Use of ^{99m}Tc-Tilmanocept as a Single Agent for Sentinel Lymph Node Identification in Breast Cancer: A Retrospective Pilot Study

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^{99m}Tc-tilmanocept received recent Food and Drug Administration approval for lymphatic mapping in 2013. However, to our knowledge, no prior studies have evaluated the use of ^{99m}Tc-tilmanocept as a single agent in sentinel lymph node (SLN) biopsy in breast cancer. **Methods:** We executed this retrospective pilot study to assess the ability of ^{99m}Tc-tilmanocept to identify sentinel nodes as a single agent in clinically node-negative breast cancer patients. Patients received a single intradermal injection overlying the tumor of either 18.5 MBq (0.5 mCi) of ^{99m}Tc-tilmanocept on the day of surgery or 74.0 MBq (2.0 mCi) on the day before surgery by a radiologist. Immediate 3-view lymphoscintigraphy was performed. Intraoperatively, SLNs were identified with a portable γ-probe. A node was classified as hot if the count (per second) of the node was more than 3 times the background count. Descriptive statistics are reported. **Results:** Nineteen patients underwent SLN biopsy with single-agent ^{99m}Tc-tilmanocept. Immediate lymphoscintigraphy identified at least 1 sentinel node in 13 of 17 patients (76.5%). Intraoperatively, at least 1 (mean, 1.7 ± 0.8; range, 1–3) hot node was identified in all patients. Three patients (15.8%) had 1 disease-positive SLN. **Conclusion:** In this small, retrospective pilot study, ^{99m}Tc-tilmanocept performed well as a single agent for intraoperative sentinel node identification in breast cancer. A larger, randomized clinical trial is warranted to compare ^{99m}Tc-tilmanocept as a single agent with other radiopharmaceuticals for sentinel node identification in breast cancer.

Key Words: tilmanocept; sentinel node biopsy; lymphatic mapping; breast cancer

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Sentinel lymph node (SLN) biopsy is the standard of care for axillary staging in early-stage clinically node-negative breast cancer patients. Numerous lymphatic mapping agents of various strengths and with various limitations are commercially available to surgeons. In addition to the numerous dyes available (e.g., isosulfan blue, methylene blue, and indocyanine green), the radiopharmaceutical ^{99m}Tc-sulfur colloid has been used in the United States to validate the technique of SLN biopsy in breast cancer (*1*). However, in 2013 a newer agent, ^{99m}Tc-tilmanocept, received Food and Drug Administration approval for lymphatic mapping in breast cancer.

^{99m}Tc-tilmanocept, a small, receptor-targeted lymphatic mapping agent with demonstrated technical success in numerous tumor types (*2–5*), accumulates in SLNs by binding to the CD206 receptor residing on the surface of lymph node macrophages and dendritic cells (*6*). The agent consists of multiple units of diethylenetriaminepentaacetic acid and mannose, each covalently linked to a dextran backbone (*7,8*). Mannose binds the CD206 receptor, and the diethylenetriaminepentaacetic acid moieties serve as the binding site for ^{99m}Tc (*6–8*). ^{99m}Tc-tilmanocept is a macromolecule with an average diameter of 7 nm (*7,8*). This size differs significantly from that of the other radiopharmaceutical used in the United States for lymphatic mapping—^{99m}Tc-sulfur colloid—whose filtered particles vary in size between 100 and 220 nm (*9*). Regarding the sizes of radiopharmaceuticals used outside the United States, ^{99m}Tc-nanocolloid human serum albumin ranges from 5 to 100 nm and ^{99m}Tc-antimony trisulfide particles range from 3 to 30 nm (*9*).

Although axillary SLN biopsy is typically performed with 2 agents (radiopharmaceutical and blue dye) (*10*) to increase SLN identification, numerous studies have found that SLN biopsy with radiotracer alone is successful, thus questioning the utility of blue dye (*10–13*). To our knowledge, no prior studies have investigated the use of ^{99m}Tc-tilmanocept as a single agent for SLN biopsy in breast cancer. Thus, we executed this retrospective pilot study to evaluate the technical outcome of the use of ^{99m}Tc-tilmanocept as a single agent in breast cancer.

MATERIALS AND METHODS

We queried our prospectively maintained, Institutional Review Board–approved SLN database to identity patients undergoing single-agent lymphatic mapping and SLN biopsy with ^{99m}Tc-tilmanocept. The Institutional Review Board granted a waiver of consent for this retrospective review. After Food and

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Drug Administration approval in March 2013, ^{99m}Tc-tilmanocept was added to our institutional radiopharmacy formulary and became the routinely ordered radiopharmaceutical for sentinel node imaging in breast cancer. Patients with previous axillary surgery or known node-positive disease, or who were undergoing lymphatic mapping with 2 or more agents, were excluded from this analysis.

