of clinical trials of magnetic fluid treatment...
for recurrent prostate cancer. Wrapped by aminosilicone, the core diameter of magnetic fluid is 15 nm, the concentration of iron particles is 112 mg/mL. A CT scan was used for the first and last treatment to record the distribution of magnetic nanoparticles and location of temperature measurement probe. AMIRA software was used to calculate the temperature distribution within the prostate. Magnetic field frequency was 100 kHz, magnetic field strength was 4.0–5.0 kA/m, once a week for treatment, 60 min for every time, continuing 6 times. The invasive thermometry was used at the first and last treatment. During the first treatment, the maximum temperature was 48.5°C, and the minimum temperature was 40.0°C. During the sixth treatment, the maximum temperature was 42.5°C and the minimum temperature was 39.4°C. Based on the first preliminary experiment, Johannsen et al.26 conducted the phase I clinical study, reported the results of 10 patients with local recurrence of prostate cancer who had received magnetic induction hyperthermia, to explore the feasibility, toxicity and effect on quality of life. Within 1 year, hyperthermia nanoparticles can still be explored in the prostate. No systemic toxicity was observed for 17.5 months (3–24 months) of the median follow-up. The acute urinary retention was found in four patients with a history of urethral stricture. No significant treatment-related discomfort was found, the effect on quality of life was only temporary. PSA decreased in eight patients after treatment. Using an MFH for treatment of local recurrence of prostate cancer is feasible, well tolerated without significant side effects.

**Magnetic fluid hyperthermia and magnetic induction hyperthermia treatment for malignant glioma**

Maier-Hauff et al.27 used magnetic nanoparticles hyperthermia combined with radiation therapy for treatment of 14 patients with recurrent malignant glioma. External alternating magnetic field frequency was 100 kHz, and magnetic field strength was 2.5–18 kA/m. Magnetic nanoparticles were wrapped by amino silicone, with a core diameter of 15 nm, the concentration of iron particles of 112 mg/mL. According to MRI images, the specialised treatment program software was used to design the dose and spatial distribution of magnetic fluid. About 0.1–0.7 mL (median 0.2 mL) of magnetic fluid per millilitre was injected into the tumour tissues. Patients without undergoing radiotherapy after 60 Gy irradiation were given 10 Gy added boost, whereas relapsed patients after radiotherapy were given 20–30 Gy of irradiation. Intra tumoural median maximum temperature reached 44.6°C (42.4°C–49.5°C). Magnetic nanoparticles for treatment of malignant gliomas are feasible, and the improvement of the nanoparticle injection method can improve the distribution of nanoparticles in the tumour tissues, and increase the therapeutic effect. Van Landeghem et al.28 firstly reported the pathological findings of autopsy for a dead patient with malignant glioma after treatment of an MFH. After three patients with malignant glioma had received the local tumour magnetic fluid injection, two cases conducted a magnetic induction hyperthermia; one case did not undergo hyperthermia. The autopsy conducted after death showed magnetic fluid accumulation at the tumour necrosis, its distribution limited to the injection site. Macrophage endocytosis of magnetic nanoparticles can be found, and there was also a small amount of magnetic nanoparticles distribution within glioma cells. More macrophage endocytosis of magnetic nanoparticles was found in patients after hyperthermia treatment, which may be related to magnetic induction hyperthermia-induced tumour necrosis that subsequently activates macrophage phagocytic function. Thermal bystander effect was not observed in the magnetic fluid. An MFH for malignant glioma patients is safe and effective.

