MINI-REVIEW

Nanoparticles Promise New Methods to Boost Oncology Outcomes in Breast Cancer

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Abstract

Different types of treatment are available for patients with breast cancer, the most being radiotherapy, chemotherapy, hormonal therapy and combination therapy. Recently, nanoparticles have been emerging as promising agents for cancer therapy and are being investigated as contrast agents, drug carriers, radiosensitizers and also for hyperthermia effects. In this review the focus is on approaches for targeted treatment of breast cancer by combining nanoparticles, chemodrugs and radiation. The availble data suggest the possibility of increased roles for combined therapy, particularly by reducing the dose of each treatment modality, and consequently minimizing related side effects.

Keywords: Breast cancer - chemodrugs - doxorubicin - nanoparticles - radiation therapy - 2-deoxy-D-glucose

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Introduction

Breast cancer is the most frequently diagnosed cancer in women and is the major cause of cancer death among women worldwide (Elstner et al., 2002; Kaabinejadian et al., 2008; Loh et al., 2011). common treatment modality of breast cancer involve surgery, chemotherapy, radiation therapy, hormonal therapy, or combination therapy. Unfortunately, some limitation exists in this therapeutic methods such as radio-drug resistance, being special for certain type of cancer, undesirable injury to normal tissue surrounding of the tumor and etc; hold forth researchers attempt to improve methods of therapy to overcome at this limitation (such as use more sensitized compound, more localization of tumor, increase toxicity of chemodrug with reducing in side effect and etc.) and novel strategies require to boost the oncologic outcome (Aghaee et al., 2012; 2013; Jain et al., 2014).

Nowadays, nanoscience has emerged as one of the most hopeful application in medicine to enhance medical imaging output and also improve the rate of cancer therapy. In the field of cancer therapy most attention is investigated nanoparticles as a drug carrier, hyperthermia inducer, and also radiosensitizer agent (Selim and Hendi, 2012; Verma et al., 2013; El-Kassas and El-Sheekh, 2014; Jain et al., 2014; Nogueira et al., 2014).

Breast Cancer

The common risk factors for breast cancer includes: age (only, age at menarche and menopause, and age at first pregnancy), geographical variation, family history of breast cancer, hormonal mechanism, previous benign breast disease, radiation, life style, high fatty diet, oral contraceptive (McPherson et al., 2000; Aghaee et al., 2012).

In the field of medical imaging, common methods for diagnosis of breast cancer involved mammography, MRI, ultrasound and PET/CT (Yang et al., 2008).

In treatment of cancer after conservative surgery, radiation therapy is now of routine value to diminish regional tumor recurrence. In addition, closely 60% of all cancer treatments include radiation (alone or with surgery and chemotherapy). Furthermore, some limitation such as undesirable damage to normal, healthy tissue, presence of hypoxic and intrinsically radio resistance tumor cells limited the utilization of radiation therapy; moreover, chemotherapy immediately helps to radiotherapy by means of localization and sensitization of tumor with ionizing radiation (Cobb et al., 1996; Dwarkanath et al., 2001; Schwarz et al., 2008; Ghilotti et al., 2010; Aghaee et al., 2012).

In cancer chemotherapy, today's active researches are focused on taking advantage of biochemical differences between cancer cells and normal cell metabolism, such as energy metabolism to generated ATP for aerobic glycolysis from oxidative phosphorylation (Cheng et al., 2012). Enhance in the rate of glucose uptake and glycolysis as compared to corresponding normal tissue are characterization of malignant tumor(Warburg; Mentis et al., 2010). Studies suggest that in human cancer cell via metabolic oxidative stress, glucose deprivation can induce cytotoxicity (Ahmad et al., 2010).

2-Deoxy-D-Glucose (2DG) is a structural analog of

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glucose and is one of functional chemodrug that is best known as an inhibitor of glucose metabolism. In vitro and *in vivo* studies were shown that 2DG is cytotoxic and also is known as a tumor sensitizer to irradiation and chemotherapy, which help improve the rates of therapy and capable induce radiosensitization in human cancer cells by means of glucose deprivation (Ahmad et al., 2010; Aghaee et al., 2012).

2DG undergoes expedite diffusion into cell via glucose pathway. Inside the cell, 2DG alternation to 2DG-6-phosphate by hexokinase phosphorylation, and this formation of 2DG, 2DG-6-P, is not further metabolized by cell and the pentose phosphate pathway gets reduced, consequently 2DG-6-P accumulated in the cell until dephosphorylated by phosphorylase (Aghaee et al., 2012).

Doxorubicin (Dox) is one of the most toxic chemodrug by generating reactive oxygen species however the use of this drug limited for several side effects such cardiomyopathy (Takanashi and Bachur, 1976; Kong and Lillehei, 1998; Quiles et al., 2002). In a study of combining 2DG and Doxorubicin they conclude combination of 2DG\ Dox can be increase toxicity and reduce side effect of Doxorubicin with utilizing the low dose of Doxorubicin (Ahmad et al., 2010; Aghaee et al., 2013).

Nanoparticles in Medical Imaging as Contrast Agents

In the field of medical imaging, to enhance image contrast, nanoparticles were used as contrast agents. In a study on computed tomography (CT), 2DG labeled gold nanoparticles (AuNP) was studied as a contrast enhancement, and achieved significant contrast improvement in the A-549 liver cancer cell lines regarding to the unlabeled AuNP in multiple CT slice (Aydogan et al., 2010).

