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Journal of Medical Imaging and Radiation Sciences xx (2018) 1-7

Journal of Medical Imaging and Radiation Sciences

Journal de l'imagerie médicale et des sciences de la radiation

www.elsevier.com/locate/jmir

Research Article

Multiphysics Modelling of Background Dose by Systemic Targeted Alpha Therapy

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Received 20 March 2018; revised 1 May 2018; accepted 13 June 2018

ABSTRACT

Introduction: Nontargeted molecules of alpha-immunoconjugate (AIC) intravenously injected in clinical trials of targeted alpha therapy (TAT) could be transported by convection and diffusion along with blood or lymphatic circulation.

Materials and Methods: A coupled model based on the Geant4 Monte Carlo microdosimetry technique and computational fluid dynamics was established. The transient drug delivery process and background dose to the cells along the pathway were investigated using the model. A mesoscale numerical simulation in a simple 2D capillary was performed to determine the transient toxicity of the alpha-immunoconjugate to the DNA of a targeted cell.

Results: The simulation results indicate that the multiphysics simulation is essential to improve the accuracy of TAT simulation.

Conclusion: In this work, a solution strategy for modelling AIC delivery in a blood vessel at a mesoscale level has been established. This work is the first to model different phenomena through the multiphysics simulation to investigate the whole picture of TAT.

RÉSUMÉ

Introduction : Les molécules non ciblées de conjugués d'immunothérapie alpha administrés par injection intraveineuse dans le cadre des essais cliniques de thérapie alpha ciblée (TAT) pourraient être transportées par convection et par diffusion en plus de la circulation sanguine et lymphatique.

Matériel et méthodologie : Un modèle couplé basé sur la technique de micro-dosimétrie et les calculs de dynamique des fluides. Le processus transitoire d'administration du médicament et la dose en bruit de fond ont été étudiés au moyen du modèle. Une simulation numérique à méso-échelle dans un capillaire 2D simple a été effectuée afin de déterminer la toxicité transitoire du conjugué d'immunothérapie alpha pour l'ADN de la cellule ciblée.

Résultats : Les résultats de la simulation indiquent que la simulation multi-physique est essentielle pour améliorer la précision de la simulation de TAT.

Conclusion : Cette étude est la première à modéliser différents phénomènes par la simulation multi-physique dans le but d'étudier l'ensemble de la TAT.

Keywords: targeted alpha therapy (TAT); alpha-immunoconjugate (AIC); Monte Carlo (MC); computational fluid dynamics (CFD); linear energy transfer (LET)

Introduction

Targeted alpha therapy (TAT) is a promising method of targeted radioimmunotherapy for the treatment of hematologic malignancies and can be extended to treat various solid cancers. Alpha-immunoconjugate (AIC) is the therapeutic radiopharmaceutical compound used in clinical trials of TAT [1]. Two essential elements of AIC must be present: a targeting antibody as a carrier that tends to attach to the molecules on the surface of a specific tumour cell, and emitter radionuclide that undergoes alpha decay to kill the targeted cell [2]. With the use of such a targeted high linear energy transfer (LET) radiation therapy, highly targeted treatment to microscopic tumour cells with AIC shows great potential for local and systemic cancer treatment. Research and clinical trials show that alpha-emitting radionuclides can kill targeted tumour cells effectively and efficiently and have fewer toxic

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https://doi.org/10.1016/j.jmir.2018.06.002

side effects compared with most conventional radiotherapy due to the selective discrimination between target and normal tissues and the fact that far less radioactivity is required to exhibit a cytotoxic effect [3–5].

During clinical trials, AICs can be systemically injected into the bodies of patients to kill cancer cells and cell clusters and prevent the cancerous cells growth and development by inducing apoptosis. The short path length of an alpha particle is assumed to result in more alpha particle hits on the targeted cancer cells and do less harm to normal cells and organs [6]. However, the tumour uptake of AICs is heterogeneous and nontargeted or unlabelled AICs with the alpha emitter after the intravenous injection could circulate within the blood, posting a background dose to the blood volume and vascular walls. In addition, decay daughters are expected to accumulate in dose-limited organs, such as the kidneys [7], consequently causing a high renal radiation dose. This radiation hazard might be a stochastic cause of secondary cancers observed in clinical trials [8]. It is therefore important to understand the potential background damage of alpha radiation to the patient before a subsequent dose is administrated.