**Magnetic fluid hyperthermia and magnetic induction hyperthermia treatment for other malignancies**

Wust et al.29 conducted magnetic fluid magnetic induction hyperthermia treatment for 22 patients with relapsed tumour entities in different parts to evaluate the feasibility of the technology, tolerance and the temperature distribution achieved by the treatment. The patients were also treated with radiation therapy or chemotherapy. Wrapped by the amino silicone, the magnetic fluid had a core diameter of 15 nm and the concentration of iron particles was 112 mg/mL. Depending on the sites of a tumour, three different imported techniques were used: an MFH import by CT, by transrectal ultrasound or X-ray fluoroscopy and intraoperative visualisation. No discomfort or mild discomfort was observed in patients during the treatment. For the pelvis tumours, the magnetic field strength selected was 3.0–6.0 kA/m, for neck and chest tumours, 7.5 kA/m and for the head, >10.0 kA/m. Specific absorption rate was 60–380 W/kg. Eighty-six per cent of the tumour areas reached 40°C, whereas 42°C of the temperature distribution was not satisfactory. Using the treatment of CT imported technology, at 30% of the tumour areas, the temperature reached 42°C, using transrectal ultrasound or X-ray fluoroscopy imported technology and only at 0.2% of the tumour areas temperature reached 42°C. The authors considered that as improvement of imported technology; increase in the amount of magnetic fluid and the magnetic field strength can improve the temperature of tumour therapy. Matsumine et al.30 used calcium phosphate bone cement containing Fe$_3$O$_4$ magnetic nanoparticles for treatment of 16 bone lesions in 15 patients with metastatic bone tumours, and have...
evaluated therapeutic effects. Seven lesions were fixed with intramedullary nailing after scraping out, one lesion was conducted with the prosthesis implantation after an excision and the remaining eight lesions were fixed by intramedullary nailing for the involved bones, and these lesions were filled with calcium phosphate bone cement containing Fe$_3$O$_4$ magnetic nanoparticles. Magnetic induction hyperthermia treatment started 1 week after the surgery. In addition, eight patients did not undergo radiotherapy and hyperthermia treatment after surgery and 22 patients underwent postoperative radiotherapy. In the magnetic induction hyperthermia group, patients’ alleviated pain can be movable, and there were no significant complications. For the postoperative magnetic induction hyperthermia group, 87% were effective, 38% in the surgery alone group and 91% in the postoperative radiotherapy group. The postoperative magnetic induction hyperthermia group was significantly better than the surgery alone group (P = 0.0042), no significant differences were found in the postoperative magnetic induction hyperthermia group compared with the postoperative radiotherapy group. Magnetic induction hyperthermia treatment had a more satisfactory local control rate for metastatic bone tumours.

Conclusion

Magnetic induction tumour treatment technology has had 50 years of history since the suggestion of the concept till date. With the continuous development of material science, magnetic devices, biotechnology and other disciplines, this technology has achieved encouraging study results. A prominent advantage of this treatment method is to greatly increase the specificity of the hyperthermia, which can sufficiently reduce thermal damage to normal tissues, and be prepared to overcome the poor specificity and many side effects and other defects of conventional hyperthermia; that is, to create a new treatment model to improve the efficacy of tumour deep hyperthermia treatment. However, there are still some factors that affect the further applications of magnetic induction tumour therapy in cancer therapy and a number of key issues to be resolved, mainly focusing on the research and development of magnetic media, magnetic induction tumour treatment system and other aspects. At present, domestic and foreign scholars are committed to research in this area, and have made an internationally significant progress in the design theory and equipment development of magnetic induction tumour treatment. Since 2002, the German Jordan study group developed an alternating magnetic field heating device available for medical experiments, they had improved this device based on the experiments, and had jointly developed the world’s first MFH (R) 300F-type magnetic induction hyperthermia instrument available for clinical treatment with the Berlin Magforce company, and began to use it in clinical treatment. Tang research team of Tsinghua University had also developed and trial manufactured a clinical magnetic induction hyperthermia machine through 10 years of experimental studies. In February 2010, Tsinghua University combined with Hunan Provincial Tumour Hospital and Fujian Provincial Tumour Hospital successfully started a magnetic induction hyperthermia cancer clinical trial in China, initially confirmed the safety and effectiveness, and an alternating magnetic field therapy device and gold-coated alloy thermoseed were approved by China’s State of Food and Drug Administration. In addition, an MFH with magnetic nanoparticles as treatment media has completed all preclinical studies; the current clinical trial of nano-hyperthermia has only been conducted in Germany. China is expected to become the world’s second country after Germany in the application of cancer nanotechnology into clinical research treatment, and is expected to gain new progress in medical innovation technology.

Abbreviations list

CT, computed tomography; Ir, iridium; MFH, magnetic fluid hyperthermia; MRI, magnetic resonance imaging; PSA, prostate-specific antigen.

References


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