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Journal

The Breast Journal, 24(4)

ISSN

1075-122X

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Publication Date

2018-07-01

DOI

10.1111/tbj.13002

Peer reviewed

HHS Public Access

Author manuscript

Breast J. Author manuscript; available in PMC 2019 July 01.

Published in final edited form as:

Breast J. 2018 July ; 24(4): 526–530. doi:10.1111/tbj.13002.

Outcomes of "One-Day" versus "Two-Day" Injection Protocols Using Tc-99m Tilmanocept for Sentinel Lymph Node Biopsy in Breast Cancer

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Abstract

Introduction—No prior studies have compared Tc-99m tilmanocept (TcTM) one-day and two-day injection protocols for sentinel lymph node (SLN) biopsy in breast cancer (BC).

Methods—We retrospectively identified clinically node-negative BC patients undergoing SLN biopsy at our institution. Patients received a single, intradermal peritumoral injection of TcTM on day-of surgery or day-prior to surgery in addition to an intraoperative injection of isosulfan blue dye. Univariable and multivariable Poisson regression count models were constructed to assess the effects of injection timing, radiologist, patient, and surgeon characteristics on the number of removed SLNs.

Results—617 patients underwent SLN biopsy with TcTM and blue dye. Sixty-seven (10.9%) patients were injected with the two-day protocol. Patients in the one-day protocol had a mean of 3.0 (standard deviation (SD) 1.9) SLNs removed compared to 2.7 (SD 1.4) SLNs in the two-day protocol, p-value = 0.13. On multivariable analysis, patient age and operating surgeon significantly affected the number of removed SLNs; however, the injection timing and the nuclear radiologist did not influence the number of removed SLNs.

Conclusions—The performance of Tc-99m tilmanocept did not differ significantly between one-day and two-day injection protocols. These results are similar to other radiotracers used for SLN biopsy in BC.

Keywords

tilmanocept; sentinel node biopsy; lymphatic mapping; breast cancer

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Conflict of Interest: The other authors have no conflicts of interest to report.

Introduction

Axillary staging with sentinel lymph node (SLN) biopsy represents the standard of care in clinically node-negative breast cancer patients. Numerous lymphatic mapping agents exist on the market offering variable clinical performance and reliability. While a few agents have Food and Drug Administration (FDA) approval in the United States, no standard clinical protocol exists for the timing, dosing and administration of these agents in the clinical setting.

Tc-99m tilmanocept (Lymphoseek, Navidea Biopharmaceuticals, Inc. Dublin, OH) received initial FDA approval for lymphatic mapping in March 2013.(1) While prior studies have examined the timing on the use of Tc-99m sulfur colloid(2-5), Tc-99m nanocolloid(6), Tc-99m antimony sulfide colloid(7), no prior studies have compared clinical outcomes of same day and day-prior to surgery injection protocols of Tc-99m tilmanocept in breast cancer.

Tc-99m tilmanocept selectively binds to mannose receptors on dendritic cells and macrophages within lymph nodes on the cell surface marker CD206.(8, 9) The 7 nm diameter and homogeneity of tilmanocept allows for fast injection site clearance, and its specific binding in lymphatic tissue may facilitate sustained SLN uptake.(10, 11) As a result, varying the timing of Tc-99m tilmanocept injection may influence the number of SLNs a surgeon removes.

We sought to compare the number of removed SLNs between “one-day” and “two-day” Tc-99m tilmanocept injection protocols in axillary lymphatic mapping in breast cancer. Additionally, we sought to determine if the injecting radiologist influenced the total number of removed SLNs.

Methods

After Institutional Review Board (IRB) approval, a retrospective review of our clinical sentinel node database was conducted on breast cancer patients undergoing sentinel lymph node biopsy at our institution. We included patients since the addition of Tc-99m tilmanocept to our institution’s pharmaceutical formulary in May 2013 until July 2016. We extracted patient and technical data for patients undergoing dual-tracer SLN biopsy with Tc-99m tilmanocept and isosulfan blue dye. Clinically node-negative breast cancer patients eligible for lymphatic mapping and SLN biopsy were analyzed. Patients were analyzed as “one-day” or “two-day” protocol groups if they received Tc-99m tilmanocept injection on the day-of surgery or day-before surgery, respectively. Patients with known positive-nodes, previous axillary surgery and/or undergoing single agent mapping were excluded.