Radiopharmaceutical Preparation

^{99m}Tc-tilmanocept was prepared and quality control performed by a local central radiopharmacy (Cardinal Health) per the instructions on the package insert (Navidea Biopharmaceuticals, Inc.). Radiolabeling was performed offsite at Cardinal Health, and the agent was delivered during 1 of 3 delivery time-windows based on the timing of the scheduled injection. The agent was delivered in a single, 27-gauge tuberculin syringe to the Nuclear Medicine Department of the hospital. On arrival and immediately before injection, the agent was routinely surveyed for radioactivity by trained nuclear medicine technicians using a Capintec CRC-25R dose calibrator.

Injection Protocol

Injections were performed or supervised by 1 of 3 licensed radiologists. Per protocol, after confirming that the patient and injection-side were correct and positioning the patient supine, the radiologist used an alcohol wipe to clean the patient's skin overlying the tumor, relying on the prior biopsy scar and patient confirmation to determine the location of the tumor. Patients in the 1-d protocol received a single intradermal 0.1-mL injection of ^{99m}Tc-tilmanocept (~18.5 MBq [0.5 mCi]; mean ± SD, 19.6 ± 0.74 MBq [0.53 ± 0.02 mCi]) approximately 2–3 h before surgery. Patients in the 2-d protocol received a single intradermal 0.1-mL injection (~74.0 MBq [2.0 mCi]; mean ± SD, 76.2 ± 2.96 MBq [2.06 ± 0.08 mCi]) approximately 15–20 h before surgery. A skin wheal confirmed the success of the injection. Residual radioactivity within the syringe was not routinely surveyed.

Lymphoscintigraphy

Images were obtained with a Philips (ADAC) Forte γ-camera, with a 20% energy window and a low-energy general purpose collimator. Images were acquired for 180 s, and 3 views were typically obtained (anterior, oblique, and lateral). The acquisition typically began 5 min after injection. However, if a patient was summoned immediately to the operative area, lymphoscintigraphy was not performed.

Surgery

Operations were performed by an experienced surgical oncologist who had more than 15 y of experience with SLN biopsies. Intraoperatively, background radioactivity levels were measured using a handheld intraoperative probe (Neoprobe) (programmed to read out in counts per second). For a node to qualify as hot, its intraoperative count had to exceed the background count (using either one 10-s count or the average of three 2-s counts, with the background measured directly on the patient ~20 cm from the primary site) plus 3 times the SD of the background.

Removed lymph nodes were submitted to the Pathology Department for either frozen sectioning or permanent histopathologic staining. Frozen sections are typically obtained within 1 h of lymph node removal, and a positive result may warrant a patient's immediately undergoing axillary lymph node dissection, depending on the clinical scenario. Permanent-section results are typically finalized by 5–7 d after surgery.

Statistical Methods

We report on baseline patient and technical characteristics. Descriptive statistics were calculated using R (https://www.r-project.org, version 3.1.2).

RESULTS

From May 2013 to July 2016, a total of 19 patients underwent SLN biopsy after single-agent injection with ^{99m}Tc-tilmanocept. Patient characteristics are summarized in Table 1. In brief, most patients had breast-conserving surgery (84.2%), T1/T2-sized tumors (78.9%), and hormone receptor–positive tumors (89.5%). Additionally, most patients (78.9%) underwent the 2-d protocol. Of the patients who underwent immediate imaging with lymphoscintigraphy, 76.5% had at least 1 visualized node. Two patients did not undergo lymphoscintigraphy because they were summoned to the operative area before imaging could be completed.

At least 1 intraoperative SLN was identified in each patient. In total, 32 radioactive nodes were detected and

TABLE 1
Patient Characteristics

Parameter	Data
Age (y)	57.5 ± 7.4
Body mass index (kg/m^2)	27.2 ± 3.3
Injection protocol	
1-d	4 (21.1%)
2-d	15 (78.9%)
Surgery	
Lumpectomy	16 (84.2%)
Mastectomy	3 (15.8%)
T stage	
Tis	1 (5.3%)
T1	7 (36.8%)
T2	8 (42.1%)
T3	3 (15.8%)
Estrogen receptor	
Positive	17 (89.5%)
Negative	2 (10.5%)
Progesterone receptor	
Positive	17 (89.5%)
Negative	2 (10.5%)
Her2 receptor	
Positive	1 (5.3%)
Negative	18 (94.7%)
Lymphoscintigraphy	
Performed	17 (89.5%)
Nodal uptake	13 (76.5%)
Not performed	2 (10.5%)

Data are mean ± SD or number followed by percentage in parentheses (n = 19 patients).

