REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY 16 (2011) 21–31

available at www.sciencedirect.com

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journal homepage: http://www.rpor.eu/

Original article

Therapeutic potential of atmospheric neutrons

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A R T I C L E I N F O

Article history:
Received 29 June 2010
Received in revised form
5 October 2010
Accepted 3 November 2010

Keywords:
NBCT
Neutron
Boron
Atmospheric
Glioblastoma

A B S T R A C T

Background: Glioblastoma multiform (GBM) is the most common and most aggressive type of primary brain tumour in humans. It has a very poor prognosis despite multi-modality treatments consisting of open craniotomy with surgical resection, followed by chemotherapy and/or radiotherapy. Recently, a new treatment has been proposed – Boron Neutron Capture Therapy (BNCT) – which exploits the interaction between Boron-10 atoms (introduced by vector molecules) and low energy neutrons produced by giant accelerators or nuclear reactors.
Methods: The objective of the present study is to compute the deposited dose using a natural source of neutrons (atmospheric neutrons). For this purpose, Monte Carlo computer simulations were carried out to estimate the dosimetric effects of a natural source of neutrons in the matter, to establish if atmospheric neutrons interact with vector molecules containing Boron-10.
Results: The doses produced (an average of 1 μGy in a 1 g tumour) are not sufficient for therapeutic treatment of *in situ* tumours. However, the non-localised yet specific dosimetric properties of 10B vector molecules could prove interesting for the treatment of micro-metastases or as (neo)adjuvant treatment. On a cellular scale, the deposited dose is approximately 0.5 Gy/neutron impact.
Conclusion: It has been shown that BNCT may be used with a natural source of neutrons, and may potentially be useful for the treatment of micro-metastases. The atmospheric neutron flux is much lower than that utilized during standard NBCT. However the purpose of the proposed study is not to replace the ordinary NBCT but to test if naturally occurring atmospheric neutrons, considered to be an ionizing pollution at the Earth's surface, can be used in the treatment of a disease such as cancer. To finalize this study, it is necessary to quantify the biological effects of the physically deposited dose, taking into account the characteristics of the incident particles (alpha particle and Lithium atom) and radio-induced effects (by-stander and low dose effect). One of the aims of the presented paper is to propose to experimental teams (which would be interested in studying the phenomena) a simple way to calculate the dose deposition (allometric fit of free path, transmission factor of brain).

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doi:10.1016/j.rpor.2010.11.002

Nomenclature

D_{ij}	dose deposited by the reaction *i* and the nucleus *j* (Gy)
N_0	total number of neutron (NU)
E	energy variable (J)
t	time variable (s)
S	surface variable (m)
N_j	number of nuclei *j* (NU)
V	volume (m^3)
$\sigma_{\iota\varphi}$	cross section for reaction *i* and nucleus *j* (m^2)
E_{ij}^n	energy deposited after the reaction *i* on the nucleus *j* (J)
x	depth (m)
m	mass (kg)
Ψ	differential neutron flux (J^{-1} s^{-1} m^{-2})
ρ	density (g cm^{-3})
μ_{en}/ρ	attenuation coefficient (J kg^{-1})
$E_{a,s,b}$	neutron energy in air, skull and brain (J)
$L_{s,b,t}$	mean free path (m)
$T_{s,b,t}$	transmission factor for skull, brain and tumour (NU)
Depth	tumour depth in brain (m)
$F(E)$	cumulative distribution function for neutron related to energy (NU)
n_i	number of neutron with energy i (NU)
N_a	Avogadro constant (mol^{-1})
A_j	atomic mass number for nucleus *j* (atomic mass unit, u)
$\sigma(E,j)$	total cross section for the nucleus *j* and the energy *E* (m^2)
$P_{E,j}$	capture probability on nucleus *j* with the energy *E* (NU)
m_{rec}	mass of recoil nucleus during elastic collision (kg)
m_n	neutron mass = 1.0087 u
φ_{rec}	deflexion angle in the system of the center of mass (rad)
E_0	energy of incident particle (J)
$w_r(E)$	weighting factor designed to reflect the different radiosensitivity of the tissues (NU)
$E_{i,f}$	initial and final neutron energy (J)

