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Monte Carlo simulations of dose distributions with necrotic tumor targeted radioimmunotherapy

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HIGHLIGHTS

- A representative necrotic tumor geometry was created in the Geant4 Monte Carlo toolkit.
- Custom designed particle tracking was performed allowing for separation of deposited doses from different decay particles.
- Post-processing of the data included relative biological effectiveness of the different decay particles and effects of cell oxygenation.
- Physical and equivalent doses resulting from ^{177}Lu and ^{212}Pb were compared by means of dose maps and dose profiles.
- ^{212}Pb appears to be a promising isotope for necrotic tumor targeted α-therapy and will be pursued in future *in vivo* studies.

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ABSTRACT

Radio-resistant hypoxic tumor cells are significant contributors to the locoregional recurrences and distant metastases that mark failure of radiotherapy. Due to restricted tissue oxygenation, chronically hypoxic tumor cells frequently become necrotic and thus there is often an association between chronically hypoxic and necrotic tumor regions. This simulation study is the first in a series to determine the feasibility of hypoxic cell killing after first targeting adjacent areas of necrosis with either an α- or β-emitting radioimmunoconjugate.

1. Introduction

It has been shown in preclinical studies that DNA damage is more readily repairable in the absence of oxygen. If oxygen is available, it will react with the broken ends of the DNA and form organic peroxides that are not easily repaired by a cell (Moeller et al., 2007). Therefore, hypoxic tumors are more resistant to conventional low linear energy transfer (LET) and external beam radiotherapy (EBRT) (Harrison et al., 2002) due to increased repair efficiency in hypoxic tumor cells. This can lead to incomplete local tumor control and locoregional recurrence.

An alternative approach to increase the efficiency of tumor cell killing is by utilizing high-LET radiation, *i.e.* densely ionizing radiation, which is largely unaffected by the cell oxygenation level. The probability of causing complex, clustered DNA damage and DNA double strand breaks is much greater with high-LET radiation, as it has the ability to generate a high density of delta electrons along its passage through tissue and cause direct DNA damage. Since cells cannot usually repair multiple double strand breaks successfully, the oxygenation level of the tissue does not play as significant a role in cell survival.

Alpha particles are an example of high-LET radiation, which consist of two protons and two neutrons. Alpha particles produced by radioactive decay have a high kinetic energy (generally ≥ 5 MeV) and a sub-millimeter range in tissue. While external beam α-therapy has been proposed for many years, it is still not a common form of radiation therapy. This is primarily due to the cost and size of the accelerating equipment needed to generate α beams of therapeutic energies. Targeted alpha therapy (TAT) is a systemic and potentially a more cost effective approach for

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delivering high-LET radiation to tumor tissue. TAT consists of chelating an α-emitting radioisotope to an antigen-specific vector, commonly a monoclonal antibody (mAb), to form a radioimmunoconjugate (RIC). The RIC is then delivered throughout the body, congregating in the target tissue in larger densities than in other non-target tissues. Thus, TAT has the potential to treat both primary and metastatic disease, something not achievable with external beam therapy. For an extensive review of TAT, see Allen (2006).

Tumor hypoxia develops through two independent mechanisms. Chronic hypoxia, also termed as diffusion limited hypoxia, arises when tumor cells are too far from a nutrient supply (blood vessel) and receive only a limited amount of oxygen. This is a characteristic of tumor tissues where the vasculature grows in irregular and disjointed networks. Acute hypoxia, also termed as perfusion limited hypoxia, arises when a blood vessel becomes occluded, cutting off supply to the dependent tissue. This form of hypoxia is often transient, and does not play as significant a role in treatment failure as chronic hypoxia.

Chronically hypoxic regions in tumors are often closely associated with necrotic regions (Hoogsteen et al., 2012; Huang et al., 2012; Olive et al., 2001; Petersen et al., 2003; Santiago et al., 2010; Thomlinson and Gray, 1955). Moreover, there is some evidence, at least in glioblastoma, that tumor repopulating cells associated with chemo- and radio-resistance may occupy hypoxic or even necrotic niches in tumor tissues (Heddleston et al., 2010). Necrotic tissue is a conglomeration of dead cells that have not been cleared by the mononuclear phagocyte system (Al-Ejeh et al., in press). Recently, it has been found that over-expression of La/SSB antigen, an RNA-binding protein necessary for life, is associated with the malignant phenotype (Al-Ejeh et al., 2007a; Sommer et al., 2011a, 2011b). Necrotic tumor cells can be specifically targeted using the La antigen-specific murine monoclonal antibody DAB4 (also known as APOMAB®), which when radiolabeled acts as an *in vivo* marker of tumor cell death (Al-Ejeh et al., 2007b). Indeed, APOMAB® labeled with Indium-111 has been used to assess the effectiveness of chemotherapy in inducing tumor cell death in tumor-bearing mice, with prior cytotoxic chemotherapy treatment augmenting the antigen-specific uptake of DAB4 in necrotic tumor tissue with a tumor accumulation half-life of 4 h (Al-Ejeh et al., 2009a). In contrast, chemotherapy did not alter DAB4 uptake in normal, healthy tissues. A following study showed that targeted delivery of therapeutic β-emitting radionuclide Yttrium-90 (^{90}Y) via DAB4 mAb resulted in effective killing of tumor cells and tumor regression in the radiosensitive EL4 lymphoma tumor model (Al-Ejeh et al., 2009b). In contrast, radioimmunotherapy with ^{90}Y-DAB4 was not as effective in treating radio-resistant tumor models such as the Lewis Lung carcinoma model. Similar results have now been demonstrated in the same model using ^{177}Lu-DAB4 (Staudacher et al., 2014). A possible reason for this was the presence of radio-resistant regions of hypoxic cells which did not respond to the treatment.

