Smaller Agents for Larger Therapeutic Indices: Nanoscale Brachytherapy with ^{177}Lu-Labeled Gold Nanoparticles

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It is estimated that more than 240,000 cases of breast cancer will be diagnosed in the United States this year (*1*). Locally advanced breast cancer (LABC) is found in women with stage II or III cancers and generally has a poorer prognosis than tumors diagnosed in earlier stages. Current standard-of-care treatments for LABC include neoadjuvant chemotherapy, hormonal therapy, and surgery (*2*). The use of neoadjuvant treatments may, in some instances, reduce the primary tumor size such that breast-conserving surgery may be a viable option over a full mastectomy, thereby greatly improving the quality of life for these breast cancer patients.

In this issue of *The Journal of Nuclear Medicine,* Yook et al. presented a novel neoadjuvant treatment for LABC, involving the use of intratumorally injected gold nanoparticles (AuNPs) labeled with the radiotherapeutic isotope ^{177}Lu (half-life [$t_{1/2}$], 6.7 d; maximum β-energy, 498 keV) (*3*). Using mice with human breast cancer MDA-MB-468 xenografts, the authors described the effects of localized internal radiotherapy on the inhibition of tumor growth. ^{177}Lu-labeled AuNPs targeted to the epidermal growth factor receptor using panitumumab, as well as the same constructs without active targeting, were used. In both cases, complete survival of the mice out to 120 d was observed. Emboldened by these results, the authors described a theoretical treatment plan for LABC patients using these agents that may enable a pathologic complete response.

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Brachytherapy (BRT) has found applications in breast cancer as part of postsurgery partial breast irradiation for lumpectomy patients (*4*), rather than the preoperative use proposed in this study. It has been shown that recurrence of breast cancer most often occurs near the previously resected area, indicating microscopic tumor growth that was not removed (*5*). Thus, the use of a radiotherapeutic treatment in and around the lumpectomy bed is thought to help eliminate some of the infiltrating disease. External-beam treatments, using either photon radiation after surgery or electrons intraoperatively, have formed the backbone of these treatments traditionally (*6*). However, with improvements in BRT techniques, the highly localized dose profiles of these agents have recently found applications in breast cancer patient management. Whether the ^{177}Lu-AuNPs in this study qualify as BRT agents, in the conventional sense of the word, is up for debate. Although standard BRT agents use a solid encapsulation of radioisotopes such as ^{192}Ir ($t_{1/2}$, 74 d; average β-energy, 0.38 MeV), ^{125}I ($t_{1/2}$, 59.4 d; average β-energy, 0.028 MeV), and ^{90}Y ($t_{1/2}$, 64.1 h; maximum β-energy, 2.28 MeV) with sizes on the order of a centimeter, the agents in this study are approximately 30 nm in diameter and conjugated with ^{177}Lu (*7*). Traditional BRT agents are placed in the tumor volume using a catheter, whereas these ^{177}Lu-AuNPs were injected intratumorally in saline.

Intratumoral injections have been used in several clinical trials in oncology (*8–10*), often with gene therapy and viral agents. However, internal radiotherapy with intratumorally injected agents has not seen much clinical translation. Often, radiosensitizers may be injected intratumorally and combined with external-beam radiotherapy. Similarly, AuNPs are often used to sensitize tissues to radiation (*11*), rather than to provide a vehicle for the radiation itself, as investigated in this study. The intratumoral injection technique used here helps to alleviate the normal-tissue toxicity concerns that are found with many inorganic nanoparticles when administered intravenously, as they often accumulate in the liver and spleen (*12,13*). In addition, the lower normal-tissue uptake found here increases the therapeutic index of these treatments significantly over traditional internal radiotherapy treatments.

