Oregon Health & Science University
School of Medicine

Scholarly Projects Final Report

Title *(Must match poster title; include key words in the title to improve electronic search capabilities.)*

Effect of Lab Timing on Detection of Toxicities in Patients Undergoing ^{177}Lu-DOTATATE Treatment for Neuroendocrine Tumors

Student Investigator's Name

Laura Meeker

Date of Submission *(mm/dd/yyyy)*

3/17/2023

Graduation Year

2023

Project Course *(Indicate whether the project was conducted in the Scholarly Projects Curriculum; Physician Scientist Experience; Combined Degree Program [MD/MPH, MD/PhD]; or other course.)*

Scholarly Projects Curriculum

Co-Investigators *(Names, departments; institution if not OHSU)*

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Mentor's Department

Department of Radiology

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Concentration Lead's Name

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Project/Research Question

For patients receiving ^{177}Lu-DOTATATE therapy (four cycles every 8 weeks) for treatment of neuroendocrine tumors, does timing of laboratory assessment between treatment cycles have an impact on proportion of patients that must continue therapy at a reduced dose, proportion of patients that must postpone a subsequent infusion, or proportion of patients that must discontinue the therapy?

Type of Project *(Best description of your project; e.g., research study, quality improvement project, engineering project, etc.)*

Retrospective research study

Key words *(4-10 words describing key aspects of your project)*

Nuclear medicine, theranostics, radionuclide therapy, lutetium, lab timing

Meeting Presentations

If your project was presented at a meeting besides the OHSU Capstone, please provide the meeting(s) name, location, date, and presentation format below (poster vs. podium presentation or other).

Publications *(Abstract, article, other)*

If your project was published, please provide reference(s) below in JAMA style.

Submission to Archive

Final reports will be archived in a central library to benefit other students and colleagues. Describe any restrictions below (e.g., hold until publication of article on a specific date).

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Next Steps
What are possible next steps that would build upon the results of this project? Could any data or tools resulting from the project have the potential to be used to answer new research questions by future medical students?

Inclusion of data from multiple institutions would allow for greater sample size and more data at the 6 week post-treatment time point.

Please follow the link below and complete the archival process for your Project in addition to submitting your final report.

https://ohsu.ca1.qualtrics.com/jfe/form/SV_3ls2z8V0goKiHZP

Student's Signature/Date *(Electronic signatures on this form are acceptable.)*
This report describes work that I conducted in the Scholarly Projects Curriculum or alternative academic program at the OHSU School of Medicine. By typing my signature below, I attest to its authenticity and originality and agree to submit it to the Archive.

X _____
Student's full name

Mentor's Approval *(Signature/date)*

X 3/16/23
Mentor Name

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Report: *Information in the report should be consistent with the poster, but could include additional material. Insert text in the following sections targeting 1500-3000 words overall; include key figures and tables. Use Calibri 11-point font, single spaced and 1-inch margin; follow JAMA style conventions as detailed in the full instructions.*

Introduction *(≥250 words)*

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a diverse category of tumors which include gastrointestinal carcinoid tumors as well as pancreatic islet tumors. However, one shared feature of GEP-NETs is an overexpression of somatostatin receptors (SSTRs). These receptors have long been targeted for treatment via octreotide (Sandostatin), a somatostatin analog, and for gamma-imaging with Indium-111 pentetreotide (OctreoScan) or positron emission tomography (PET) with Gallium-68 DOTATATE (NetSpot). In recent years, peptide receptor radionuclide therapy (PRRT) has, for the first time, provided the opportunity to provide treatment based on somatostatin receptor expression as well. In PRRT for NETs, a therapeutic radionuclide (Lutetium-177) is attached to a somatostatin analog such as octreotide or octreotate via a chelator. This is similar to how the SSTR-imaging is done, with the major difference being the isotope selection – in PRRT, the isotope is selected for its ability to ablate targeted tissues, through beta-emission.[1,2]