Radiopharmaceutical preparation

Tc-99m tilmanocept was prepared by a central radiopharmacy (Cardinal Health) according to manufacturer (Navidea Biopharmaceuticals, Inc. Dublin, OH) package insert. The agent was delivered in a single, 27-gauge tuberculin syringe to the hospital’s Nuclear Medicine

Department. Upon arrival, the agent was routinely surveyed for gamma activity by trained nuclear medicine technicians.

Tc-99m tilmanocept injection

Injections were performed or supervised by one of three licensed Nuclear Medicine physicians. Per protocol, after confirming the correct patient and side for injection, the radiologist uses an alcohol wipe to clean off the patient's skin above the tumor. For "one-day" injections, patients received a single intradermal 0.1ml 0.5mCi (actual 0.48mCi +/− 0.04) Tc-99m tilmanocept injection approximately 2-3 hours prior to surgery. Patients in the "two-day" protocol received a single intradermal 0.1mL 2.0miCi (actual 1.8mCi +/− 0.59) Tc-99m tilmanocept injection approximately 15-20 hours prior to surgery on the day before surgery. A skin "wheal" confirms successful injection. Lymphoscintigraphy was typically performed 5 minutes post-injection at the discretion of the nuclear radiologist.

Surgery

After induction of anesthesia, one of two breast surgeons injected 2-3ml of isosulfan blue dye intradermal or subcutaneous in the peritumoral vicinity. Intraoperatively, SLNs were determined by one of three criteria. A SLN was defined as radioactive "hot", "blue" and/or a palpably suspicious node. A radioactive "hot" node activity was measured by a portable gamma probe and had a count > 3 times higher than background count.

Removed lymph nodes were submitted to pathology for either a frozen section or permanent histopathologic staining. Frozen sections are typically performed within one hour of lymph node removal and a positive-result may warrant a patient to undergo immediately axillary lymph node dissection depending on clinical scenario. Permanent section results are typically finalized in 5-7 days postoperatively.

Statistical Methods

Baseline patient and technical characteristics between "one-day" and "two-day" protocols were assessed with t-test for continuous variables and Chi-square/Fisher's exact test for categorical variables. We performed univariable and multivariable Poisson count modeling regression to assess the injection protocol, injecting radiologist and other characteristics on the number of removed SLNs. Statistical analysis was carried out using R (https://www.r-project.org, v. 3.1.2). A p-value < 0.05 was used for statistical significance.

Results

A total of 668 patients received an injection of Tc-99m tilmanocept during the study period. Fifty-one patients did not meet inclusion criteria and were excluded (18- only received single agent injection, 23- had prior SLN biopsy or axillary node dissection, and 10- had known node-positive disease prior to chemotherapy and attempt of SLN biopsy). We had 617 patients included in our retrospective analysis. At least one SLN was detected in 100% of patients. The overall mean number of removed SLNs was 2.98 (standard deviation (SD) 1.83) Ninety-five (15.4%) patients had ≥ 1 positive SLN. At least one radioactive "hot" node was identified in 609 (98.7%) patients and ≥ 1 "blue" node in 550 (89.1%) patients. Sixty-

seven (10.9%) patients underwent injection with the “two-day” protocol. Table 1 lists patient characteristics of the two treatment groups.

The mean number of removed SLNs was 3.01 (SD 1.87) nodes in the “one-day” group vs. 2.73 (SD 1.38) nodes in the “two-day group”, p-value 0.125. The proportion of ≥ 1 “hot” node was 544/550 (98.9%) in the one-day group vs. 65/67 (97.0%) in the two-day group, p-value 0.21.

On univariable Poisson regression analysis (Table 2), patient age (incident rate ratio (IRR) 0.995, p-value = 0.02), mastectomy (IRR 0.814, p-value < 0.01), surgeon #2 (IRR 1.293, p-value < 0.01), the use of neoadjuvant chemotherapy (IRR 1.232, p-value < 0.01), and the use of frozen section (IRR 0.888, p = 0.046) significantly influenced the number of removed SLNs. Neither the injection protocol nor the injecting radiologist influenced the number of removed SLNs.

