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Review

Breast cancer: early diagnosis and effective treatment by drug delivery tracing

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Abstract

Breast cancer is the most frequent cancer in women and it is the main reason of cancer-related deaths of women worldwide. Different types of breast cancer diagnostic examinations are also available, such as mammography, MRI, biopsy, ultrasound and molecular imaging. Radionuclide-based imaging methods including SPECT and PET are useful in early diagnosis and treatment of the cancer. The radiolabeling of chemo drugs with nanoparticles should be recommended from the standpoint of an early diagnosis and effective treatment of breast cancer.

KEY words: breast cancer, radiotracer, diagnosis, chemotherapy

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Background

Incidence of breast cancer, as the most frequent cancer in women, has globally increased in recent years. Therefore, breast cancer is the main reason of cancer-related deaths of women worldwide [1–3]. In 2014, an estimated 232,670 new cases of invasive breast cancer were expected to be diagnosed in women in the U.S.; along with 62,570 new cases of non-invasive (in situ) breast cancer. About 40,000 women in the U.S. were expected to die from breast cancer during 2014. Family history, gender, age, genetics, bad lifestyle are risk factors in breast cancer, especially gender (being a woman) and age (growing older) [1, 4–7].

Conventional treatments available for breast cancer include surgery, chemotherapy, radiation therapy, hormonal therapy, or combination therapy [1, 6]. The accurate and early non-invasive detection of malignant disease is an important factor in the treatment and prognosis of a cancer patient [8]. Different types of breast cancer diagnostic examinations are also available, such as mammography, breast MRI, biopsy, ultrasound and molecular imaging. Early detection of the disease is a key to beat breast cancer and improve the chance of treatment successful at early stages. However, early detection will not prevent breast cancer, but it can help find when the probability of successful treatment is the greatest [6].

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Significant improvement in diagnosis and therapeutic efficacy can be achieved only by developing effective approaches based on a comprehensive understanding of the molecular mechanisms of tumor metabolism [9]. Many studies show that being aware of the precise pathway molecular mechanisms in the term of cellular diagnosis in initial stages of the growth of a tumor could have a significant impact in successful treatment. Molecular imaging may provide a non-invasive assessment of biological and biochemical processes in living subjects [9–11].

Molecular imaging is now extending the applications of imaging in drug discovery and development in the initial stages of clinical trials and has the potential to considerably accelerate the treatment and diagnosis process [10–12]. Another important application of the technique in the area of diagnosis and treatment of cancer is the localization, staging, monitoring the response to treatment, making the pathologists cancer [9]. Nuclear imaging devices, such as PET and SPECT scans uses radioactively tagged tracer molecules to create functional images on the biochemistry or physiology of the subject (e.g. by chemotherapeuticals) [13, 14]. Nuclear imaging diagnosis modalities play also an important role for conducting research on the biology of human diseases and developing new treatment approaches.

Chemotherapy for breast cancer

Chemotherapy is the use of anti-cancer drugs as a systemic treatment to treat cancer [6, 15–17]. Chemotherapy modalities adjuvant therapy and neoadjuvant chemotherapy chemotherapeutics delivered after and before surgery, respectively [6, 15]. Many types of chemotherapy drugs are used to treat breast cancer that works in different ways and can be given in different combinations [15, 16]. Some drugs that are used in together includes Cy-

clophosphamide (Cytoxan), Doxorubicin (Adriamycin) or Epirubicin (Ellence), 5-fluorouracil (Adrucil), Methotrexate (Rheumatrex), Paclitaxel (Taxol) or Docetaxel (Taxotere), Herceptin and 2-deoxy-D-glucose (2DG) [1, 17]. A number of previous studies have shown that combination chemotherapy is the most effective treatment regimens based on just one drug [16–18]. This is because the different drugs act in slightly different ways, so together they increase their ability to kill cancer cells and by having a potentially greater impact induce the less severe side effects [15, 17].