The NETTER-1 (Neuroendocrine Tumors Therapy) trial resulted in the first FDA approval of a PRRT therapy in 2018. The NETTER-1 trial examined the efficacy of ^{177}Lu-DOTATATE, now with the brand name Lutathera, for treatment of "advanced, progressive, somatostatin-receptor-positive midgut neuroendocrine tumors." ^{177}Lu-DOTATATE was found to result in a significantly higher rate of progression-free survival (65.2% of patients at 20 months) compared with long-acting high-dose intramuscular octreotide (10.8% of patients at 20 months).[3] Additionally, a follow up analysis showed that ^{177}Lu-DOTATATE provides a quality of life benefit compared with octreotide alone.[4]

After the FDA-approval, there are now many (>150) centers offering ^{177}Lu-DOTATATE therapy across the United States. The treatment typically consists of four 200mCi IV doses, given every 8 weeks – the same dosing and timing as in the NETTER-1 trial. Patients must meet certain guidelines to start and continue treatment. The most common toxicities are hematologic and labs are typically drawn between cycles in order to monitor for those toxicities. Decisions to discontinue therapy or reduce the dose are then made based upon the results of these laboratory assessments, following general guidelines in the Lutathera package insert.[5]

However, unlike in the clinical trial, there is less consensus about the appropriate time to perform lab monitoring between each cycle of ^{177}Lu-DOTATATE. Assessment was performed at 4 weeks (the mid-point between doses) in the NETTER-1 trial, but no official recommendation is made in the Lutathera package insert. Some centers choose to draw labs at 4 weeks after each dose administration, others at 6 weeks, and some as late as 8 weeks (just prior to administration of the next dose). If the timing of laboratory assessment after each dose has an impact on the laboratory results, then decisions to reduce the dose or discontinue therapy could also be affected, and could lead to heterogeneity in care across different centers using different approaches.

Although laboratory assessments are routinely performed at 4 weeks and at 8 weeks post-treatment at OHSU, any abnormalities at 4 weeks trigger follow up labs at 6 weeks. This allows for comparison of lab values and toxicity detection at the aforementioned time points.

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Methods *(≥250 words)*

Inclusion and Exclusion Criteria

This study was a retrospective chart review. Included patients were those who initiated ^{177}Lu-DOTATATE treatment at OHSU between June 2018 and September 2021 and who completed at least 2 cycles of treatment. As depicted in Figure 1, 11 patients were excluded who initiated treatment during the specified time period but who completed only one cycle of treatment. A total of 82 patients met criteria, between whom 237 treatment cycles were completed. The average age of included patients was 64.7, with 55% male and 45% female.

In addition to criteria for patient inclusion, lab values from individual treatment cycles had to meet lab timing criteria. In order for a lab value to be counted as a "4 week" lab, it had to have been drawn 28 days +/- 7 days from the date of most recent treatment. Similar criteria were in effect in order for lab values to count as a "6 week" lab or an "8 week" lab, as summarized at the bottom of Figure 1. Treatment cycles meeting 4 week, 6 week, and 8 week lab timing criteria were identified and used for comparison across these time points. Because few treatment cycles included 6 week labs (OHSU only draws 6 week labs if toxicity is observed at 4 weeks), a separate set of treatment cycles were identified which met lab timing criteria at 4 weeks and 8 weeks, but not necessarily 6 weeks.

