Sulfur-33 Nanoparticles: A Possible Target for Neutron Capture Therapy of Cancer

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ABSTRACT

In this work a new idea for a selective radiotherapy of cancer is presented. It is based on the delivery of an isotope of sulfur (\(^{33}\)S), not previously studied, in the form of nanoparticles and the irradiation by low-energy 13.5 keV neutrons. This would result in a high equivalent dose delivered to the tumour cells, greater than the one received by the surrounding healthy tissue. The present proposal, which is based on results from Monte Carlo simulations, could be a stimulus for further advances in the present day techniques of neutron capture therapy.

Keywords: sulfur nanoparticles, neutron capture therapy, Monte Carlo simulation, cancer radiotherapy.

1 INTRODUCTION

The use of nanostructures for imaging and targeted therapies of cancer is a very active line of research nowadays [1,2]. This lies on the fact that they can be selectively uptaken by tumors, and therefore could be useful carriers of chemotherapy drugs, radionuclides or contrast agents for early diagnostics. There are well documented mechanisms responsible of the tumor uptake: one of them is the passive targeting by means of the enhanced permeation and retention (EPR) effect [2,3]: the tumor vasculature, which is rapidly growing, is not well structured and presents fenestrations which allow the passage of particles of a size up to a few hundreds of nanometers, and once in the tumor domain, they can be retained because the lymphatic drainage is seriously compromised. Another option is active targeting by surface functionalizing the nanostructures with specific ligands, such as antibodies, aptamers, folic acid, transferrin or other molecules which recognize a particular receptor which is overexpressed in the tumoral cells [2]. The role of both processes is discussed in the literature [4], and the number of papers with research results published in recent years is enormous and continuously growing, and therefore an important progress can be expected in the fight of cancer diseases by means of these techniques.

However, there are some biological barries that must be overcomed, such as the clearence by macrophages, for which an important breakthrough was coating the nanoparticles with hydrophilic polymers [5]. Another key problem in the case of tumor drug delivery by nanostructures is the drug release inside the cell, because the active chemicals should reach the cell nucleus. These release is pursued by means of pH changes, magnetic fields or heat or light sources [6,7].

An interesting field of application of nanoparticles, not so well known, is neutron capture therapy [8]. This is a binary therapy which is based on the combined presence of a particular isotope in the tumor and the irradiation with low energy neutrons. The isotope should have a large probability (cross section) of suffer a neutron induced nuclear reaction producing charged heavy ions which deposit their energy in a range similar to the cell size. The most common used nuclide for this application is \(^{10}\)B, which has a very large cross section for the \((n,\alpha)\) reaction if the neutron has an energy below 1 eV (thermal). Clinical trials in different parts of the world by means of neutron sources from research reactors have led to promising results [9]. One of the major problems of boron neutron capture therapy is to reach tumor boron concentrations above 30 ppm with a tumor/normal tissue ratio as high as possible.

In this work the possibility of using a different isotope, \(^{33}\)S, for neutron capture therapy is discussed in the context of cancer nanotechnology. The author has shown in a previous work [10] that the presence of this isotope with a high concentration in a particular location would enhance the neutron radiation dose from a monoenergetic 13.5 keV-source. This constitutes a new research problem for which no previous data is available: tumor targeting with sulfur nanoparticles, that would remain inactive except when irradiated by such a neutron source and only in the region exposed to the radiation field. Sulfur is an interesting element for tumor uptake because it plays an important role in cellular metabolism, being present in organic compounds like cysteine, methionine and iron-sulfur clusters, among others. Naturally, it can be present in tissues at concentrations above 1 mg/g.

2 PROPERTIES OF SULFUR-33

Sulfur-33 is a very special nuclei in the sense that its cross section, which reflects the probability of a given interaction process, for the \((n,\alpha)\) radiative capture for certain neutron energies. This feature is not common for most nuclei. That means that when capturing a neutron it is much more likely to emit an alpha particle than a high energy photon. Alpha particles have a much greater biological effectiveness for destroying...
cells, than photons (they can produce double strand breaks in DNA), and they deliver their energy in a very short path, of the order of a cell size. The case with a higher (n,α) cross-section corresponds to a neutron low energy of 13.5 keV.

