Commentary

Positron-emitting ^{18}F-2-deoxy-2-fluoro-D-glucose: potential 'hot' new therapy

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Abstract

Preclinical studies suggest that ^{18}F-2-deoxy-2-fluoro-D-glucose (^{18}F-FDG) kills breast cancer cells without significant marrow toxicity or parenchymal toxicity. Radiation dose calculations estimated from fluorodeoxyglucose positron emission tomography images in women with metastatic disease indicate that ^{18}F-FDG should be a feasible and safe option in humans. Because the available radiotherapeutic agents, strontium 89 and samarium 153 provide palliation to a limited population of women with bony metastases, new radiopharmaceutical agents with broader applicability are needed. The development of ^{18}F-FDG as the first positron-emitting radiotherapeutic has the potential to be an innovative treatment, not only in osteoblastic disease, but also in osteolytic disease and in soft tissue metastases.

Keywords: breast cancer, ^{18}F-2-deoxy-2-fluoro-D-glucose, positrons, therapy

Moadel and colleagues have explored the potential use of ^{18}F-2-deoxy-2-fluoro-D-glucose (^{18}F-FDG), a positron-emitting agent, as a radiomolecular therapy in the management of advanced breast cancer. In two separate transgenic mouse models of breast cancer, they demonstrated the feasibility and the efficacy of ^{18}F-FDG as a treatment for metastatic disease. After ^{18}F-FDG treatment, the mammary glands were removed from the mice and were examined for evidence of tumor cell kill. Apoptotic changes were observed in small tumors (<1 cm) and necrosis was observed in larger lesions. To determine what the radiation dose would be in patients with breast cancer, the authors extrapolated the preclinical information to the fluorodeoxyglucose positron emission tomography (FDG PET) images from five women with widely disseminated breast cancer. The dose of radiation delivered was calculated according to the standard uptake value at the site of disease. Moadel and colleagues conclude that ^{18}F-FDG therapy could be safely administered to these individuals without the risk of significant red marrow toxicity [1].

Samarium 153 and strontium 89 are the only radiopharmaceutical agents to date that are used to treat women with breast cancer. Both are approved for the management of bone metastases, which develop in more than 70% of women with advanced breast cancer and are the source of significant morbidity. Both agents are most effective in patients who have diffuse osteoblastic disease and who are also treated with external beam radiation to areas of significant tumor burden. These two available agents appear to be equivalent in efficacy, although samarium 153 may produce less myelosuppression [2,3]. Samarium 153 and strontium 89 may also provide meaningful but short-lived palliation of bone pain. However, bone metastases are rarely the sole site of metastatic disease. An obvious advantage of ^{18}F-FDG is that it could be used to treat both skeletal disease and extra-skeletal disease.

Presumably if a lesion can be imaged by FDG PET then it can also be treated with ^{18}F-FDG. Because FDG PET has been shown to be superior to conventional radiography, the Food and Drugs Administration has approved FDG PET imaging in the staging of advanced breast cancer and in the assessment of response to treatment [4–8]. In women with locally advanced breast cancers, FDG PET

^{18}F-FDG = ^{18}F-2-deoxy-2-fluoro-D-glucose; FDG PET = fluorodeoxyglucose positron emission tomography.

may be more accurate than computerized tomography in identifying internal mammary and mediastinal nodes [9].

Similar to multiple myeloma, the bone lesions produced by breast cancer may be purely osteolytic. In such instances the serum alkaline phosphatase and bone scintigraphy may be entirely normal. FDG PET may be more effective than conventional radiography and bone scintigraphy in identifying osteolytic disease [10]. If this is the case ^{18}F-FDG may prove superior to samarium 153 and strontium 89. If FDG PET identifies disease with greater resolution than conventional radiography, then presumably ^{18}F-FDG may also be able to control more disease.

With our present resolution capabilities, FDG PET is unlikely to supplant surgery for staging newly diagnosed breast cancers. Sentinel node mapping appears to be superior to FDG PET staging of the axilla as FDG PET is unable to identify micrometastatic disease and small amounts of macrometastatic disease in the axilla. It seems unlikely at this time that ^{18}F-FDG will have a role in the treatment of early stage disease [11].

The uptake of ^{18}F-FDG varies according to the tumor histology, the microvasculature, the proliferative rate, the tumor cell density and the degree of necrosis. ^{18}F-FDG uptake requires the tumor to have the ability both to incorporate glucose into the cell and to phosphorylate glucose to glucose-6-phosphate [12,13]. Breast cancer is a heterogeneous disease with distinct natural histories defined by histologic type, by tumor grade, by the presence or absence of hormone receptors and by the her-2 expression. Recognizing the variability of the disease, it is not surprising that ^{18}F-FDG uptake varies from patient to patient and may even vary from metastasis to metastasis in the same patient [12,14]. Because the delivered dose of radiation is calculated by the standard uptake value, the differences in FDG PET uptake have implications for determining the radiation dose at different sites following ^{18}F-FDG therapy.

Even in the palliative setting, the toxicity of treatment must be minimized. At present, most of the women who receive strontium 89 or samarium 153 already have some degree of marrow compromise as a result of prior cytotoxic therapy, external beam irradiation and tumor infiltration. Even small doses of radiation to the red marrow may impact blood counts.

Moadel and colleagues acknowledge that uptake of ^{18}F-FDG by the brain is "impossible to avoid" and provides a dose of 570 cGy [1]. Similarly muscle, both skeletal muscle and cardiac muscle, may incorporate ^{18}F-FDG. The muscle uptake of ^{18}F-FDG may be decreased by the patient fasting or by administering benzodiazepines. Whether corticosteroids will decrease edema and inflammation in the brain will need to be determined.

More than 80,000 women each year are diagnosed with metastatic breast cancer. In this setting the goal of intervention with chemotherapy and hormonal therapies is to provide palliation. After hormonal therapies have been exhausted, sequential single-agent chemotherapy is advocated. Even combinations of cytotoxic chemotherapy do not appear to alter patient survival. The addition of the humanized antibody to the her-2 protein Herceptin has recently been shown to improve survival when it is co-administered with first-line chemotherapy [15].

Newer agents that are targeted at unique aspects of tumor biology are the hope for the future. These targeted agents are often used in conjunction with conventional agents. ^{18}F-FDG will possibly be used in combination with other systemic therapies. The refinement of ways to target radiation therapy to the tumor is an important avenue to pursue. Moadel and colleagues are to be congratulated for taking the steps to develop a positron-emitting agent for use in the breast cancer arsenal.

Competing interests

None declared.

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