Simulation of fractionated and continuous irradiation in photodynamic therapy: study the differences between photobleaching and singlet oxygen dose deposition

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Received: 21 September 2010 / Accepted: 8 March 2011 / Published online: 30 March 2011 © Australasian College of Physical Scientists and Engineers in Medicine 2011

Abstract This study aims to compare the continuous irradiation with fractionated irradiation for photodynamic therapy (PDT) of solid tumors with intraperitoneally administered 5-aminolaevulinic acid (ALA). Therefore, considering the complex physiology of solid tumors and in order to inform simulations well, we did experiments on Balb/c mice using non-invasive fluorescence spectroscopy to have a feedback of protoporphyrin IX (PpIX) concentration in tumor just before irradiation and during treatment. PDT simulations were performed based on delivery of 36 J cm$^{-2}$ total laser energy (630 nm) at the fluence rate of 40 mW cm$^{-2}$ either for continuous or fractionated illumination. Based on the calculated amounts of $^1$O$_2$ dose deposition and comparing these amounts with the $5 \times 10^{18}$ molecules cm$^{-3}$ threshold of reacting $^1$O$_2$, simulation results demonstrate that fractionated illumination with alternating light and dark periods of 60 s improved the tumor response further for PpIX-mediated PDT.

Keywords Photodynamic therapy (PDT) · Simulation · Fractionated light · Singlet oxygen · Photobleaching

Introduction

Photodynamic therapy (PDT) involves administration of a photosensitizer followed by the exposure of tumor to light of a specific wavelength. The light-excited photosensitizer interacts with ground state oxygen to form reactive oxygen species (predominantly singlet oxygen, $^1$O$_2$) which leads to depletion of tissue oxygen [1–5]. The photochemical reactions are cytotoxic and vasculotoxic and result in cytokine release, causing blood vessel stasis and further hypoxia. This initial hypoxic phase is reversible in the early stage of PDT, depending on fluence rate and fractionation [6–8]. However, the cumulative effects of the photochemical reactions lead to tumor necrosis. PDT efficiency depends on tissue photosensitizer concentration, light dose, fluence rate, and tissue oxygenation. Suggested strategies of improving tumor response include lowering fluence rate, fractionating light illumination, and increasing tumor oxygen tension during PDT [9, 10]. Splitting the light dose into fractions by pausing the light source for a certain time is supposed to enable reoxygenation of the irradiated tissue and may increase the generation of singlet oxygen thus enhancing PDT [11, 12]. A low-dose PDT is supposed to result in slower oxygen consumption and therefore allows oxygen to be continuously supplied compared with high-dose PDT [11–13]. Photodynamic efficiency of the fractionated irradiation in PDT is not currently understood in detail. The effectiveness of PDT using a fractionated light source varies greatly with the operating conditions, for instance, repetition rate, pulse width and pulse energy [14, 15]. Mathematic modeling is a useful method to discuss the differences in the efficacy between fractionated and continuous irradiation.

Predicting the therapeutic outcome of photodynamic therapy using fractionated and continuous irradiation requires knowledge of the amount of photosensitizer in target...