In addition to this, not only the (n,α) cross section is much greater then radiative capture, but also it exceeds, for this neutron energy of 13.5 keV, the cross sections of all other mechanisms of interaction with the atoms present in tissue. In particular, elastic scattering by hydrogen is the most common mechanism of interaction of neutrons with human tissue, with a cross section of the order of 20 barns (b). In this case, a 13.5 keV neutron would eject a proton with an energy of about 7 keV. This is the main mechanism that produces a dose in the medium (not distinguishing between malignant or healthy cells). But if sulfur-33 is present in the medium, it can have a noticeable impact because in the (n,α) reaction with 33S, with a cross section of 25 b, an energy of 3.5 MeV (500 times greater) is released locally. In addition to this, the biological effectiveness of such an energy deposition would be even greater, because it is close to the maximum for any kind of radiation, for the values of the linear energy transfer of the alpha particle emitted.

Moreover, if we irradiate a 33S-containing sample with 13.5 keV neutrons, these particles would produce the reaction without the need of previous collisions for losing part of their energy, therefore the sulfur activation would only happen in the trajectory of the original beam.

In addition to this, sulfur is a chemical element that has a wide presence in non-toxic organic compounds. This may increase expectations that sulfur containing compounds can be delivered to the tumour cells in a high concentration. Presumably, it will be necessary to enrich natural sulfur because of the low (0.75%) abundance of this isotope. This can be achieved by means of laser isotope separation methods, that been specifically applied for the enrichment on this isotope [11]. Sulfur-33 is currently available at enrichments up to 99%.

Another interesting property of this nucleus is that it is a stable isotope, and the product of the (n,α) reaction, the isotope Si-30, is also a stable one, so no radioactive material must be introduced or would be created. All these features makes of the use of S-33 a very attractive candidate for low energy neutron capture therapy.

3 MONTE CARLO SIMULATION OF SULFUR NEUTRON CAPTURE THERAPY

The radiation dose that can be delivered by means of the addition of 33S to a tumor can be estimated by means of a Monte Carlo simulation of neutron transport in a representative average human tissue recommended by the International Commission on Radiation Units (ICRU). This tissue has the following mass composition: H: 10.1174%, O: 76.1826%, C: 11.1000% and N: 2.60%.

The Monte Carlo simulation is performed with a code developed by the author, in which individual neutrons are sampled in the medium and suffer different interactions according to their relative probabilities. The main interaction processes are the elastic collisions with all species, (n,p) reactions with 14N and (n,α) reactions with 33S. Radiative capture from hydrogen has not been considered.

The interaction probabilities are determined by the energy dependent cross sections. These have been taken from the ENDF/B-VII [12] nuclear database and fitted to simple analytical forms, except for the reactions with 33S, for which experimental data of the resonances, have been employed by fitting Breit-Wigner formulae.

The absorbed dose at different points in the medium has been weighted by quality factors depending on the different secondary particles which produce the energy deposition, as a function of the linear energy transfer, according to the ICRP recommendations as it was done in a previous paper [10] to evaluate the equivalent dose. This weighted dose rate H, which can be used for estimating the biological effect of the neutron irradiation, has been evaluated from the energy deposition determined from the Monte Carlo simulation as a function of depth in a medium, in which alternating shells of normal tissue and tissue with a concentration of 10 mg/g (representing tumor for testing the possibilities of its uptake) have been modeled.

Figure 1: Estimation, by means of Monte Carlo simulation, of the equivalent radiation dose delivered to normal tissue (white zones) and to particular regions with a concentration of 10 mg/g of S-33, representing tumor (yellow zones), when all are irradiated by a monoenergetic source of 13.5 keV-neutrons as a function of depth.

