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Boron Neutron Capture Therapy: A New Generation of Targeted Charged-Particle Radiotherapy

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Abstract

Radiation therapy plays an important role in standard cancer treatment. However, patients who are resistant to traditional radiation therapy or who have relapsed after conventional radiation therapy are often encountered in clinical practice. There is therefore a need for a new radiation therapy for this type of patient. Although boron neutron capture therapy is not a new concept of radiation therapy, due to technological breakthroughs and conceptual improvements at the start of the 21st century, this therapy, which covers multidisciplinary technologies, such as medical physics, atomic science and technology, boron-containing drug synthesis, radiobiology, and clinical oncology has advanced greatly, and has gradually matured to a clinically useful therapy for patients with cancer. This article provides a brief introduction to the latest breakthroughs and progress in this technology.

Keywords: Boron Neutron Capture Therapy; Radiotherapy; Glioblastoma; Theranostic

Introduction

Boron neutron capture therapy (BNCT) is not a new concept in the field of radiation oncology. In the 1930s, not long after the British physicist James Chadwick (l891-1974, 1935 Nobel Prize winner of physics) proposed verification of the existence of neutrons, some researchers proposed that, after using thermal neutrons to irradiate boron-10 atom (in the natural world, four-fifths of boron is boron 11, while one-fifth is boron-10; boron-10 is non-radioactive isotope), boron-10 will be cleaved into two particles with high biological effects, namely an α particle (helium nucleus) and a lithium nucleus. These two biologically active particles not only have an excellent damaging effect on tumor tissue and DNA, but also have a range of effects, limited to 5-10μm (a normal cell diameter is about 20μm), and thus has little damaging effect on the surrounding normal tissues. Therefore, if a specific boron-10-containing drug can be administered selectively to the tumor cells, and a sufficient flux of thermal neutron radiation is applied, it can induce tumor destruction. Therefore, this concept has always been an ideal for targeted charged-particle radiation therapy in the field of clinical radiation oncology [1].

Although the principles seem to be ideal, the implementation of this concept in clinical practice still has many limitations and difficulties. The main technical limitation is whether boron-containing drugs can be specifically absorbed by tumors. The other is the high-throughput, quality, thermal neutron source. The source of the tumor dose involves a combination of a reactive boron-10 dose, the neutron dose, and the gamma ray dose. In the 1950s, at the Massachusetts General Hospital in the United States, neurosurgeon Dr. William Sweet led the world's first BNCT clinical trial in human

patients with malignant brain tumors (glioblastoma; WHO grade IV), using the Brookhaven Medical Research Reactor (BMRR) was conducted in Long Island, New York. Although the nuclear technology was not accurate at the time, and the boron-containing drugs used did not have high specificity (Borax; Na2B4O7·10H2O), this trial was not expected to achieve a particularly good efficacy on malignant brain tumors [2]. However, it was globally considered an important treatment. Japan, Finland, Sweden, the Netherlands, the Czech Republic, Taiwan and other countries worldwide followed the example of this trial and successively proposed various clinical trials using BNCT to treat malignant brain tumors, and also presented the therapeutic advantage of this therapy, of gradually improving the condition of such tumors. In the clinical treatment of brain tumors in Japan, in particular, it was reported that the patient's disease control period post-BNCT was significantly superior to that after traditional photon therapy alone, with patients not only surviving for more than 2 years, but also having excellent quality of life. In addition, for recurrent head and neck cancer, melanoma, liver cancer, and mesothelioma, etc., all countries have reported inspiring clinical trial results [3-8]. Therefore, with further improvement, this highly bioactive targeted radiotherapy will be able to assist a variety of clinical patients.

Development of New Boron-10-Containing Drugs and Breakthroughs in the Concept of Radiobiology

One of the key technologies for BNCT is the high tumor-specific uptake of boron-10-containing drugs. The main drugs used in the past involved delivery of BPA (L-BPA [L-(4-10borophenyl) alanine]) and BSH (sodium borocaptate). BPA mainly induces a large amount of drug intake by tumor cells due to its structural similarity to the human essential amino acid phenylalanine, while BSH is an icosahedron with a considerable number of boron-10 structures, which can effectively produce therapeutic benefits. In recent years, the international BNCT medicinal chemistry research and development community has attempted to develop various new promising boron-containing drugs, such as GB-10, boric acid etc. [9-11]. If these new boron-containing drugs can be delivered into tumor cells specifically and efficiently, this would form an important basis for the successful clinical treatment implementing BNCT. In addition, the biological benefits of BNCT differ from traditional photon and proton therapies, etc. In addition to tumor tissues, different normal tissues also have different degrees of biological responses to BNCT. Therefore, BNCT introduces the biological concept of the compound biological effectiveness factor. Experimental calculations in the biological laboratory can facilitate an accurate grasp of BNCT dose calculation. In recent years, the concept of ABE factor also emerged, which can provide a more accurate concept of the BNCT dosage calculation [12].

PET Exam with 18F-Labeled BPA

As mentioned above, the key to the success of BNCT is specific absorption of drugs containing boron-10. Therefore, it is important to be able to assess the distribution of drugs in the human body effectively. In recent years, a major breakthrough in the BNCT drug research has been the use of nuclear medicine technology to label therapeutic BPA drugs radioactively with fluorine-18. After injection, the patient undergoes positron-emission tomography (PET) to evaluate whether the BPA drug in the human body is specifically distributed in the tumor tissue [13]. This mode of using drugs to assist both treatment and diagnosis is a common concept in nuclear medicine technology: "Theranostic" (a combination of the concepts of "Therapy" and "Diagnostic"). After the patient has completed FBPA-PET, the clinician must assist in interpreting the Tumor/Normal tissue ratio (T/N ratio) of the boron-containing drug (BPA) in the tumors and in normal tissues. It is considered that, only when this T/N ratio exceeds 2.5, will the clinical treatment response be advantageous, and a too-low ratio indicates that the treatment is not suitable [14-15].

Breakthroughs in Neutron Sources

In recent years, due to the dramatic breakthroughs in atomic science and technology, through the reconstruction of traditional reactors, the neutron source required by BNCT could be upgraded from thermal neutrons to epithermal neutrons, thereby improving tissue penetration depth to treat deeply located tumors. However, most of the international clinical trial institutions are still limited by the need for an atomic reactor to provide neutron sources. In recent years, the international BNCT community has been actively pursuing the development of neutron accelerators, produced by heavy industry technology, to replace traditional atomic reactors as a stable source of neutrons. Compared with the atomic reactor, the accelerator has better controllability and safety, without the problem of nuclear waste disposal, and it is more suitable to serve as a formal medical device in a medical institution. Internationally, Japan, the United States, Italy, Israel, Russia, and other countries all have BNCT programs for the development of accelerator systems [16]. In particular, Japan's accelerator for BNCT is about to complete clinical trials (in malignant brain tumors and recurrent head and neck cancer). It will become one of the regular formal medical devices in the near future. With the help of high-quality accelerator neutron equipment, BNCT can be quickly and routinely promoted in hospitals [17].

Conclusion

Cancer treatment is an important and global human health issue and breakthroughs in effective treatment are urgently required. By the joint efforts of various experts, the prospects of BNCT implementation has gradually been revealed. In Asia, Japan is the pioneer of BNCT and is about to promote BNCT as a formal standard of care for cancer. In Taiwan, more than 60 patients have been treated with this therapy in clinical trials and as emergency medical treatment with compassionate use. We hope that in the near future, we can help this high-quality treatment mode, with high tumor damage and low peripheral tissue damage, to become the official standard of care for cancer, to allow more patients to obtain more effective tumor control.

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