Although the use of an intratumoral technique certainly relieves concerns about normal-tissue toxicity, the treatment itself may also suffer from the resulting heterogeneous distribution in the tumor. This has been one of the downfalls of standard BRT, and further investigation on the impacts of such heterogeneity is warranted (*14*). In this study, the ^{177}Lu-AuNPs obviously exhibit some diffusivity, evidenced by the accumulation in other normal tissue. However, more detailed evaluation of the distribution in the tumor itself is needed before future clinical translation. Because this is a preclinical study, the tumor volumes found here are much smaller than those that would be found in a clinical case. Thus, the impact caused by heterogeneity would only increase in potential clinical studies. The use of ^{177}Lu, with an approximately 2-mm β-range, will smoothen the dose distribution to a certain extent. However, in the case of LABC, tumor diameters of at least 5 cm will certainly require more than one injection of the agent. Perhaps the conjugation of AuNPs with other radioisotopes (such as ^{90}Y; maximum β-range, 1.1 cm) will reduce the heterogeneity of radiation dose delivered in larger tumor volumes.

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One initially unexpected finding of this study is the similar performance of targeted (using panitumumab to target epidermal growth factor receptor) and nontargeted ^{177}Lu-labeled AuNPs. Both agents led to complete survival of treated mice out to the 120-d endpoint of the study, with similar absorbed doses to the tumor (~30 Gy for targeted and 22 Gy for nontargeted, respectively). Targeted nanoparticles had a greater retention in the tumor but with a more heterogeneous dose distribution due to specific binding. No significant difference was found in normal-tissue accumulation between the two agents, which then begs the question—is there a benefit to the targeted agent for this scenario? Nontargeted agents are much easier to implement in the clinic, and, as seen in Figure 4 in the article by Yook et al. (*3*), the increased diffusivity of the nontargeted ^{177}Lu-AuNPs may allow for smoothing of the dose distribution, theoretically improving long-term impacts. Indeed, the authors concluded that "nontargeted gold nanoseeds . . . would broaden the approach to tumors expressing many different phenotypes."

Intratumoral injection of radiotherapeutic agents, in theory, has promise in many cancer sites. Anywhere that traditional BRT is performed can also be accessed for intratumorally injected BRT agents as well. However, the relative simplicity of intratumoral injection in a xenograft model is not mirrored in the clinical setting—image guidance will likely be required for proper injections to be performed, because clinical tumors are normally not as superficial. Cine MRI, ultrasound, or fluoroscopic techniques may need to be used. Regarding the evaluation of therapeutic response, precision caliper measurement was used in this study. However, this is not a feasible technique in clinical trials—other methods should also be used. Injection of PET agents such as ^{18}F-FDG, monitoring tumor metabolism, may provide a more reliable picture of the disease status (*15*). CT and MRI may also find use in more accurate evaluation of tumor response, although their applications in breast cancer have been limited to date.

Considering the requirements of image guidance, as well as the dose heterogeneity of these ^{177}Lu-AuNPs as BRT agents, is there a benefit of intratumoral nanoparticle delivery systems over traditional BRT or radionuclide therapy techniques? The answer seems to have two opposing sides: the limited diffusivity of AuNPs limits the normal-tissue toxicities but also degrades the tumor dose distribution. A nanoparticle system with enhanced diffusivity would improve homogeneity of the radiation doses in the target site but may end up behaving more like an intravenously injected agent. Thus, much optimization is still required to find the right balance and ideal formulation. Future considerations such as the size of the AuNPs, different surface modifications, and the use of other radioisotopes may be worthwhile in pursuit of therapeutic optimization for LABC.

Overall, this intriguing study presents a topic that, if successfully clinically translated, may have immense impact in cancer outcomes. However, like all preclinical research, many aspects need to be optimized before clinical investigation, such as reducing the heterogeneity of dose distribution and employment of image-guided injections. Importantly, because the nontargeted agent was found to be as effective as the targeted agent, these ^{177}Lu-AuNPs may hold promise in the treatment of not only LABC, but also many other cancer types/subtypes as well. We look forward to future preclinical and clinical studies with radiolabeled AuNPs in the years to come.

DISCLOSURE

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