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Progress in the use of gadolinium for NCT

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ABSTRACT

The evaluation of possible improvement in the use of Gd in cancer therapy, in reference to gadolinium in cancer therapy (GdNCT), has been analysed. At first the problem of the gadolinium compounds toxicity was reviewed identifying the Motexafin Gadolinium as the best. Afterwards, the spectrum of IC and Auger electrons was calculated using a special method. Afterwards, this electron source has been used as input of the PENELOPE code and the energy deposit in DNA was well defined. Taking into account that the electron yield and energy distribution are related to the neutron beam spectrum and intensity, the shaping assembly architecture was optimised through computational investigations. Finally the study of GdNCT was performed from two different points of view: macrodosimetry using MCNPX, with calculation of absorbed doses both in tumour and healthy tissues, and microdosimetry using PENELOPE, with the determination of electron RBE through the energy deposit. The equivalent doses were determined combining these two kinds of data, introducing specific figures of merit to be used in treatment planning system (TPS). According to these results, the GdNCT appears to be a fairly possible tumour therapy.

1. Introduction

The gadolinium neutron capture therapy (GdNCT) is a recently reproposed therapy, mainly based on the action of Auger and IC electrons, generated by ^{157}Gd after neutron capture.

The reference to the use of gadolinium is derived mainly from the consideration of its quite higher neutron capture cross sections (254 000 b for ^{157}Gd) vs. boron (3835 b for B-10) that implies a huge dose delivery in proximity of the tumour region.

The research on the use of gadolinium as neutron absorber in NCT, even if appears quite complex, presents some promising future applications. The evaluation of improvements in the use of gadolinium in cancer therapy, through the treatment planning system (TPS) assessment, is one of the topics currently analysed by our group. In fact the first issue is to save the patient's health ("primum non nocere"). This item suggests to deeply analyse the toxicity of gadolinium compounds and the effect on healthy tissues of parasitic reactions.

Gadolinium neutron capture reactions release a wide range of particles: prompt gamma rays, internal conversion electrons, X-rays and Auger electrons. The spectrum of the secondary particles emitted by gadolinium (mainly electrons) is complex and, among others, the presence of strong gammas spreads out the dose delivery to a broad region, thus limiting the selectivity of the therapy. The photons emitted in the (n,γ) reactions interact with the tissues but deposit energy over a longer path length than the boron reaction products. This is the main drawback of GdNCT.

However, if ^{157}Gd uptake is strictly limited to tumour bulk, having a size of the order of some cm^3 by volume, then an additional effect, in the increasing of tumour dose and in the attenuation of the capture photons yield, will be added.

Conversion and Auger electrons are also emitted after the Gd neutron capture, at hundreds of discrete energies. These electrons have energy-dependent ranges in water as short as 0.8 μm at 5 keV. However the range due to the most commonly yielded electron energies exceeds the size of a single cell. Electrons with very low energies (few tens of eV) are also emitted; having a desired short range and bringing a very high contribute to the local dose delivery in GdNCT.

Even if the energy carried out by these electrons is limited to about 1% of total energy released by the ^{157}Gd(n,γ)^{158}Gd reaction only, their contributions is nevertheless very effective due to the high electron LET, if the emitter is bound to DNA. Therefore the DNA double-strand break occurs with consequent cell killing. Furthermore Auger cascade electrons display a very complex energy spectrum, dominated by a large number of very

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low-energy electrons (down to few eV) with ranges of macromolecular dimensions in biological matter.

2. Gadolinium compounds toxicity and localization in tissues

Although Gd^{3+} ions are toxic, there are some gadolinium compounds (e.g. Gd-DTPA and other chelate compounds) that show a very low toxicity. These substances are given intravenously to the patient. They are already used in MRI and considered even more safe than iodised contrast agents as far as kidney damage is concerned.

Recently a new compound, Motexafin Gadolinium (MGd) has been developed by pharmaceutical industry (Evens, 2004). MGd, that is a type of metalloporphyrin complex, have been studied because it may make tumour cells more sensitive to radiation therapy, improves tumour image quality using magnetic resonance imaging and itself kills cancer cells. A number of toxicological studies have been conducted on this substance leading to the statement that its intravenous delivery is well tolerated. Furthermore in this case plasmatic concentration is maintained at high levels for longer periods in comparison to current paramagnetic contrast agents.

The dose to a biological target depends in part on the cumulated quantity of gadolinium in the target and its surroundings. The extreme short range of Auger electrons may require accurate data acquisition on the spatial localization of the emitters relative to the targets with nanoscale resolution. Unfortunately such information cannot readily be obtained even from patient, animal or cell culture studies.