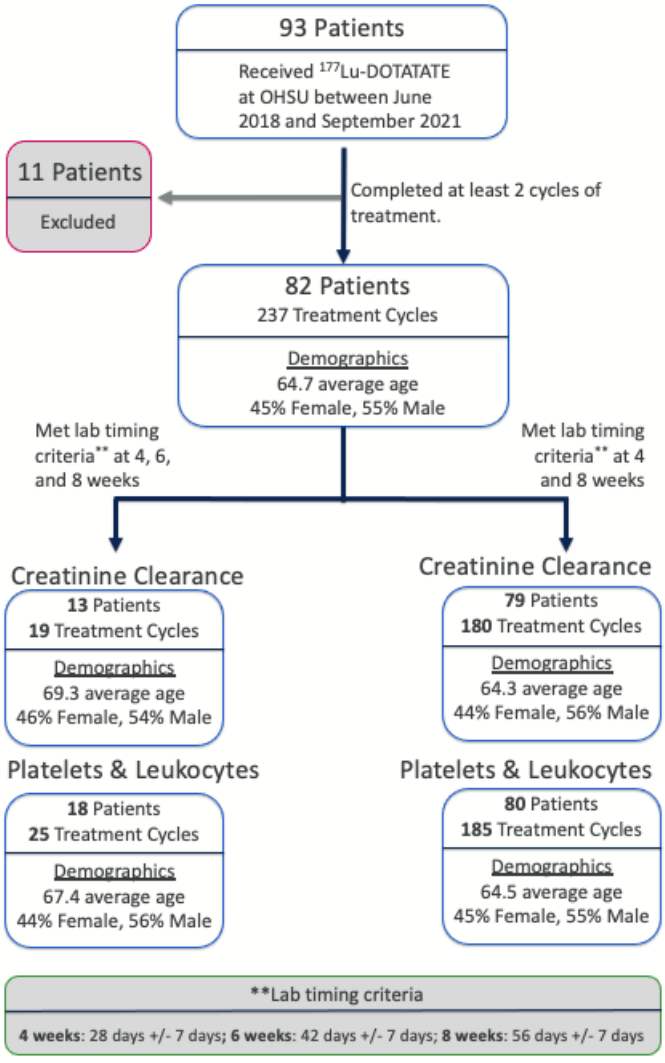

Figure 1. Inclusion and lab timing criteria

Toxicity

Toxicity was determined based upon definitions in the Lutathera package insert (see table 1 below).[5]

Thrombocytopenia	Leukopenia	Renal Toxicity
CTCAE Grades 2, 3, or 4: • Platelet count under 75,000/µL	CTCAE Grades 3 and 4: • WBC < 2,000/mm^3	• Creatinine clearance < 40 mL/min OR • A 40% decrease in baseline creatinine clearance

Table 1. Definition of toxicity as described in the Lutathera package insert.

Statistics: The proportion of patients with toxicity at 4, 6 and 8 weeks was calculated from treatment cycles meeting inclusion criteria described above. Confidence interval was calculated with $\alpha = 0.05$ and statistical difference between 4, 6, and 8-week toxicity proportion was assessed with McNemar's test. In addition, ANOVA with repeated measures and Bonferroni correction (using SPSS Statistics software) was used to compare pre-treatment, 4 week, 6 week, and 8 week mean values of platelets, leukocytes, and creatinine clearance.

Results *(≥500 words)*

Comparisons between labs drawn at 4 weeks, 6 weeks, and 8 weeks were made in two main ways. First, the proportion of treatment cycles which met toxicity criteria was determined for each of the aforementioned time points.

Second, mean lab values for platelet count, leukocyte count, and creatinine clearance were compared across time points in order to capture trends across all patients and treatment cycles regardless of whether those values met criteria for toxicity.

Proportion of Treatment Cycles with Toxicity, 4 weeks vs 6 weeks vs 8 weeks

Thrombocytopenia

A total of 25 treatment cycles met lab timing criteria at 4 weeks, 6 weeks, and 8 weeks. Of these, 11 cases of toxicity due to thrombocytopenia were detected at 4 week labs, 9 cases were detected at 6 weeks, and 13 were detected at 8 weeks. There was no statistically significant difference in proportion of cycles with toxicity when comparing the three time points.