Doxorubicin (DOX), as an anticancer drug anthracycline antibiotic with potent antineoplastic has effective properties against a wide variety of malignancies, such as non-Hodgkin's lymphoma, acute lymphoblastic leukemia and is also considered as the most effective drug in the treatment of breast cancer [12, 19, 20]. The planar aromatic chromophore portion of doxorubicin interact with topoisomerase II by inhabitation of normal function of the enzyme which hinders relegation of the DNA strands and ultimately induces irreversible DNA breaks [12, 19–21]. Despite of the effectiveness of chemotherapy by doxorubicin, the therapeutic dose in a single application causes severe side effects, especially on myocard [19].

The glucose analog, 2DG, is clinically proven an inhibitor of glycolysis and preferentially accumulate in cancer cells. 2DG is an anti-cancer drug also for breast cancer which has the ability to poison the cells *in vitro* and inhibits the tumor growth *in vivo*. This anti cancer also considered as an ideal adjuvant for enhancing the efficacy of chemotherapy in the treatment of the drug-resistant cervical cancers [1, 19, 22]. Enhancing the cytotoxicity of cisplatin and doxorubicin is one of the abilities of 2DG [1, 22].

Many chronic side effects of Doxorubicin has limited the prescribed dose for a patient [22]. According to the results of previous studies, the combination of 2DG and doxorubicin have a significant cell killing capability in breast cancer cells [1, 22].

Nanoparticles for therapy breast cancer

Nanoparticles (NPs) were well defined in character and size with the dimensions from 1 nm to 100 nm that can be prepared using different targeting agents in the design of tumor-targeting carriers, resulting in the enhanced diagnosis and/or therapy of cancer [23–25]. Different nanoparticle types contain Iron Oxide, Gold, Silver, Carbon Nanotubes, Quantum Dots, polymer- or liposome-based [23].

One of the greatest challenges is defining the ideal targeting agent or agents to selectively and effectively transport nanoparticle structures in cancerous tissue [26, 27]. Generated smart agents with drug delivery and molecular targeting capabilities, developed by loading nanoparticles using antibodies is also accounted a therapeutic approach for breast cancer therapy [26, 27]. Doxorubicin has been framed with a liposome delivery system into nanoparticle, it was shown that the compound preserves the efficacy of the drug and reduces cardiac toxic effects [28]. Encapsulated dextran–doxorubicin conjugate using chitosan nanoparticles as a carrier have been used in tumor targeted delivery. After 4 weekly injections, intravenously, in mice, the tumor volume of those treated with the encapsulated conjugate being only 60% of treated with the conjugate alone [29].

Conjugates of 2DG and poly (ethylene glycol)-co-poly (trimethylene carbonate) nanoparticles (DGlueNP) of ~71 nm diameter have been developed as a potential dual-targeted drug delivery system in glioma treatment. *In vivo* fluorescent image indicated that DGlueNP had high specificity and efficiency in intracranial tumor accumulation. After intravenous administration at a dose of 100 mg/kg blank DGlueNP per day for a week, acute toxicity to hematological system, liver, kidney, heart, lung and spleen in mice, in initial safety tests, was not shown. In comparison with nonglucosylated nanoparticles (NP), a significantly higher amount of DGlueNP was internalized by RG-2 glioma cells through caveolae-mediated and clathrin-mediated endocytosis [30].

2-DG conjugated meso-2,3-dimercaptosuccinic acid coated γ-Fe2O3 nanoparticles were incubated with Hela cells for 4, 8 and 12 hours, the 2-DG-conjugated nanoparticle showed a significant uptake in cells compared to the non-targeted counterparts [31].

Early detection of breast cancer in molecular stage

Radionuclide-based imaging methods including SPECT and PET, are useful in early diagnosis and treatment of the cancer in the initial stages of clinical testing [12, 23]. The technique can be used in early detection of a wide variety of malignancy, also breast cancer. Some radioisotope for SPECT imaging involves [^{99m}Tc]-technetium, [^{111}In]-indium, [^{67}Ga]-gallium, [^{131}I] iodine. ^{99m}Tc is the most commonly used radioisotope because of its ideal physical properties, such as its short half-life (approximately 6 h) and with γ-photon emission of a single energy at 140 keV. These properties are favorable from the point of view of both effective imaging and patient safety. In addition, it can be also easily produced by a generator system (99Mo/99mTc generator) [14, 23, 24].