On multivariable Poisson regression (Table 3), patient age (IRR 0.993, p-value < 0.01) and operating surgeon #2 (IRR 1.250, p-value < 0.01) significantly influenced the number of removed SLNs. Again, neither the injection protocol nor the injecting radiologist influenced the number of removed SLNs. Neither the use of mastectomy, neoadjuvant chemotherapy, nor frozen section was statistically significant on the multivariable Poisson count model.

Discussion

Our data represents the largest clinical report on use of Tc-99m tilmanocept in breast cancer since FDA agent approval in March 2013. Overall, a single intradermal injection of Tc-99m tilmanocept was detected surgically in the axilla of 98.7% of total patients undergoing dual-tracer SLN biopsy for breast cancer. Additionally, we found that neither the timing of Tc-99m tilmanocept injection nor the injecting nuclear radiologist influenced the number of axillary lymph nodes removed by surgeons during SLN biopsy. Our results are consistent with prior reports of other radiotracers demonstrating minimal or no statistical differences between one-day and two-day protocols for Tc-99m sulfur colloid(4), Tc-99m nanocolloid(6) and Tc-99m antimony sulfide colloid(7).

Initially, we were concerned the small size and rapid injection site clearance(9) of tilmanocept may lead to fewer removed lymph nodes as time elapsed from initial injection. However, the CD206-specific tilmanocept receptor binding within the lymph nodes(10) facilitated consistent lymph node retention in the “two-day” protocol. These characteristics provide flexibility in patient scheduling. At our institution, patients are required to be injected with radiopharmaceuticals by a licensed nuclear medicine physician in the Nuclear Medicine Department and scheduling “backups” occur around scheduled morning operations. However, we have found that injecting Tc-99m tilmanocept the day prior to surgery reduces Nuclear Medicine Department congestion and allows surgeons to start their cases earlier the following morning.

We have had success with a single, preoperative intradermal injection of Tc-99m tilmanocept overlying the tumor. Patients have reported less pain(12) and we have consistent clinical outcomes.(13) While prior studies have shown the benefit of intradermal Tc-99m

tracer injection(14) and the influence of surgeons performing intraoperative radiotracer injection(15), to our knowledge no prior study has examined the injecting radiologist as a covariate in surgical outcomes. With a single injection, we were concerned that the nuclear radiologist performing the injection may influence the number of surgical removed nodes. However, our results indicate that the radiologist did not influence the detection of “hot” nodes or the total number of surgical removed lymph nodes.

While neither the injection protocol nor radiologist influenced the number of removed SLNs, our multivariable model indicates age and surgeon significantly influenced the number of removed SLNs. Increasing age was associated with fewer removed SLNs. Prior studies have shown reduced lymph node yield with increasing age in a number of clinical scenarios.(16, 17) This may relate to age associated lymph node depletion(18) and/or decreased ability of lymph nodes to retain the lymphatic mapping agent. Thus, lymphatic mapping and SLN biopsy may be more difficult in elderly patients. Additionally, our surgeons differed in the average number of removed nodes. This has been reported previously in several trials looking at techniques of SLN biopsy.(19, 20) While both surgeons in this study have > 10 years of experience with SLN biopsy in breast cancer and use the same lymphatic mapping agents, subtle differences related to dissection technique may exist that alter the number of removed SLNs.

Our study is the largest cohort to date to examine patients injected with Tc-99m tilmanocept. However, this study is not without possible limitations. First, blue dye was used in all cases and may assist the surgeon in finding a “hot” node. While we believe Tc-99m tilmanocept may be used as a single agent, we are a training institution and it is easier to training surgical residents in the technique of SLN biopsy when they can visualize the blue dye. However, the blue dye injection protocols stay consistent between cases and any differences should have been attributed to the timing of the Tc-99m tilmanocept injection.

Conclusion

Injection of Tc-99m tilmanocept the day prior to surgery did not significantly alter the number of removed axillary sentinel lymph nodes in clinically node-negative breast cancer patients. These results are similar to other radiotracers used for sentinel lymph node biopsy in breast cancer.

