Review paper

Metallic nanoparticle radiosensitisation of ion radiotherapy: A review

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ABSTRACT

The use of gold nanoparticle (GNP) and other metal nanoparticle (MNP) radiosensitisers to enhance radiotherapy offers the potential of improved treatment outcomes. Originally intended for use with X-ray therapy, the possibility of enhanced hadron therapy is desirable due to the superior sparing of healthy tissue in hadron therapy compared to conventional X-ray therapy. While MNPs were not expected to be effective radiosensitisers for hadron therapy due to the limited Z dependence of interactions, recent experimental measurements have contradicted this expectation. Key experimental measurements and Monte Carlo simulations of MNP radiosensitisation for hadron irradiation are reviewed in the current work. Numerous experimental measurements have found a large radiosensitisation effect due to MNPs for proton and carbon ion irradiation. Experiments have also indicated that the radiosensitisation is due in large part to enhanced reactive oxygen species (ROS) production. Simulations have found a large radial dose and ROS enhancement on the nanoscale around a single MNP. However, the short range of the dose enhancement is insufficient for a large macroscale dose enhancement or enhanced biological effect in a cell model considering dose to the nucleus from GNPs in the cytoplasm (a distribution observed in most experiments).

1. Introduction

Radiotherapy is a common modality used in the treatment of cancer. The use of heavy charged particles for external beam radiotherapy over the conventional 6–25 MV X-ray beams has the advantage of greater sparing of normal tissue. This is due to the nature of the energy deposition of heavy charged particles where most of the energy is deposited over a short distance prior to the particle stopping; known as the Bragg peak. The Bragg peak is particularly advantageous for treating tumours near the brain or spinal cord (i.e. base of skull chordoma), as well as the treatment of paediatric cancers. The objective of radiotherapy is to maximise the therapeutic ratio, i.e. the ratio of the probabilities that the tumour is controlled and of normal tissue complications. The majority of improvements in the therapeutic ratio for external beam radiotherapy have been achieved by increasing the conformity of the radiation beam to the tumour by improved treatment delivery techniques and treatment planning. Now however, the prospect for further improvements to conformity is limited. As such, alternative methods are being explored for improving the therapeutic ratio. One such method is the use of radiosensitisers, agents that increase the effect of radiation on tissue. Radiosensitisers can improve the therapeutic ratio by either having a higher concentration in the tumour tissue than the surrounding normal tissue or by having a greater effect in the conditions of the tumour tissue than in the conditions of the surrounding normal tissue.

A type of radiosensitiser frequently considered in literature are gold nanoparticles, i.e. particles of gold with a diameter of 100 nm or less. A variety of other MNPs have also been explored. GNPs were considered ideal radiosensitisers due to their high density and atomic number Z, in addition to good biocompatibility. GNPs were mostly expected to be effective radiosensitisers for radiation interactions with a strong dependence on Z, such as photoelectric and pair production interactions of x-rays. Another benefit of nanoparticles is their ability to passively accumulate in higher concentrations in tumour tissue than surrounding normal tissue when injected into the bloodstream. This occurs due to the enhanced permeation and retention (EPR) effect [1], where nanoparticles in the bloodstream can more easily permeate through the capillary wall of the blood vessels in tumour vasculature than normal vasculature. This occurs due to the fact that as a tumour grows it will recruit its own blood supply. However, the result of tumour

angiogenesis is rapidly grown vasculature that is haphazard in its structure. The tumour vasculature has leaky capillary walls that allow for nanoparticles to easily pass through the wall. This is aided by the irregular vasculature with shunts, dead ends and temporary occlusions. This preferential accumulation of GNPs in tumour tissue is what enables them to be effective at increasing the therapeutic ratio even without targeted delivery mechanisms.

Heavy charged particles such as protons, alpha particles and carbon ions primarily interact via ionisation. As these interactions only depend weakly on the atomic number of the material the radiation is passing through, it was not expected that GNPs would have a large macroscopic radiosensitising effect for proton and ion radiotherapy. However, this has been contradicted by recent experimental measurements.

2. Objectives and search strategy

The aim of this work is to collate the published works on experimental measurements and simulations of the enhancement of proton and heavy ion therapy by metallic nanoparticles. Key papers are summarised and discussed to provide an overview of experimental measurements of the enhancement of proton and ion therapy with metallic nanoparticles, indications from the experiments of the radiosensitisation mechanisms and the current state of simulations of the radiosensitisation.

A literature search was performed using the Scopus database, the search strategy and results for proton therapy are shown in Table 1. For these resulting papers the abstracts were reviewed and relevant papers were selected for further study. A similar search strategy was used for heavy ion therapy.