Other studies have also performed in the field of medical imaging such as magnetic nanoparticles for MRI improvement (Lu et al., 2009; Yen et al., 2013), silica nanoparticles for ultrasound imaging (Casciaro et al., 2010), improve sensitivity of PET signal (Nahrendorf et al., 2008) and gold nanoparticles for X-ray contrast enhancement (Hainfeld et al., 2014) and etc.

Nanoparticles as drug carrier

Recent studies were demonstrated that labeling nanoparticles with chemo drug not only improve the rate of therapeutic and enhance localization of the tumor cells but also reduce side effects of the chemodrugs (Mitra et al., 2001; Jain et al., 2014).

In the previous study experimental data shown that conjugating tio2 with Doxorubicin increase the Doxorubicin localization in tumor cells, improve anticancer activity and also reduce toxic side effects of the Doxorubicin chemo drug (Chen et al., 2011).

In another study of Paclitaxel as one of the highly toxic anti cancer drug with adverse effects in healthy tissue, they were used N-isopropylacrylamide/ vinyl pyrrolidone as polymeric nano drug carrier on the MCF7 breast carcinoma and B16F0 skin cancer cell line and show high therapeutic efficiency of nano loaded Paclitaxel by safe delivery to the cancer cells and sustained release action for the longest period of time and reduce the side effects (Yadav et al., 2014).

In vivo study in mouse models with curcumin loaded nanoparticles also resulted that curcumin-nanoparticles were effective to inhibit the growth of human lung cancer with little toxicity to normal tissue while the poor solubility of curcumin limits its further application in the treatment of cancer (Yin et al., 2013).

Nanoparticles Induce Hyperthermia

Hyperthermia widely used to induce apoptosis in many tissue and also to increase localized treatment in combination with chemo drug, radiation, radiofrequency waves, micro waves or ultrasound; but some limitation, such as lack of specifically for tumor tissue, has been restrict hyperthermia (Vernon et al., 1996; van der Zee et al., 2000; Wust et al., 2002; Issels et al., 2010).

In recent years, study on role of nanoparticles to resolve restriction of this problem have shown that magnetic nanoparticles such as iron oxide nanoparticles could be a useful technique for local hyperthermia treatment of cancer (Basel et al., 2012). In the same study, researchers applied magnetic Hydroxyapatite nanoparticles on a mouse model and demonstrated therapeutic effects *in vivo* with little toxicity at normal tissue (Hou et al., 2009).

Nanoparticles as Radiosensitizers

Less toxicity and also less injury to healthy surrounding tissues of the tumor and delivery high accuracy of damage with ionization radiation or visible light in cancer treatment, lead researchers to focus on developing photosensitizer such as quantum dots for superficial tumor with visible light and also nanoparticles as radiosensitizer with ionization radiation for patients with tumor in internal organs (Juzenas et al., 2008).

In a study on human prostate carcinoma cell line, bonding glucose with gold nanoparticles it was demonstrated that gold nanoparticles with or without bonding to glucose enhances radiosensitivity on prostate cancer cell line. Furthermore, there were significantly increase in cell uptake and also enhanced cell killing effect compared to gold nanoparticles without glucose bonding (Zhang et al., 2008).

In a research on linking gold nanoparticles with DNA scaffold it has been shown enhancement of radiosensitivity caused by an increased absorption of radiation energy by means of gold nanoparticles, also very few gold nanoparticles bounded to DNA molecule are needed to considerably increase the damage to this molecule by a 60 keV electron beam; however the role of high energy particles cannot be ignored in the study (Zheng et al., 2009).

In vitro study on the size of gold nanoparticles demonstrated that 1.9nm gold nanoparticles were uptaked by breast cancer cell lines and caused radiosensitivity with kV and MV photons in cell lines, but this radiosensitization is cell dependent. Also this effect was observed in MDA-

MB-231 cells, but not observed in DU-145 or L-132 breast cancer cell lines in spite of uptake take place in this cell lines. In addition, sensitization of MDA-MB-231 cells was shown at kV and MV photon energy and also with MV electrons which is inconsistent with prognostication from Monte Carlo simulation modeling (Cho, 2005; Jain et al., 2011).

Conclusion

The application of nanoparticles may an effective approach in induction of apoptosis and also preventing of tumor cell growth. On the other hand, the coating materials used for nanoparticle have demonstrated to enhance radiosensitivity on the tumor cells. The other mechanisms related for nanoparticles are producing local hyperthermia which resulting in tumor cell necrosis. Doxorubicin is considered to be the most effective agent in the treatment of breast cancer patients. Unfortunately, resistance to this agent and also severs cardiotoxicity are common, representing a major obstacle to successful treatment. 2-Deoxy-D-Glucose causes cytotoxicity in cancer cells by disrupting thiol metabolism while for Doxorubicin by generating reactive oxygen species. Research activity aimed towards developing and improving nanoparticle targeting systems has expanded tremendously in the past years with new ways of delivering the drugs to tumors as well as new types of drugs. Therefore, combined nanoparticle with anticancer drugs, 2-Deoxy-D-Glucose and Doxorubicin, can have the benefit of increased breast cancer cure by means of more localization chemodrug, enhanced radiosensitization, increased cytotoxicity in tumor cells, decreased the dose used for radiation and chemodrug and also decreased side effects of chemo-radiotherapy.

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