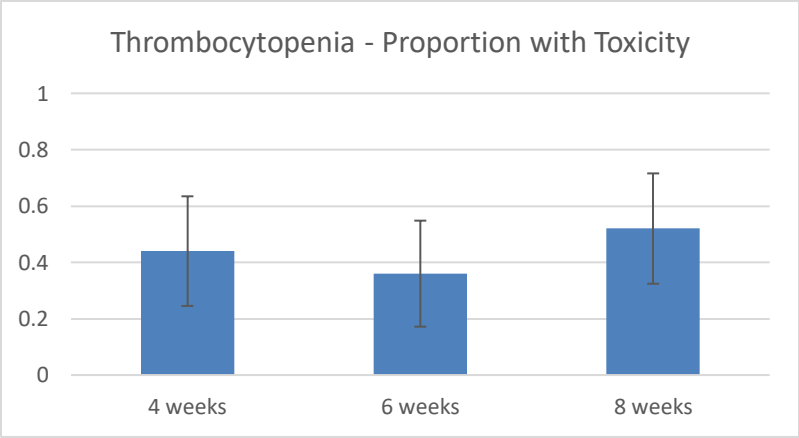

Figure 2. Proportion of treatment cycles meeting toxicity criteria at 4 weeks, 6 weeks, and 8 weeks.

Leukopenia

A total of 25 treatment cycles met lab timing criteria at 4 weeks, 6 weeks, and 8 weeks. Of these, there were no cases of toxicity due to leukopenia detected at 4 week labs, 2 cases were detected at 6 weeks, and 3 were detected at 8 weeks. There was no statistically significant difference in proportion of cycles with toxicity when comparing the three time points.

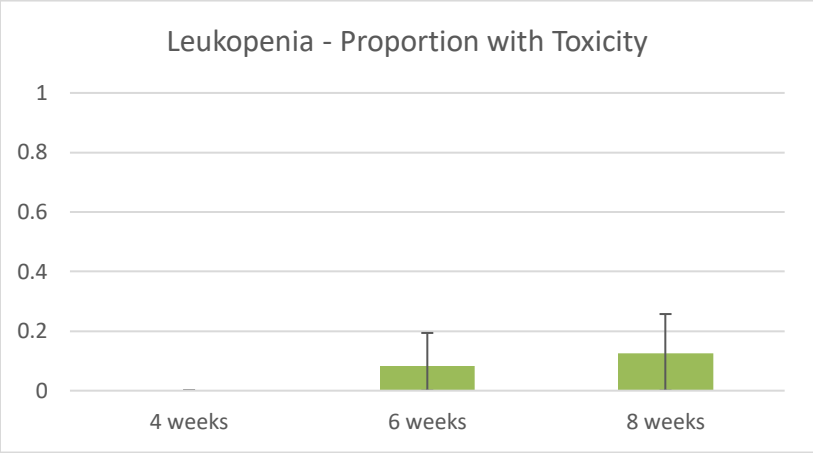

Figure 3. Proportion of treatment cycles meeting toxicity criteria at 4 weeks, 6 weeks, and 8 weeks.

Renal toxicity

A total of 19 treatment cycles met lab timing criteria at 4 weeks, 6 weeks, and 8 weeks. Of these, 2 cases of renal toxicity were detected at 4 week labs, 4 cases were detected at 6 weeks, and 5 were detected at 8 weeks. There was no statistically significant difference in proportion of cycles with toxicity when comparing the three time points.

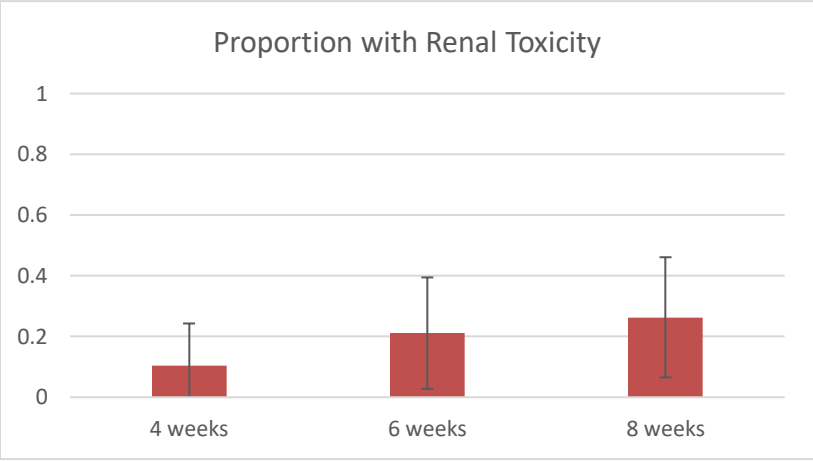

Figure 4. Proportion of treatment cycles meeting toxicity criteria at 4 weeks, 6 weeks, and 8 weeks.