3. Experimental measurements

The first experiment that measured a radiosensitisation effect due to MNPs for cells irradiated with a proton beam was performed by Liu et al. [2]. In this experiment, the decrease in cell survival fraction due to the presence of GNPs was found for a variety of radiation sources, including protons. The surviving fraction was found using clonogenic assays of CT26 and EMT-6 cancer cells irradiated with a variety of doses from several radiation sources with and without 6.1 nm GNPs coated with polyethylene glycol (PEG). Most of the sources were X-ray sources with varying energy spectrums as these were expected to result in a large GNP induced radiosensitisation. However, as a proton source was available, EMT-6 cells with and without GNPs were irradiated with a 3 MeV proton beam. It was found that there was a 2–12% decrease in survival fraction of the irradiated cells depending on the irradiation time. This observed radiosensitisation effect is contrary to expectations from an earlier experiment by Wyer et al. [3], where a slight radioprotective effect was observed due to the presence of GNPs. However, the dehydrated plasmid target used, and issues with sections of the target being protected from irradiation due to limited beam range, make correlation of the observed measurements with a radioprotective effect in biological conditions difficult. While the results of the experiment by Liu et al. [2] were not statistically significant they motivated further experimental investigation and measurements of GNP radiosensitisation of cells irradiated with a proton beam.

Table 1
Scopus search strategy for nanoparticle enhanced proton therapy.

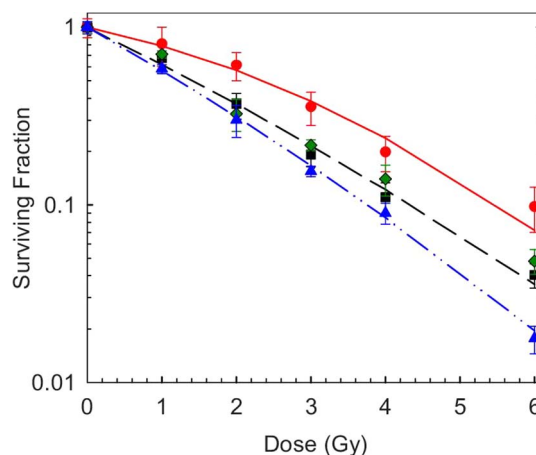| Search criteria	Remaining results
Proton OR "proton beam" OR "proton thera*"	511,267
Nanopart* OR nano*	18,085
Radiothera* OR "radiation thera*" OR "proton thera*"	136
Exclude non-English and conference papers	97

Fig. 1. Survival curves for cells not treated with GNPs irradiated using Co-60 (circles) and a proton beam (squares) as well as cells treated with the nano-phage only (diamonds) and GNPs and nano-phage (triangles) irradiated with a proton beam. Courtesy of Polf et al. [4].

3.1. Quantitative radiosensitivity measurements

With the experiment conducted by Liu et al. [2] providing an indication of a radiosensitisation effect due to GNPs irradiated with a proton beam further experiments were performed that more accurately measured the radiosensitisation

Polf et al. [4] measured the radiosensitisation due to GNPs irradiated with a proton beam in an in vitro experiment. In the experiment, DU145 human prostate carcinoma cells were irradiated with doses ranging from 0 to 6 Gy from either a Cobalt-60 irradiator at the depth of dose maximum, 5 mm from the radiation source, or a 160 MeV clinical proton beam with a 12 cm range and a 10 cm spread-out Bragg peak (SOBP) at 9 cm from the radiation source. Cells not treated with GNPs (untreated) were irradiated with both photon and proton sources while cells treated with 44 nm GNPs with an infiltrating phage nano-scaffold and the nano-scaffold alone were irradiated with the proton source. The surviving fraction of cells after the irradiations was determined by clonogenic assays. The survival curves are shown in Fig. 1. It was found that there was no significant difference between the survival curves of the untreated cells and the cells treated with the nano-scaffold only when irradiated with a proton beam. The survival curve was then fitted with the linear quadratic model for the untreated cells irradiated with the proton and photon sources and the GNP treated cells irradiated with the proton source. The model was then used to calculate the dose required for a 50% and 10% survival fraction for each of the irradiation cases. The Cobolt-60 irradiation data was used to calculate the relative biological effectiveness (RBE) for the proton irradiations with and without GNPs for the 50% and 10% survival fractions. It was found that there was an increase in RBE of 19% and 15% at the 50% and 10% survival fractions respectively due to the presence of the GNPs during the proton irradiation.

Kim et al. [5] performed an in vivo experiment to measure the radiosensitisation due to gold and iron nanoparticles for proton irradiation, following on from an initial investigation by Kim et al. [6]. Balb-c mice were injected with 10^5 CT26 cancer cells in either the leg or the flank one week prior to irradiation. Tests were performed to find the concentration of nanoparticles in the tumour, surrounding muscle tissue and the blood stream at various times after the administration of a nanoparticle solution via tail vein injection. It was found that the concentration of nanoparticles in the tumour and the ratio of nanoparticle concentrations in the tumour and healthy tissue were at a maximum 24 h after injection. As such, the mice were injected with 100 or 300 mg/kg body weight of either 14 nm GNPs or FeNPs one day prior to irradiation. The mice were treated with a single fraction from a