Acknowledgments

Funding: Project was partially funded by the National Institutes of health Grant UL1TR001442 of CTSA funding beginning August 13, 2015 and beyond (Proudfoot)

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Synopsis

Injecting Tc-99m tilmanocept the day before sentinel lymph node biopsy did not significantly affect the number of removed lymph nodes in clinically node-negative breast cancer patients.

Table 1

Patient Characteristics “One-Day” versus “Two-Day” Protocols

Variable	“One-Day”	“Two-Day”	p-value
	n = 550	n = 67	
Age (years)	58.3 (12.8)	57.9 (13.2)	0.81
BMI (kg/m^2)	26.6 (6.2)	26.0 (6.4)	0.42
Neoadjuvant Therapy			0.83
None	454 (89.1%)	55 (10.8%)	
Chemotherapy	80 (87.9%)	11 (12.1%)	
Hormonal	16 (94.1%)	1 (5.9%)	
Surgeon			<0.01*
#1	249 (81.6%)	56 (18.4%)	
#2	301 (96.5%)	11 (3.5%)	
Surgery Performed			<0.01*
Mastectomy	163 (82.3%)	35 (17.7%)	
Lumpectomy	378 (92.9%)	29 (7.1%)	
SLN biopsy only	9 (75.0%)	3 (25.0%)	
Nuclear Radiologist			0.66
#1	264 (89.8%)	30 (10.2%)	
#2	268 (88.7%)	34 (11.3%)	
#3	18 (85.7%)	3 (14.3%)	
Use of Frozen Section	202 (36.7%)	36 (53.7%)	0.01*
≥ 1 Positive-Node	85 (15.4%)	10 (14.9%)	1.00
≥ 1 “Hot” node	544 (98.9%)	65 (97.0%)	0.21
≥ 1 “Blue” node	489 (88.9%)	61 (91.0%)	0.75

Variables represent frequencies n (percentages) or means (standard deviation)

Legend: SLN: sentinel lymph node

* statistically significant

Table 2

Univariable Poisson Count Regression for Total Removed Sentinel Lymph Nodes

Variable	IRR	95% Confidence Interval		p-value
		LL	UL	
Age (years)	0.995	0.991	0.999	0.021 *
BMI (kg/m^2)	0.997	0.988	1.006	0.533
Neoadjuvant Therapy				
none	Ref			
Chemotherapy	1.232	1.060	1.426	<0.01 *
Hormone	1.300	0.940	1.747	0.180
Day Protocol				
“One-day”	Ref			
“Two-day”	0.861	0.707	1.038	.125
Radiologist				
#1	Ref			
#2	1.002	0.894	1.124	0.970
#3	1.237	0.918	1.630	0.145
Surgery				
Lumpectomy	Ref			
Mastectomy	0.814	0.717	0.922	<0.01 *
SLN biopsy only	0.788	0.489	1.192	0.292
Surgeon				
#1	Ref			
#2	1.293	1.155	1.449	<0.01 *
Frozen Section				
No	Ref			
Yes	0.888	0.789	0.997	0.046 *

Legend: IRR: Incident Rate Ratio, LL: lower limit, UL: upper limit, SLN: sentinel lymph node

* statistically significant

Table 3

Multivariable Poisson Count Regression for Total Removed Sentinel Lymph Nodes

Variable	IRR	95% Confidence Interval		p-value
		LL	UL	
Age (years)	0.993	0.988	0.998	<0.01 *
BMI (kg/m^2)	0.999	0.989	1.008	0.77
Neoadjuvant Therapy				
None	Ref			
Chemotherapy	1.193	0.995	1.422	0.053
Hormone	1.350	0.972	1.829	0.061
Day Protocol				
"One-day"	Ref			
"Two-day"	0.989	0.806	1.202	0.914
Radiologist				
#1	Ref			
#2	1.013	0.902	1.137	0.828
#3	1.175	0.864	1.565	0.285
Surgery				
Lumpectomy	Ref			
Mastectomy	0.884	0.703	1.112	0.290
SLN biopsy only	0.813	0.503	1.237	0.366
Surgeon				
#1	Ref			
#2	1.250	1.106	1.410	<0.01 *
Frozen Section				
No	Ref			
Yes	0.857	0.684	1.073	0.180

Legend: IRR: Incident Rate Ratio, LL: lower limit, UL: upper limit, SLN: sentinel lymph node

* statistically significant