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Nanomaterial applications as radiosensitizer in radiation therapy for cancer treatment

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ABSTRACT

Treatment of cancer is done with three mode- Surgery, radiation therapy and chemotherapy. Preference of application depends on clinical indications. Among all three modalities, use of radiation therapy and combined with other modalities is popular due to its vast coverage area as well as effective marginal consideration for microscopic level. Nanomaterial's have unique properties such as enhanced permeability, superparamagnetism and retention effect which are well appropriate for application in radiation oncology. Radiosensitizer, a drug that makes tumor cells more sensitive to radiation with greater tumor inactivation. Nanoparticle enhances the effect of radiation by generating reactive oxygen species (ROS) or influence cell cycle. Nanomaterial's also have in diminishing the intercurrent damage caused by radiotherapy of malignant tumors. To make the tumors highly radiosensitive which are relatively resistive to radiation and to improve the therapeutic ratio of radiotherapy for better dose distribution for cancer treatment using nanomaterial, a review is carried out. A summary of application of nanomaterial's as radiosensitizers useful for radiation therapy modality for cancer treatment has been studies. Detail results and conclusion obtain from this study will discuss on during conference.

Key Words: Cancer, Radiosensitizers, Nanomaterial's, Radiotherapy.

INTRODUCTION

Radiation therapy as an important modality for treatment of cancer which uses high energy radiation to shrink tumors and kill cancer cells. Mainly X-rays, gamma rays, and charged particles are types of radiation which is used for cancer treatment. Application of physics using Biology gives the evaluation of a new field era known as Medical Physics. Therapeutic approach of Ionizing radiation generate various DNA damage and leads to radiation -induced cell death at target locations of lesions. Since cancer cells divide in an unregulated manner, they are more susceptible and prone to radiation-induced DNA damage (1-4). Cancer cells whose DNA is damaged beyond repair stop dividing or die. Today, more than 60% of cancer patients receive radiotherapy during their anti-cancer treatment (5), which is applied through various techniques, including external beam (electrons, protons, photons) and brachytherapy (internal therapy). Its mode of application depends on the clinical indications .Radioisotopes (radionuclide) emits energy from the nucleus and generates ionized atoms and free radicals to induce single strand cleavages in DNA. Radioisotopes applied in the clinical oncology include beta-emitters, like ^{186}Re, ^{188}Re, ^{166}Ho, ^{89}Sr, ^{32}P, and ^{90}Y, as well as alpha-emitters, like ^{225}Ac, ^{211}At, and ^{213}Bi (6). When used in vivo, beta-emitters have profound tissue penetration (20–130 mm) but low linear energy transfer, whereas alpha-emitters have limited penetration (50–80 μm) but a short half-life and the ability to inflict more damage to the cells.
There are different type mechanisms which show the elimination of radioisotopes in human body.

Dependence of whose basis on half-life and properties of radioisotope. Many of the radioisotopes undergo rapid clearance by the kidney. In particular, renal clearance is size dependent, for which size smaller than 5 nm will be excreted rapidly. Radioisotopes having molecular size suffer short circulation time in blood and are unable to achieve therapeutic effect. Another possible elimination process of the radioisotopes is by opsonization, by which a pathogen is marked for ingestion and eliminated by a phagocyte. However, through loading or conjugating of the nanocarriers, radioisotopes are able to escape from these biological elimination mechanisms. For example, the physical half-life of ^{89}Sr is 50.5 days, but it is cleared from plasma with an average half-life of 47 h. Nanoparticles such as liposomes, micelles, or polymeric complex are usually more than 10 nm, which greatly decreases the renal clearance and increases their half-life in blood due to the distinct pharmacokinetic properties and the increased size effect (7-9). Also, the nanocarriers can prevent opsonization through PEGylation. The presence of polyethylene glycol (PEG) on the surface of nanoparticles produces steric hindrance, which prevents the adsorption of opsonins. This particular characteristic of nanocarriers helps prolong the half-life of radiotherapeutic agents in blood. In a tumor-bearing mice model, the half-lives of ^{111}In- and ^{177}Lu- PEGylated liposomes in blood were 10.2 and 11.5 h, respectively; whereas the half-life of ^{111}In-DTPA in blood was extremely short as no longer than 2 hour (10).