The characteristics of a nontargeted alpha delivery process in a vascular environment after a systematic injection are very complex. The efficacy and toxicity of TAT is closely related to the blood circulation in tumour and normal vasculature, respectively. Some AICs injected intravenously may miss the biological target and could travel by convection and diffusion along with blood or lymphatic circulation, causing damage to the normal cells along its pathway. Furthermore, the bonding between the emitter and antigen tends to break due to the recoil energy. As a result, the decay daughters will travel a longer distance, resulting in damage to surrounding tissues or organs.

To better understand the transient toxicity of alpha particles to normal cells and provide a more effective guidance for clinical trials, a multiphysics modelling approach is essential to investigate this problem through the coupling of dose evaluation and hemodynamic models. Clinical trials found that conventional macrodosimetry models cannot explain the results of some experiments [9]. Consequently, a framework of microdosimetry that takes into account the stochastic nature of energy deposits at mesoscale or nanoscale levels is essential to evaluate the dose in cell nuclei from alpha particles based on the following reasons. The high energy of alpha particles is deposited in a short range and varies from cell to cell. This makes it very hard for an in vivo detector [10] to measure the actual dose experimentally. The alpha track length is at the micrometre level. This inevitably causes high LET to be deposited within a tiny volume. Stochastic behaviour of the cytotoxicity plays a role in nature for such a short range of action due to the small target volume. Finally, the heterogeneous tumour uptake leads to variable spatial microdosimetric distributions of AIC [9]. The activity distribution also changes spatially and temporally in the targets [11]. When the radiolabeled antibody distribution is nonuniform, techniques of dose averaging over volumes greater in size than the individual target volumes can become inadequate predictors of the biological effect. This makes the estimated absorbed dose in a tumour cell very misleading. Nevertheless, current microdosimetry analysis for systemic TAT still focuses on a stand-alone mode of simulation. The source of the emitter is assumed to be targeted on the tumour surface or penetrated internally and nontargeted AICs are treated as stationary [8]. The present work focuses on the investigation of the transient behaviour of the background dose caused by AIC in transit through coupling of the microdosimetry and hemodynamic models. To the best of our knowledge, this work is the first one to model different phenomena through the multiphysics simulation to investigate the whole picture of TAT. The contribution of this article indicates that the multiphysics simulation is essential to improve the accuracy and timeliness of dosimetric calculations for TAT.

Methodology of Multiphysics Modelling

To evaluate the background dose in clinical trials, a coupled multiphysics framework is established to integrate the drug delivery or hemodynamics model, dose distribution or microdosimetry model, and numerical damage model.

Within the framework illustrated in Figure 1, the drug delivery model tends to simulate the transport of nontargeted AICs or decay daughters. A pharmacokinetic profiling can be predicted by the model. The resulting location of AICs could be sent to a microdosimetry model to predict the dose distribution. The predicted deposited energy or dose can be sent to a nuclear damage evaluation model to predict the deformation of the blood capillary or collect the data from medical imaging. The displacement of the capillary geometry will be transferred to the drug delivery model. This new multiphysics coupling methodology takes all the physical phenomena occurring in clinical trials into account and provides a more accurate guidance to the clinician who is performing a series of clinical trials or doing preclinical studies for a particular patient. The influence such as vasculature damage to the drug delivery can be investigated by the coupled model.

Note that the prototype of a nuclear damage model based on a thermomechanical model is still under development. Therefore, only the code coupling between the drug delivery model and dose distribution model is tested in this work as indicated in Figure 1.

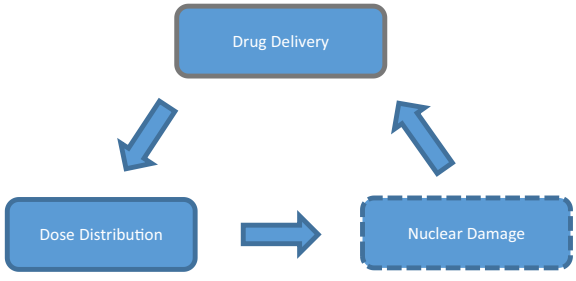

Figure 1. Coupling of multiphysics models.