



Combined Photodynamic and Radiotherapy Synergistic Effect in Cancer Treatment



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Abstract

This review aims to increase the success rate in the treatment of cancer when both photodynamic therapy and radiotherapy are used together as a combined therapy and it is aimed to inform this direction.

Keywords: Photodynamic therapy; Cancer; Radiotherapy

Abbreviations: PS: Photosensitizer; PDT: Photodynamic therapy; ROS: Reactive Single Oxygen; UV: Ultraviolet; FRET: Fluorescence Resonance Energy; CT: Chemotherapy; IT: Immunotherapy; RT: Radiotherapy; SPECT: Single Photon Emission Computed Tomography; PET: Positron Emission Tomography;

Introduction

Photodynamic therapy (PDT) is a noninvasive method in cancer treatment. Nowadays, it has been used in clinical successfully to the treatment of skin, esophagus and lung cancer [1-3]. PDT occurs which a certain wavelength light is excited the photosensitizer (PS). As a result of this photo-excitation, reactive single oxygen (ROS) species form locally and cause cancer cell death [4-7]. When applied the light to PS is excited from ground state to short live singlet state and then converted triplet state with long live. Triplet state of PS can produce ROS via two different photochemical reactions; type I and type II. In Type I PS in the triplet state reacts with water or biomolecules and then generated free radicals, superoxides and peroxides. In type II, singlet oxygen which is very reactive occurs from reaction the triplet state and molecular oxygen in the tissue oxygen.

In PDT of cancer, PDT effect of organic PSs (e.g., phthalocyanine [8-11] Porphyrin [12-13], chlorine [14-16], etc.) is carried out with Type II mechanism, On the other metal ion-centered PS (Zn, Cu etc.) mechanism is Type I in the PDT [17] and semiconductors (e.g. CdSe [18], ZnO [19] etc.) and photocatalysts (e.g. TiO₂ [19], W₁₈O₄₉ [20] etc.) have been successfully used in treatment of specific tumors.

The excitation wavelength of most PSs is in the ultraviolet (UV) and visible (vis) region ($\lambda \approx 400-700\text{nm}$) [21]. When wavelength of light is below 800 nm, tissue penetration is poor [22]. It is possible to increase the success of PDT accessing internal organs or tumors in hypodermis by using optical fibers via endoscopy [23-24]. Moreover, owing to nanotechnology, in PDT systems, instead

of direct light excitation of PSs, their indirect light excitations are possible [25]. For example, some photovoltaic NPs transfer Fluorescence Resonance Energy (FRET) to PS. Thus traditional PDT's tissue penetration restriction may be able to overcome and efficiency of the method increases [26-29].

Although, the efficacy of PDT is increased by different methods, there are many new and successful studies with combination of chemotherapy (CT), immunotherapy (IT) and radiotherapy (RT). There is a synergetic effect enhanced by the combined treatment which improves the success of each method positively. As previously mentioned, in PDT ROS by photochemical reaction generates to destroy cancer cells and cause DNA damage [30]. Also, in RT free radicals are generated via high-energy ionizing radiation and create DNA damage. Consequently the main goal of both methods is to damage DNA. There is synergistic interaction between these two methods that may cause permanent cell death [31].

Currently, in cancer treatment radionuclides, radiolabeled compounds, X-ray, electron beams which can be classified as external and internal radiotherapy and these radiation sources widely used in clinical [32]. In RT the growth of cancerous cells is kept under control with ionizing radiation effect. To prevent of the recurrence of cancer before and after surgical removal of primer malign tumors, RT is used in the clinic. In monitoring of therapy response, radionuclide-based imaging techniques; Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) are commonly used [33-35]. In addition, these techniques also provide the detection of deep-seated tumors

and inform about the pathophysiology and pathobiochemical processes of the tumor. In literature apoptosis mechanism was carried out by using radiotracer and PS (64Cu-DOTA-biotin-ZnPcS2 and AlPcS2) in combined PDT and RT [36]. On the other hand, nuclear imaging and PDT is possible with combined some radioisotope/radiopharmaceutics and PS targeting metabolic actions such as hypoxia (¹²³I-IAZA/^{99m}Tc-HMPAO-PII) [37-38], vascular damage (^{99m}Tc-HMPAO-PII) [39], proliferation (¹⁸F-FL-ATP-S₁₀ (Na)) [40], membrane renewal (¹¹C-Choline-Pc4) [41] or mitochondrial resistance and glucose metabolism (Bolus 18F-FDG-PII and AlPcS/Bolus ¹⁸F-FDG-ADMP06/Bolus ¹⁸F-FDG-Anti-CD104-isothiocyanato porphyrin conjugate) [42-44]. In another PDT/RT combined treatment when NIR and X-ray on indocyanine green were applied during cancer treatments some favorable results were obtained. For instance the combined method, viability rate of MCF-7 cells was determined as 26% when only PDT was applied. When they were exposed only RT; the viability rate of MCF-7 cells was 84%. Whereas the viability rate of MCF-7 cells was found as 3% when both combined methods were used. It is observed that the combined treatment has favorable synergistic effect [45]. Besides the effective results of the combined treatment in cancer treatment, it is important that the side effects of light intensity and X-ray dose are minimized. In summary, multiple approaches for PDT/RT combined therapy have shown success synergistic effect on the treatment of cancer [46-50].

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