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What is meant by the term "theranostics"?
A theranostic agent generally means using a radioactive imaging agent and paired (or identical) therapeutic agent that both have uptake at the same molecular target, receptor, or process, for use in both therapy and diagnostics—therefore "theranostics".

What are some of the common theranostic agents in clinical use?
Perhaps the most established example of a theranostic agent is I131. One can perform imaging on a gamma camera and treat thyroid disorders with I131. This allows you to first image to confirm if the intended targets show uptake with I131 and then confidently treat the patient with a therapeutic dose of I131, with good assurance that the therapy will localize to the affected tissue since this was first confirmed on imaging. Thereafter, one can image post-therapy to confirm uptake in the intended target, and thereafter image for surveillance of disease—all provided with the I131 theranostic agent. In this example, the gamma rays emitted by I131 allow diagnostic imaging and the beta particle of I131 allows therapy. Note that I123 also exists for imaging only and can be part of radioactive iodine theranostics when paired with I131 for therapy. However, as I123 has no beta particle, this can only be used for thyroid imaging.

More recent theranostic agents are Lu177-Dotatate paired with Cu64-dotatate or Ga68-dotatate that can be used in PET/CT imaging (Cu64 and Ga68 are positron-emitting) and therapy (Lu177 emits a beta particle). This theranostic pair can be used for various somatostatin-positive malignancies to include various neuroendocrine tumors. Another example is Lu177-PSMA paired with F18- or Ga68-PSMA which can be used for the diagnosis and treatment of metastatic prostate cancer in certain scenarios.

What radioactive particles are typically used in nuclear medicine therapies?
Alpha and beta particles are used in most current nuclear medicine therapies. I131, Y90, and Lu177 all use beta particles. Radium223 and Actinium225 are examples of current and emerging radionuclides that use alpha particles for therapy.

Considering alpha and beta particles, which particle is larger?
The alpha particle, containing 2 protons and 2 neutrons as in a helium nucleus, is larger than a beta particle which, for therapy, are electrons. Alpha particles are something like 8,000 times larger than beta particles.

Which particle travels a greater distance in human soft tissues: alpha particles or beta particles?
Beta particles travel a greater distance in soft tissues than alpha particles. Beta particles are smaller and highly energetic, allowing them to penetrate around 3-4 mm in human soft tissues. In comparison, the much larger alpha particle only travels something like 50-100 micrometers (0.05-0.1 mm) in human soft tissues.

So, one could ask themselves which particle is superior for nuclear medicine therapies. The answer I have arrived at for now is it depends. Alpha particles undoubtedly cause more local damage and are more lethal in the local environment in which they deposit. The short traveling range also can limit off-target radiation exposure which can spare things such as adjacent normal bone marrow or lung from

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radiation exposure. On the other hand, beta particles can travel further, and, in some instances, this may be beneficial to kill a larger area of tumor than merely the region where the particle deposits, which could be particularly helpful for things like tumor heterogeneity wherein part of a tumor may take in the particle, and part of the tumor may not. Therapies based on beta particles are sometimes easier to produce.

Final point: Many nuclear medicine therapeutic agents deliver some dose to the bone marrow as well as liver, kidneys, bladder and possibly colon as part of excretion. Therefore, many therapies require adequate renal and liver function levels, blood counts (WBC, RBC, hemoglobin, platelets), as well as frequent urination and defecation during therapy to minimize toxicity resulting from treatment.

Lu177-Dotatate:

Lu177-Dotatate can be used for treatment of certain somatostatin-positive neuroendocrine tumors. What are the most common sites of neuroendocrine tumors?
Gastrointestinal sites are most common (small intestine>rectum>colon>pancreas>appendix>stomach) followed by the respiratory system. Note that 5-year survival is higher for small intestine neuroendocrine tumors (at about 70%) compared to rectal neuroendocrine tumors (at about 30%).

True or false? Lu1777-Dotatate is considered a peptide receptor radionuclide therapy (PRRT)?
True. PRRT's involve a radiopharmaceutical connected to a peptide that binds a specific receptor to selectively target and treat cancerous cells. As mentioned, Lu177-dotatate emits a beta particle (high-energy electron) which kills tumor cells via free radical formation following receptor binding and internalization into the cell. Gamma rays are also released which can be imaged using a gamma camera.

What receptor type does Lu177-Dotatate bind to?
Lu177-Dotatate is a radiolabeled somatostatin analog that binds to somatostatin receptors with highest-affinity binding for somatostatin type 2 receptors.