In addition to the enhancement of circulatory half-life by the nanoparticles, the abnormal vasculatures in tumor may also help to extend the retention time of radiotherapeutics through the EPR effect. The abnormal tumor vasculatures possess aberrant branching components and leaky arterial walls, resulting from rapid proliferation of endothelial cells and a decrease in the number of pericytes. These abnormal vessels allow macromolecules, like nanoparticles, to easily penetrate the tumor via the circulatory system. Since the quick proliferation of tumor cells disrupts lymphatic vessels and makes them inefficient in drainage, the macromolecules that successfully perforate the tumor will be conserved inside the tumor with enhanced retention time. This is a perfect example of the EPR effect and also becoming a golden standard in drug delivery (11-12). For instance, Doxil, a PEGylated liposomal formulation of doxorubicin, is a nano-drug approved by Food and Drug Administration (FDA), showing a much slower clearance rate as 0.1 L/h compared with 45 L/h for free doxorubicin. Its AUC after a dose of 50 mg/m^2 is approximately 300-fold greater than that with free drug. Furthermore, considerable levels of doxorubicin are detected in both tumor cells and tumor interstitial fluids after Doxil administration. Moreover, the peak of drug concentration in tumors appears between 3 and 7 days post administration of Doxil, which reveals a much longer exposure time and a more enhanced concen-tration in

tumors than that after the administration of free doxorubicin (13).

Radioisotope-labeled nanoparticles have been developed to increase tumor accumulation and reduce undesired biodistribution. Li et al. applied the beta-emitter ^{64}Cu-labeled copper sulfide nanoparticles to suppress breast cancer. More than 90% of the nanoparticles were restricted in the tumor 24 h after the intratumoral injection. This radioisotope-labeled nanoparticle showed no obvious side effect, and once combined with photodynamic therapy, it helped to prolong the survival time of 4T1 bearing mice to 7.6 times longer than the control group and further reduced lung metastasis as well. Another example involved 50-nm lipid nanocapsules loaded with a lipophilic complex of ^{188}Re for internal radiotherapy of glioblastoma. The nanocapsules ensured maximum distribution of ^{188}Re within the brain 96 h after injection, compared with the solution of ^{188}Re-perrhenate. Therefore, it led to a noteworthy survival advantage in rat glioma models. Synthesized generation five dendrimers with NHAc-HPAO-PEG-FA and conjugated it with ^{131}I. Due to the modified folate ligand, the radioactive ^{131}I-labeled multifunctional dendrimers can be applied for single-photon emission computed tomography (SPECT) imaging and radiotherapy. The in vivo experiments demonstrated that the relative C6 xenografted tumor volume was only 8.78 times larger than the original one after 21 days, compared with 26.56 times for the control group (14).

Improving radiosensitizer delivery through nanomedicine

Nanoparticles application of known radiosensitizers can improve the delivery of these agents to tumor sites. For example, wortmannin is an inhibitor of phosphatidylinositol 3′ kinases and phosphatidylinositol 3′ kinase-related kinases such as DNA-dependent protein kinases. Preclinical results have shown that it is an effective radiosensitizer. However, its clinical application is limited due to less soluble ability, low stability, and high toxicity. The nanoradiosensitizer was demonstrated to be more effective than 5-FU on mice bearing KB cell xenografts and its MTD was three to five times greater than that of wortmannin (15). The same strategy was also used for DNA double-strand repair inhibitors, such as histone deacetylase inhibitor, which is an effective radiosensitizer to a variety of solid malignancies such as colorectal cancer and prostate cancer. The inhibitor enhances the response of tumor cells to radiation through the prolongation of γ-H2AX foci. However, it is inefficient at sustaining inhibition of DNA repair and highly toxic. Through encapsulation of nanoparticles, the inhibitors were released controllably for a durable effect. Conjointly, the radiosensitizers in the nano-formulation accumulated in tumors and had low distribution in normal tissue (16).