The results are shown in Figure 1. It can be noticed a large enhancement of the neutron dose due to the sulfur.
presence (yellow shells) compared to the dose delivered to healthy tissue (white shells). This means that a substantial larger damage would be produced in the malignant cells, in case of selective sulfur tumor uptake. The dose enhancement, as it is produced mainly by primary neutrons from the beam, rapidly decreases, being negligible from a depth of a few centimeters. This means that the technique here studied can be useful only for non deep-seated tumors.

However, if a large part of the water in the medium could be replaced by heavy water (D_2O), then, because the elastic scattering cross section of deuterium is about 5 times smaller than for hydrogen, an important reduction of the background dose as well as an important increase in the advantage depth will occur. Replacements up to 23% without toxicity effects have been reported [13]. This strategy would have a critical impact in a sulfur neutron capture therapy, because the primary neutrons, which are those responsible for the enhancement effect of sulfur, would have an accordingly greater mean free path. Therefore, both the depth of the selective effect and the ratio between the equivalent dose at the sulfur sites respect to the tissue would accordingly increase.

4 SULFUR NANOPARTICLES

An interesting possibility for delivering a very large local concentration of ^{33}S to tumors is the use of enriched sulfur nanostructures. Recently they have been reported by Tenne [14] nanoparticles of MoS_2 and WS_2, which concentrate more than 7000 sulfur atoms in a three-layer octahedral of a 5 nm size, for example:

(MoS_2)_{94}@(MoS_2)_{1296}@(MoS_2)_{1936}

These fullerene-like nanoparticles, called inorganic fullerenes (IF), has been synthesized by different methods: from the reaction between their respective oxides with H_2S [14] to many other more recent techniques (see [15], and references therein).

Sulfur-IF mentioned above are similar in size to Au nanoparticles which have been reported to accumulate in tumors of tumor bearing mice giving concentrations of 7 mg/g with tumor/normal tissue ratio of 8:1 [16].

Because of the novelty of the present work, there are no studies up to date about tumor targeting with these structures. However, as they are produced with different sizes and shapes, it is expectable that could be tuned for the purpose of passive targeting. A necessary condition is fulfilled by WS_2 nanoparticles as they have been reported to be nontoxic [14]. The ability of sulfur for binding to organic compounds may allow surface functionalization for active tumor targeting.

Due to the 15 μm range of the alpha particle emitted in the reaction with ^{33}S, and the strong effect along its path, it is not necessary that the sulfur structure enters the cancer cell, being enough its presence at the surface or even at the tumor interstitium.

In addition to this, in this approach it is not necessary to break the sulfur nanostructure for tumor therapy, because the neutron capture and subsequent alpha particle emission happens even if the integrity of the nanostructure is sustained (even if it is coated), and there is no any drug leak or release required.

5 POTENTIAL APPLICATIONS

It has been illustrated the potential effect of sulfur addition in tumors for producing a selective effect from low-energy neutron radiotherapy. This is particularly interesting for the application to tumors resistant to conventional radiotherapy such as melanomas. However, the rapid decrease of the sulfur effect with depth would restrict its applications to superficial tumors, specially for those cases for which surgery is not recommended.

Nevertheless, the author has also tested the sulfur enhancement effect as an adjuvant for boron neutron capture therapy [17]. As both boron and sulfur addition are synergic, a combination of both strategies could be applied to malignancies for which both a superficial and deeper dose would be required, as in some head and neck cancers [18].

6 CONCLUSIONS

A selective local enhancement of neutron equivalent dose in tissue at the places where the isotope ^{33}S is added in a high concentration has been shown. It has been proposed to achieve the sulfur tumor accumulation by means of nanoparticles, in particular by means of inorganic fullerenes of MoS_2 or WS_2.

This results open a new line of research in which there are no previous results: enhancing tumor accumulation from a external sulfur-rich compound or structure. Its composition, features, functionalization, way of delivery, even the particular tumors object of study, are all open problems.

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