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Review

Physical, dosimetric and clinical aspects and delivery systems in neutron capture therapy

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ABSTRACT

Neutron capture therapy (NCT) is a targeted radiotherapy for cancer treatment. In this method, neutrons with a spectra/specific energy (depending on the type of agent used for NCT) are captured with an agent that has a high cross-section with these neutrons. There are some agents that have been proposed in NCT including ^{10}B, ^{157}Gd and ^{33}S. Among these agents, only ^{10}B is used in clinical trials. Application of ^{157}Gd is limited to in-vivo and in-vitro research. In addition, ^{33}S has been applied in the field of Monte Carlo simulation. In BNCT, the only two delivery agents which are presently applied in clinical trials are BPA and BSH, but other delivery systems are being developed for more effective treatment in NCT. Neutron sources used in NCT are fission reactors, accelerators, and ^{252}Cf. Among these, fission reactors have the most application in NCT. So far, BNCT has been applied to treat various cancers including glioblastoma multiforme, malignant glioma, malignant meningioma, liver, head and neck, lung, colon, melanoma, thyroid, hepatic, gastrointestinal cancer, and extra-mammary Paget's disease. This paper aims to review physical, dosimetric and clinical aspects as well as delivery systems in NCT for various agents.

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1. Introduction

Neutron capture therapy (NCT) is a treatment method to selectively target malignant cells. In this method, neutrons with a spectra/specific energy are captured with an agent that has a high cross-section with those neutrons, and the neutron energy used depends on the type of the agent used. There are some agents that have been proposed in NCT including ^{10}B, ^{157}Gd and ^{33}S and treatments with these agents are called BNCT, GdNCT and SNCT, respectively. In the following sections, each of these modalities are described.

1.1. BNCT

BNCT was first described in1935 by Taylor.[1] It is a targeted radiotherapy based on the nuclear capture that occurs when ^{10}B (non-radioactive) is irradiated with thermal neutrons (energies less than 0.5 eV). It is notable that ^{10}B absorption cross-section follows a $1/v$ law (v is neutron velocity) very accurately in the energy range from 0 to 10^4 eV. Therefore, ^{10}B-n capture reaction can occur even at energies higher than the thermal energies, although the thermal energies are more effective. Following the interaction, high linear energy transfer (LET) products (alpha particles and recoiling ^{7}Li nuclei) are produced.[2–7] The deposited energies of these heavy particles are shown below[8]:

These products deposit their energies in a range of 5–9 μm. This range corresponds to the diameter of a cell,[9] and the harmful effects of these compounds with high LET are limited to boron comprising cells. Therefore, BNCT presents a method to selectively eradicate malignant cells and spare adjacent normal cells.[6] Fig. 1 shows the nuclear reaction which is related to BNCT. For a successful BNCT, an adequate amount of ^{10}B should be selectively accumulated in the tumor. Moreover, sufficient thermal neutrons should be available to create a large number of capture reactions.[10] Also, it has been reported that when the efficiency of BNCT is limited with thermal neutrons, replacing light water with heavy water can increase the maximum therapeutic depth. As Blagojevic et al. showed, concentrations of heavy water in humans is not toxic up to 23%.[11,12]Moreover, BNCT is clinically used for treatment of different tumors.[13–18]

1.2. GdNCT

Besides ^{10}B, ^{157}Gd is used as an agent for NCT. Gadolinium element has seven stable isotopes including "^{152}Gd (0.205%), ^{154}Gd (2.23%) ^{155}Gd (15.10%), ^{156}Gd (20.60%), ^{157}Gd (15.70%), ^{158}Gd (24.50%), ^{160}Gd (21.60%)".[19] Among these nuclides, ^{157}Gd and ^{155}Gd have the largest cross-sections to capture with thermal neutron, as their cross-sections of neutron capture are 255,000 and 60,800 barns, respectively.[20] These are approximately 66 and 16 times greater than those of ^{10}B, respectively. Furthermore, it is notable that cross sections of neutron capture for the other isotopes are insignificantly small for dose calculations.[19] It is shown that the highest capture cross-section for gadolinium is at energies below 0.2 eV.[21] GdNCT is not a fission reaction and is more complex than BNCT.[22] The interaction products of the GdNCT are high energy gamma-rays, internal conversion (IC) electrons, X-rays, and auger electrons. The average energy of the gamma-rays and IC electrons are approximately 2.2 MeV and 45 eV, respectively, and their path lengths are several centimeters and several millimeters, respectively. In addition, the auger electrons have very low energy, as their path lengths in aqueous solutions are several nanometers.[22] GdNCT is chiefly based on the action of internal conversion and auger electrons produced by ^{157}Gd after neutron capture.[23] In Fig. 2 the neutron capture reaction with ^{157}Gd is illustrated.

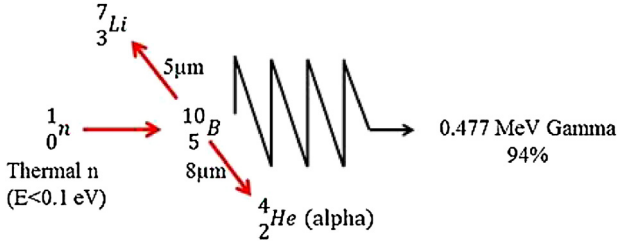

Fig. 1 – Neutron capture reaction with ^{10}B.

As this ionizing radiation is restricted to molecular dimensions, i.e. 5–40 nm, for inducting considerable DNA injury in malignant cells, it is necessary to position the ^{157}Gd atoms within the DNA helix.[22] It is notable that the success of GdNCT depends on the relative biological effectiveness (RBE) of gamma-rays, IC and auger electrons, as RBE directly relates to the placement of the ^{157}Gd atoms with regard to the DNA of cancer cells.[22] The auger electrons produced by the GdNCT reaction have a very high LET, due to their nanometer range. The auger emitters located adjacent to the DNA strands of malignant cells are able to induce a level of DNA injury which is 5–10 times greater than the high energy gamma-rays. Additionally, the RBE of the IC electrons can be considered intermediate between those of the auger electrons and the high energy gamma-rays.[22] The following reaction formula shows capturing ^{157}Gd and ^{155}Gd with thermal neutrons[19]:

1.3. SNCT

In addition to ^{10}B and ^{157}Gd, a few nuclides capture higher energy neutrons at definite energies, because of resonances in the cross-section of NCT. A particular case among these nuclides is ^{33}S that was introduced by Porras in 2008.[24] This isotope is stable and there is a small proportion for it (about 0.75%) in natural sulfur.[24] As there is sulfur in proteins related to tumor metabolism, it is a promising option for targeting tumor cell nuclei.[25] In SNCT, alpha particle emission is the most probable decay pathway in the neutron capture reaction, as opposed to photon emission, which is dominant in all elements in the chart of nuclides.[25] It has been proposed that in tumors with high concentration of ^{33}S, the presence of this isotope can supplement the effect of ^{10}B in BNCT if neutrons with energy of 13.5 keV are applied.[26] In SNCT, the most significant resonance for NCT is 13.5 keV, because of the following characteristics: "(1) this energy is in the range of the energies which are utilized in epithermal BNCT; (2) it is a low energy for the background dose in the tissue; (3) both ^{33}S and ^{30}Si (the products of the reaction) are stable; (4) practically

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