TABLE 2
Findings in the 3 Patients with Disease-Positive SLNs

Patient	Pathologic findings on…	
	SLN biopsy	Axillary node biopsy
1	1 of 3 nodes	0 of 15 nodes
2	1 of 2 nodes	0 of 19 nodes
3	1 of 2 nodes	Not applicable*

*Axillary lymph node dissection not performed.

removed (mean ± SD, 1.7 ± 0.75; range, 1–3). Three patients (15.8%) had 1 identified node that was positive for disease. Of the 3 patients with disease-positive sentinel nodes, 2 underwent axillary lymph node dissection as part of their treatment pathway. In these 2 patients, no other disease was found in the completion axillary-lymph-node-dissection specimens (Table 2).

DISCUSSION

In this retrospective pilot study, ^{99m}Tc-tilmanocept performed well as a single agent for sentinel node biopsy in early breast cancer. Intraoperatively, at least 1 SLN was identified in each patient. ^{99m}Tc-tilmanocept identified 3 nodes with pathologically proven disease in 3 patients. For the 2 patients who had completion axillary-lymph-node dissections, no further disease was found. Furthermore, patients for whom no node was identified on immediate lymphoscintigraphy still had a node identified intraoperatively with a γ-probe. Additionally, ^{99m}Tc-tilmanocept offered flexibility in patient scheduling, as SLN biopsy was successful both in patients receiving the injection on the day of surgery and in patients receiving it on the day before surgery.

In March 2013, ^{99m}Tc-tilmanocept received initial Food and Drug Administration approval for lymphatic mapping in breast cancer and melanoma. To our knowledge, no prior trial or study has evaluated the performance of ^{99m}Tc-tilmanocept as a single agent for intraoperative lymphatic mapping in breast cancer. The initial clinical trials validating the use of ^{99m}Tc-tilmanocept in breast cancer and melanoma involved comparisons and measurements of concordance with blue dye (*3,5,14*). Although the data from these trials showed the performance of ^{99m}Tc-tilmanocept to be consistent and reliable, the use of blue dye may have assisted with identification of the hot lymph nodes. In a different disease process, oral squamous cell carcinoma of the head and neck, the use of ^{99m}Tc-tilmanocept as a single agent identified at least 1 SLN in 97.6% of patients (*4*). Preliminary results from our pilot study demonstrate excellent performance for intraoperative SLN identification in breast cancer when ^{99m}Tc-tilmanocept is used as the lone injected agent.

^{99m}Tc-tilmanocept exhibits radiopharmaceutical properties ideal for SLN procedures. Ideal agents for mapping lymph nodes will clear the injection site rapidly, show rapid and sustained uptake within the sentinel node, and show low uptake within distal lymph nodes (*15*). In prior work, ^{99m}Tc-tilmanocept cleared the injection site more rapidly than ^{99m}Tc-sulfur colloid (*16*). When an agent is used alone, this trait is highly desirable as some surgeons prefer to inject the radiopharmaceutical intraoperatively (*12*). At our institution, patients are required to receive the injection while awake in the Nuclear Medicine Department by a licensed individual, and we have found that ^{99m}Tc-tilmanocept caused significantly less injection site pain than filtered ^{99m}Tc-sulfur colloid (*17*).

This study was not without a few limitations. First, the sample size, although sufficient to draw conclusions about the small subset of patients at our institution, would be bolstered by being larger. A larger, randomized, controlled study could provide more conclusive results and data about the use of ^{99m}Tc-tilmanocept as a single agent in breast cancer. Furthermore, a true false-negative rate could not be determined because axillary lymph node dissection is no longer the accepted standard of care in all breast cancer patients. However, in the 2 patients who underwent completion axillary dissection, it was found that ^{99m}Tc-tilmanocept had identified the only disease-positive lymph nodes. Lastly, as is the case for all retrospective studies, the results might have been biased by unknown confounding variables.

CONCLUSION

In this small, retrospective study, ^{99m}Tc-tilmanocept performed well as a single agent in sentinel node identification in breast cancer. A larger, randomized clinical trial is warranted to compare ^{99m}Tc-tilmanocept as a single agent with other radiopharmaceuticals for sentinel node identification in breast cancer.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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