In the current modeling study we investigate the possible improvement in equivalent dose delivery when the low-LET β-emitting isotope is replaced with a high-LET α-emitting isotope. Two isotopes were used for comparison: ^{212}Pb and ^{177}Lu. While ^{212}Pb decays via β^--decay, the two daughters (^{212}Bi and ^{212}Po) decay via α-decay. Therefore, ^{212}Pb is often considered to be an internal α-particle generator. On the other hand, ^{177}Lu is a β-emitter and may replace ^{90}Y because it has a higher maximum tolerance dose for equivalent outcome (Staudacher et al.,2014). This is likely due to lower tissue penetration (maximum tissue penetration 2 mm vs. 11 mm for ^{90}Y) and longer half-life (6.71 days vs. 2.67 days for ^{90}Y) resulting in greater absorbed radiation dose within the confines of the tumor with less radiation dose to non-target tissues.

The use of ^{212}Pb in targeted radionuclide therapy has a considerable history (Junghans et al., 1993; Kozak et al., 1986; Macklis et al., 1992; Yong and Brechbiel, 2011). Most recently ^{212}Pb has been applied to the treatment of malignant melanoma (Miao et al., 2005), in which ^{212}Pb–DOTA–Re(Arg^{11})CCMSH (a peptide analog of melanotropin) was used. While these studies led to the conclusion that TAT resulted in desirable therapeutic outcomes, researchers are yet to specifically target regions of hypoxia, where the high-LET radiation is anticipated to be highly efficacious.

In the current work we have used a Monte Carlo toolkit Geant4 (Agostinelli et al., 2003) to calculate ^{212}Pb and ^{177}Lu decay dose distributions around necrotic tumor geometries. In post-processing, we have modeled the radiobiological effectiveness (RBE) of emitted α-particles to calculate an equivalent dose. Furthermore, we have modeled the effect of tissue oxygenation on associated low-LET ($\beta-$ and γ-particles) cell killing ability. With these data, an assessment of the preferred radioisotope for necrotic tissue targeted RIC therapy is made.

2. Methods and materials

2.1. Radioisotope properties

A number of isotopes have been proposed as candidates for TAT. Aside from ^{212}Pb these include ^{211}At, ^{213}Bi, ^{225}Ac, ^{233}Ra, ^{149}Tb and ^{227}Th. See Dahle et al. (2011) for a review of radiobiological effectiveness of RICs employing α-emitters.

^{212}Pb is produced via a ^{224}Ra generator (Atcher et al., 1988) and has chemical properties suitable for labeling the DOTA chelator. The half-life of ^{212}Pb is relatively short for RIC therapy (10.6 h and 1 h for ^{212}Bi), which has both advantages and disadvantages in terms of biodistribution. The short half-life ensures that any RIC taken up in healthy tissue will decay quickly, limiting long term exposure. Conversely, the short half-life also means that some activity will decay before the circulatory system delivers the RIC to the target tissue. We believe that the half-life of ^{212}Pb provides a reasonable trade-off when considering these points.

The dual decay modes present with ^{212}Pb are particularly beneficial for necrotic tissue TAT. The most common decay chains involve 2 β^- decays and 1 α decay. This means that the highly localized dose resulting from α decay is complemented by the dose resulting from the farther ranging β decay. The primary decay schemes of both isotopes are illustrated in Fig. 1.

A possible concern when using RIC therapy with isotopes containing an extended decay chain is the disassociation of the daughter products from the targeting molecule following the initial decay. *In vivo* biodistribution studies with ^{212}Pb/^{212}Bi have found that there is no significant difference in uptake and retention levels between ^{212}Pb and ^{212}Bi (Miao et al., 2005). For our

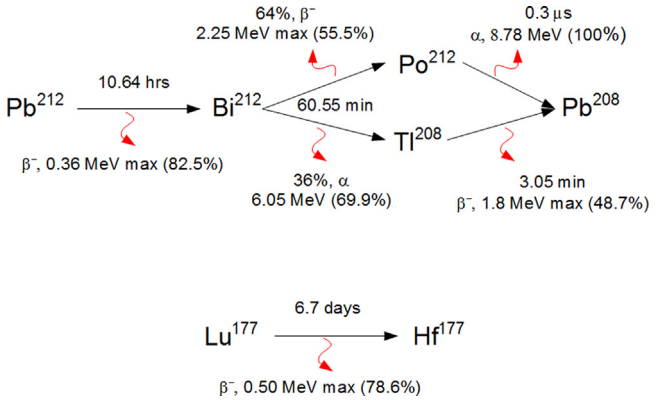

Fig. 1. Primary decay chains of ^{212}Pb and ^{177}Lu. The half-life for each radionuclide is displayed along with the decay mode, kinetic energy and branching ratio for the most probable decay mode.