De Stasio et al. (2006) made use of X-ray photo-emission electron microscopy (X-PEEM) analysis on some gadolinium coumponds (e.g. Motexafin Gadolinium) using the spectromicroscope for photoelectron imaging of nanostructures with X-rays (SPHINX) instrument but this technique was used for *in vitro* samples. Some similar analysis has been done in Japan using a single ended accelerator (Endo et al., 2004). This information plays a critical role in the evaluation of DNA damage due to gadolinium in GdNCT, and therefore is mandatory for predicting the tumour biological effects.

De Stasio et al. (2006) found that in all types of samples exposed to 100 μmol/L of MGd more than 90% of cellular nuclei contain Gd. Therefore it is demonstrated that molecules like MGd are able to carry Gd atoms especially inside the tumour DNA. This result is very encouraging with regard to the possibility of using MGd, also well tolerated, in GdNCT. Furthermore it is highly probable that pharmaceutical research can drive to new and more specific compounds. In other words we can confirm that the therapy efficacy increasing is highly dependent on the chemical–pharmaceutical progress.

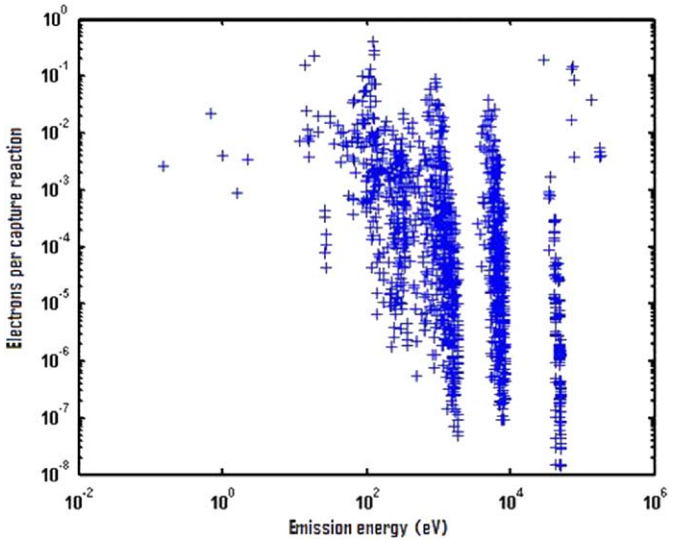

Fig. 1. Number of electrons (Auger and IC) for $^{157}Gd(n,\gamma)^{158}Gd$ capture reaction.

3. Electron spectrum determination

The Auger electron spectra are discrete, reflecting the energies of orbital transitions within the atom. The analysis of this spectrum is fundamental to study the local electron transport in order to evaluate the DNA damage.

Starting from gadolinium reaction data, the IAEA BRICC code (Kibédi et al., 2005) which provides, for allowed transitions, the internal conversion coefficients for the atomic levels, has been used. The IC electron energies were determined by difference between the transition energy and atomic orbital bound energy. The Auger and Coster-Kronig emission energies have been calculated with the EADL (Evaluated Atomic Data Library) of LLNL (Perkins et al., 1994) and the associated RELAX program (Cullen, 1992). In Fig. 1 the calculated spectrum is shown. It appears that there are too many points in this figure so it is not very clear from the graphical point of view. Therefore all the values are reported in tabular form.

This work could be used as a basis for Monte Carlo (MC) calculations in further GdNCT studies.

4. Nanodosimetry and macrodosimetry

Only 1% of neutron capture reaction energy is transported by Auger and IC electrons, but if the Gd atom is bounded to the DNA their effectiveness in killing tumour cell is very high. Molecules like MGd are able to carry Gd atoms specially inside the tumour DNA. Supposing to have an approximated knowledge of the gadolinium positioning inside the cell, the estimation of the energy fraction released by the electrons at nanoscale level is the main issue to be sorted out (Bufalino et al., 2006). Due mainly to complex cell geometry and to the stochastic nature of the phenomena, it is mandatory to use the Monte Carlo technique. The RBE of Auger electrons depends dramatically on the location of Gd inside the cells. With Monte Carlo codes it is possible to

Table 1
RBE values assigned to electrons according to Gd position.

Gd position	Mean energy released in DNA for source electron (eV)	Mean energy released in DNA for single neutron capture (eV)	Mean lineal energy (y) (keV/μm)	Associated RBE according ICRU 40 (Q)
At the centre of cylinder	75.192	380.6	32.55	12.563
On the surface of cylinder	40.560	205.3	17.56	5.97
On the proximity of the surface but outside the cylinder	11.493	58.17	4.97	1.46