Mean Lab Values, Pre-treatment vs 4 weeks vs 8 weeks

Platelet Count

Pairwise comparisons of pre-treatment, 4 week, and 8 week platelet count all showed statistically significant differences ($p<0.05$) with the exception of 4 week to 8 week difference in treatment #2.

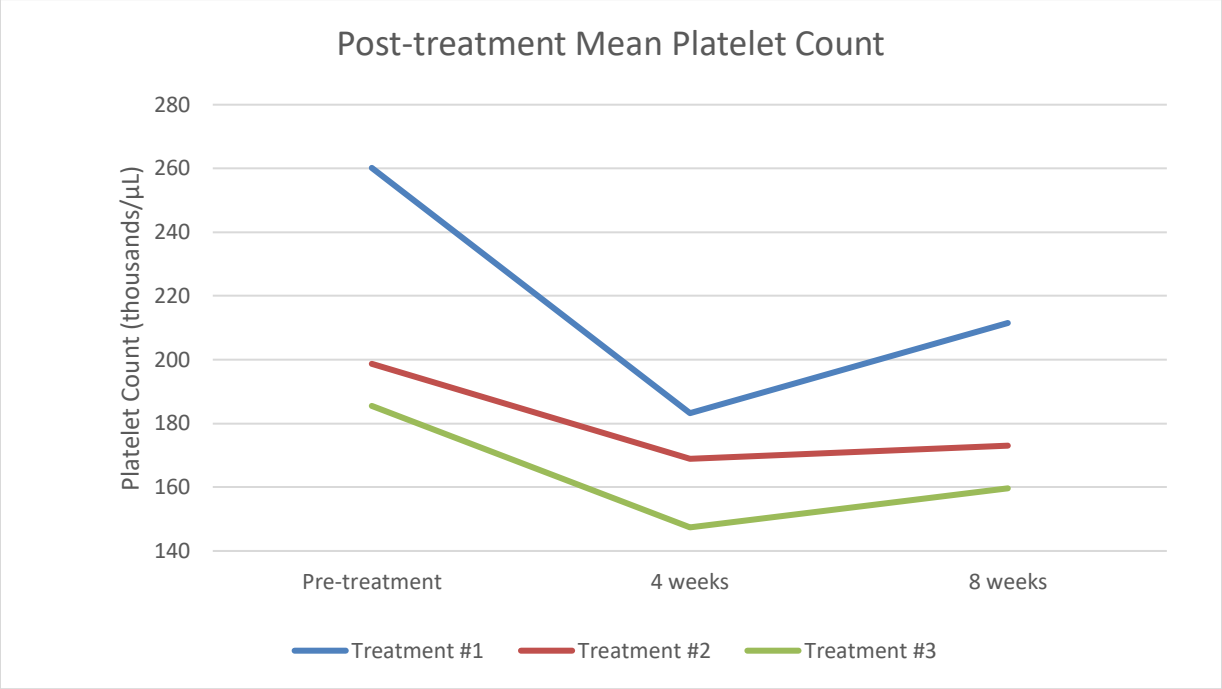

Figure 5. Mean platelet count compared across treatment cycles and between pretreatment, 4 weeks post-treatment, and 8 weeks post-treatment.

Leukocyte Count

No statistical significance was detected when comparing mean leukocyte count at pretreatment, 4 week values, and 8 week values.

Creatinine Clearance

No statistical significance was detected when comparing mean creatinine clearance at pretreatment, 4 week values, and 8 week values.

Cases of Missed Toxicity

In addition to the comparisons made above, a more qualitative look at toxicity detection was performed for the case of thrombocytopenia. There were several cases of discrepancy in toxicity detection between time points. These are summarized in Table 2 below.