In addition to the use of drug-loaded polymeric nanoparticles as radiosensitizers, some nanomaterials with high atomic numbers (*Z*) also have the potential to become radiosensitizers because the dose absorbed by any tissue is related to the Z^2 of the material. For example, gold ($Z = 79$) nanoparticles are the most broadly used high *Z* nanomaterials for radiosensitizers. Xie et al. reported the application of ultrasmall glutathione-coated $Au_{29-43}(SG)_{27-37}$ nanoclusters as radiosensitizers. The nanosensitizers had high tumor uptake of about 8.1% ID/g at 24-h post injection. The inhibition of tumor by irradiation was significantly improved when the gold nanoclusters were administered. Meanwhile, the damage to normal tissues was negligible. Gadolinium ($Z = 64$)-based nanoparticles are another type of commonly used radiosensitizers. In one study, Gd-based nanoparticles were used, with 250 kV photon irradiation, to kill SQ20B cells for increased DNA breaks and shortened G2/M phase blockage. In a SQ20B tumor-bearing mouse model, combining the Gd-based nanoparticles with 10 Gy irradiation led to significant delay of tumor growth. Shi et al. designed a rattle nanoparticle with an up conversion nanoparticle core and a hollow silica shell as radiation dose amplifiers. A hypoxia-activated prodrug, tirapazamine, was loaded to overcome the oxygen dependent radiotherapy. The rattle nanoparticles had low cytotoxicity and high in vivo histocompatibility. As radiosensitizers, the up conversion nanoparticles showed significant suppression of tumor growth. In junction with tirapazamine, they were capable of killing hypoxic tumor cells through synergetic effects. Other inorganic nanoparticles like Y_2O_3 or $ZnFe_2O_3$ are undergoing investigations for their potential in radiotherapy (17-18).

Reduction of side effects through nanomedicine:
Side effects of radiosensitizers can be reduced by decreasing distribution of radiosensitizers or radio-isotopes in normal tissues and by controlling the release of these radiotherapeutic agents (19). The side effects of radiotherapy are often caused by unexpected damage to normal tissue. By using radiosensitizers, there are additive and synergistic advantages to the tumoricidal effect of radiation. Therefore, application of nanoparticle as radiosensitizer will allow less doses of radiation to achieve the same efficiency of killing cancer cells. However, the unspecific biologically distribution of radiosensitizers will lead to toxicity to normal tissues. Similarly, to radioisotopes, whose accumulation in normal tissues will cause direct injury. Nanoparticles were shown to have less penetration to normal vasculature and capillaries in various parts of the body, such as the skin, lung, and heart (20). Therefore, controlled and sustained release of nanoparticles into the tissue prolonged exposure to the agents, which is associated with a better effect and higher tolerance for normal tissues. This was demonstrated with the clinical use of Doxil, which dramatically reduced the cardiotoxicity of doxorubicin, without compromising its anti-tumor effect. Moreover, through chemical binding between nanoparticles and radiotherapeutic agents, the release can only occur under certain circumstances. It can either respond to the tumor microenvironment such as a low pH, redox or enzymes; or respond to an external stimuli's like temperature change or a magnetic field. Such strategies dramatically decrease the release of the agents in blood vessels or normal tissues, thereby potentially limiting the side effects (21).

Application of nanotechnology with combination of other therapies:
The combination of chemotherapy and radiotherapy is one of the most effective ways to improve clinical treatment of locally advanced cancers. The concept was proposed after the discovery of fluorouracil. The concurrent chemoradiotherapy outperforms sequential therapies because chemotherapy sensitizes the tumor cells to radiation-induced killing and treatment; meanwhile the concurrent therapy avoids the repopulation of cancer cells which will occur during the course of sequential treatment (22). However, the increased toxicity, which is the price to pay for the synergism, becomes the main shortcoming of the strategy and is the limiting factor in its application in clinical trials.

Use of nanomedicine in radiation Oncology, radiation therapy uses radioactive substances, such as radio-active iodine, that travel in the blood to kill cancer cells.

Nanoparticles can increase radio sensitivity of tumor cells. This effect was shown in vivo and in vitro, at kilovltage or megavoltage energies, in reviewed studies. Focus of studies was on gold nanoparticles. Radio sensitizing effects of nanoparticles depend on nanoparticles' size, type, concentration, intracellular localization, used irradiation energy and tested cell line (23)

CONCLUSION

This study shows that use of nanomaterials is increasing day by day in nanomedicine .In future, demand of nanoapplication as radiosensitizer will definitely increase in the field of radiation treatment for cancer.

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