Considerable candidates for improved molecular imaging are NPs because of their unique size and physical properties. These properties allow bio-interaction and visualization of biological events enhanced at subcellular levels [24].

Methotrexate (MTX) is an important anticancer agent for the treatment of a variety of malignant tumors such as breast cancer. MTX and BN peptide analogs radiolabeled with ^{99m}Tc for tracing the approach. *In vitro* cell-binding and internalization on breast cancer and prostate cancer cell lines have shown a high affinity and specificity. In addition, *in vivo* the radio-conjugate approach displayed a significant internalization (values ranged between 19–35%) into the tumor cells. The combination of favorable *in vitro* and *in vivo* properties may render ^{99m}Tc-MTX-BN as a potential candidate for the targeted imaging and eventually for radionuclide therapy (when labeled with an appropriate radionuclide) [32].

In a study, Diethylenetriaminepentaacetic acid (DTPA) and deoxyglucose (DG) radiolabeled with ^{99m}Tc. Cellular uptake assay *in vitro* was performed using a human mammary cancer cell line. Biodistribution was also calculated as percentage of injected dose per gram of wet tissue *in vivo*. Tumor-to-non-target tissue ratios were calculated from the corresponding tissue concentrations. [^{99m}Tc]–DTPA–DG imaging was obtained with a dual-head gamma. The results have shown a rapid blood clearance of the complex [^{99m}Tc]-DTPA-DG with the main route of clearance via the kidneys and also suggested a potential imaging agent in the detection of the tumor [8].

In another study the bovine serum albumin nanoparticles (BSANPs) and pheophorbide-a (PH-A) were labeled with ^{99m}Tc. The biodistribution of ^{99m}Tc-PH-ABSANPs in healthy female rats showed high uptake in the breast and uterus. ^{99m}Tc-PH-A-BSANPs were taken up to human breast adenocarcinoma cell line (MCF-7). In conclusion, ^{99m}Tc-PH-A-BSANPs are suitable for imaging and drug delivery in the field of nanomedicine, and may be used as site-specific tumor imaging agent [21, 33].

Radiolabel doxorubicin with Technetium-99m as a scintigraphic marker of high DNA turnover/intercalation in malignant cells. Blood kinetics was studied in an adult rabbit after intravenous (dorsal ear vein) injection of the radiopharmaceutical and the biodistribution, and the excretory route of ^{99m}Tc doxorubicin was studied in male Wistar rats. Ehrlich ascites tumor (EAT) cell line was injected subcutaneously into Balb/c mice. Scintigraphy of tumor-bearing mice was performed after intravenous injection of ^{99m}Tc-doxorubicin into the tumor-bearing mice. This scintigraphic approach, therefore, could be a powerful tool for cancer detection at early stage especially in developing countries [21]. The doxorubicin-loaded NPs radiolabeled by ^{99m}Tc have an effective drug targeting with a potential clinical applications such as early detection [34]. Tc-99m sestamibi has good physical characteristics for scintimammography, and consequently high diagnostic accuracy. Moreover, this technique represents real advance in the noninvasive management of patient with early stage breast cancer [35, 36].

Conclusions

Molecular imaging tools including SPECT and PET are highly effective, safe and painless diagnostic imaging modality.The early detection of malignant diseases is an useful assessment to select most effective treatment. Molecular imaging is commonly used in diagnosis and treatment of breast cancer. One of the mostpromising research areas is investigational diagnostic use of nanoparticles and radioactive substances. Nanoparticle imaging with MRI, optical and nuclear medicine techniques have also been applied on a research and clinical level. Radiolabeled nanoparticles have proven to be promising tools in the diagnosis and therapy of malignant processes.

Chemodrugs such as 2DG and Doxorubicin in combination with NPs when labeled with radiotracer such as ^{99m}Tc can improve an efficiency of diagnostic and treatment of breast cancer. A multifunctional system of this nature could improve the overall effectiveness of cancer therapeutics.

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