1. Background

In 2007, cancer caused about 13% of all human deaths (7.6 million). Some of the most invasive malignant tumours are breast cancer, colorectal cancer, lung cancer, and stomach and liver cancer. Brain tumours are not very common as they account for only 1.4% of all cancers in the United States. Patients with benign gliomas may survive for many years, but in most cases of glioblastoma multiforme (GBM), survival is limited to a few months after diagnosis without treatment.[1,2] Despite being the most prevalent form of primary brain tumour, GBM occurs in only 2–3 cases per 100,000 people in Europe and North America. It is the most common and most aggressive type of primary brain tumour in humans. The usual multimodality treatment consists of open craniotomy with surgical resection of as much of the tumour as possible, followed by concurrent or sequential chemotherapy, antiangiogenic therapy with bevacizumab, gamma knife radiosurgery, standard radiotherapy, and symptomatic care with corticosteroids. Another therapeutic approach is based on the Boron Neutron Capture Therapy (BNCT) which was proposed in 1936 by Dr. Gordon Lecher only 4 years after the discovery of the neutron.[3–5] This method, which is well adapted for intra-cranial cancer treatments, is simple and well-designed in concept but complex and difficult in execution. It is based on the capacity of thermal neutrons to induce a reaction with Boron-10 nuclei, forming a compound nucleus (excited Boron-11 in Eqs. (1) and (2)) which then promptly disintegrates to Lithium-7 and an alpha particle (Fig. 1).[6–8] Both the alpha particle and the Lithium ion produce closely spaced ionizations in the immediate vicinity of the reaction, with a range of approximately 4 and 8 μm, for Lithium-7 and alpha particle respectively, or roughly the diameter of one cell (10 μm).

$$ {}^{10}_{5}\mathrm{B} + {}^{1}_{0}\mathrm{n} \rightarrow {}^{4}_{2}\mathrm{He} + {}^{4}_{2}\mathrm{Li} + 2.79\,\mathrm{MeV} \quad (6\%) \tag{1} $$

$$ {}^{10}_{5}\mathrm{B} + {}^{1}_{0}\mathrm{n} \rightarrow {}^{4}_{2}\mathrm{He} + {}^{4}_{2}\mathrm{Li} + \gamma(0.48\,\mathrm{MeV}) + 2.31\,\mathrm{MeV} \quad (94\%) \tag{2} $$

This technique is advantageous since the radiation damage occurs over a short range and thus normal tissues can be spared. The path of the reaction products is shown in Fig. 2.

The NBCT is a well recognized treatment for GBM, particularly due to its efficiency, but is unfortunately very difficult to access as only a few radiotherapy units can use a proton accelerator.[9,2] In France, this service is not available to patients.

An alternative to this would be to find a new source of neutrons that is easily exploitable. Because free neutrons are unstable (mean lifetime of about 15 min), they can only be obtained from nuclear disintegrations, nuclear reactions, or high-energy reactions such as in cosmic radiation showers or collision accelerators. Cosmic radiation interacting with the Earth's atmosphere continuously generates neutrons.[10–15] The cosmic rays (essentially 85% of Hydrogen and 12.5% of Helium) penetrate the magnetic fields of the solar system and the Earth, and as they reach the Earth's atmosphere, they collide with atomic nuclei in the air (78% Nitrogen, 21% Oxygen and 1% Argon) to create cascades of secondary radiation of every kind. The intensity and energy distribution of different particles that make up atmospheric cosmic radiation vary in 3 essential parameters: altitude, location in the geomagnetic field (correlated to latitude, it deflects low-momentum charged particles back into space), and time in the sun's magnetic activity cycle.[16–18] Table 1 shows the implication of the first two (altitude and latitude). Atmospheric shielding, correlated to altitude, is determined by the thickness of the air mass above, called atmospheric depth.

At high altitude, geomagnetic latitude has a small effect on the shape of the neutron spectrum and a very large effect on the neutron radiative flux. In Fig. 3, representing the results found by Roesler in 1998,[19] we can see how strong an influence atmospheric depth has on the neutron flux. It decreases by a factor of 100 between high altitude (20 km corresponding to an atmospheric depth of 50 g cm^{-2}) and sea level (corresponding