Thrombocytopenia – Missed Toxicity			
	Missed at 4 weeks	**Missed** at 6 weeks	**Missed** at 8 weeks
Toxicity observed at 4 weeks	-	2	5
Toxicity observed at 6 weeks	3	-	0
Toxicity observed at 8 weeks	4	4	-

Table 2. Cases of missed thrombocytopenia toxicity.

Discussion *(≥500 words)*

Although statistical significance was not achieved when comparing proportions of treatment cycles with detected toxicity, there were some interesting trends some of which were supported by mean lab value data. Namely, for both leukopenia and renal toxicity there appeared to be a steadily increasing proportion of toxicity from 4 weeks to 6 weeks to 8 weeks (figures 3 and 4). This suggests that peak leukopenic and renal toxicity may occur at a time point even beyond 8 weeks and that, perhaps, drawing labs later may result in more cases of dosage reduction or delay compared with collecting labs at an earlier time point. In contrast, the trend for thrombocytopenia (figure 2) suggests that there may be a trough time point between 4 and 8 weeks for which peak thrombocytopenia occurs, after which some degree of recovery results in detection of fewer cases of toxicity.

The suggestion of a trough time point for thrombocytopenia is supported by mean lab value data (figure 5). Although there were not a sufficient number of treatment cycles meeting lab-timing criteria at pre-treatment, 4 weeks, 6 weeks, and 8 weeks to make statistically significant comparisons, statistically significant comparisons were able to be made when looking at treatment cycles meeting lab-timing criteria at pre-treatment, 4 week, and 8 week time points (omitting the 6 week time point). For the first, second, and third treatment cycles there was a statistically significant decline in mean platelet value from pretreatment to 4 weeks ($p<0.001$). For the first and third treatment cycles, this was followed by a statistically significant partial recovery at 8 weeks ($p<0.001$, $p=0.007$, respectively). As with the trend observed in proportion of toxicity at each time point, this data suggests a transient quality to post-treatment thrombocytopenia.

The presence of transient thrombocytopenia post-treatment could have impacts on dosage delays, dosage reductions, and discontinuation of Lutathera based upon when labs are collected. Table 2 above summarizes discrepancies in toxicity detection for thrombocytopenia, and there were several patients for whom 4 week labs showed thrombocytopenia resulting in dose reduction for which thrombocytopenia was not observed at 6 weeks or 8 weeks. Likewise, there were several instances of toxicity detected at 6 or 8 weeks which were not observed at earlier time points. Due to relatively low absolute numbers of these discrepancies, no trends can be drawn but they serve as examples of the potential implication of discrepancies in toxicity detection.

Moving forward, further study with greater sample size and more routine laboratory testing at 6 weeks is needed to determine when the trough of thrombocytopenia occurs post-treatment. The trends in toxicity proportion suggest that this trough may occur closer to 6 weeks than 4, though the difference was not statistically significant. Determining a more precise time point for trough platelet count would help to inform when the greatest detection of toxicity and subsequent dosage reduction or delay may occur. In addition, greater sample size could help to establish statistically significant differences in mean leukocyte count and creatinine clearance at various time points, as ^{177}Lu-DOTATATE has more subtle impacts on these markers.

Conclusions *(2-3 summary sentences)*

A drop in mean platelet value 4 weeks after ^{177}Lu-DOTATATE treatment and subsequent partial recovery at 8 weeks suggests a transient quality to post-treatment thrombocytopenia, which could have an impact on dosage delays and dosage reductions depending upon when monitoring labs are collected. Further study with greater sample size and more routine testing at 6 weeks is needed to further elucidate when the trough of post-treatment thrombocytopenia occurs.

References *(JAMA style format)*

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2. Cives M, Strosberg JR. Gastroenteropancreatic Neuroendocrine Tumors. *CA: A Cancer Journal for Clinicians.* 2018;68(6):471-487.
3. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of (177)Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med.* 2017;376(2):125-135.
4. Strosberg J, Wolin E, Chasen B, et al. Health-Related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumors Treated With (177)Lu-Dotatate in the Phase III NETTER-1 Trial. *J Clin Oncol.* 2018;36(25):2578-2584.
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