What type(s) of neuroendocrine tumors does Lu177-Dotatate currently have approval to treat?
Lu177-Dotatate is currently FDA approved for treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

What is the typical dose and duration of treatment of Lu177-Dotatate for GEP-NETs?
Currently, a fixed dose of a 200 mCi IV infusion of LU177-Dotatate is given every 8 weeks for a total of 4 doses. If toxicity develops, the interval may be extended to 16 weeks between treatments in certain cases to allow toxicities to resolve before the next treatment dose.

True or false? You can treat a patient with Lu177-Dotatate while currently taking long-acting somatostatin analog therapy (e.g., octreotide LAR)?
False. Long-acting somatostatin analogs need to be discontinued for at least 4 weeks prior to initiating Lu177-Dotatate therapy.

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True or false? Short-acting somatostatin analogs must only be discontinued 24 hours prior to initiating Lu177-Dotatate therapy.
True. Short-acting octreotide only needs to be discontinued at least 24 hours prior to initiating Lu177-Dotatate therapy.

What is guidance for use of octreotide therapy during Lu177-dotatate treatment?
Intramuscular octreotide LAR is administered between 4 to 24 hours after each Lu177-Dotatate dose. However, octreotide LAR must not be administered within 4 weeks of each subsequent Lu177-Dotatate dose. Remember that Lu177-Dotatate is administered every 8 weeks for a total of 4 doses.

Short-acting octreotide may be administered for symptomatic relief during Lu177-Dotatate therapy but must be discontinued at least 24 hours before each Lu177-Dotatate dose.

After completion of all doses of Lu177-Dotatate therapy, octreotide LAR may be given every 4 weeks until disease progression or for up to 18 months following treatment.

True or false? Amino acid solutions are given prior to Lu177-Dotatate infusions?
True. An intravenous solution of amino acids containing L-arginine and L-lysine is given 30 minutes prior to Lu177-Dotatate administration and is continued during and for at least 3 hours following the Lu177-Dotatate infusion. The amino acid infusion and Lu177-Dotatate can both induce nausea and vomiting so antiemetics are typically given prior to starting the amino acid infusion.

Why are IV amino acids started 30 minutes prior and continued throughout and following Lu177-Dotatate infusion?
Lu177-dotatate is renally excreted. The amino acid infusion is given to protect the kidneys from excessive radiation dose and lowers radiation dose to the kidneys by up to about 50% through reducing the tubular re-absorption of Lu177-Dotatate.

What are potential treatment and management steps for cases of Lu177-Dotatate extravasation?
First, stop the injection and remove the IV catheter. Keep the IV catheter and infusion materials such as tubing to allow measurement of residual activity to determine the absorbed dose that was extravasated. Elevate the affected arm to accelerate dispersion and prevent stagnation in tissue. In certain cases, aspiration of extravasated fluid, a saline flush, application of warm compress, or heating pad may be used to increase blood flow and promote dispersion of extravasated Lu177-Dotatate. Finally, treat symptomatically for inflammation or pain.

What radioprotection measures are taken during Lu177-Dotatate treatment?
During administration isolate the patient and ensure radiation emission limits to others are not exceeded during and following the Lu177-Dotatate administration. This often requires initial isolation for something like 4-5 hours. Patients should stay well-hydrated and urinate as often as possible in a designated hospital toilet that is appropriately isolated. The patient should not be discharged until it is deemed safe to leave the designated area or hospital according to institutional or government policy.

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After leaving the hospital a patient should continue to stay hydrated, urinate frequently, and defecate at least daily, using laxatives as needed. Close contact with others should be restricted per institutional radiation safety protocols. Prior to discharge, the nuclear medicine physician must outline radioprotection rules to others.

What lab tests are typically monitored before and after Lu177-dotatate treatment?
Lab tests that are typically monitored include kidney and liver function tests, and a complete blood count before and every 4 weeks during treatment, to be continued at least 3 months following the last infusion of Lu177-Dotatate, and every 6 months thereafter to assess for any potential delayed adverse reactions.

If toxicity sufficient for dose modification occurs, how is this handled?
General principles include first withholding Lu177-Dotatate therapy and thereafter monitoring relevant labs every 2 weeks. If toxicity resolves within 16 weeks of the previous injection, Lu177-Dotatate therapy may be continued, though at half-dose. If dose limiting toxicity recurs at half-dose, treatment should cease. If the initial dose-limiting toxicity does not resolve after 16 weeks of the most recent prior injection, therapy should not be re-initiated.

A few final points:
A negative pregnancy test needs to be confirmed for individuals of child-bearing potential prior to Lu177-Dotatate administration. Patients should not breastfeed during Lu177-Dotatate treatment and for 2.5 months following the final treatment infusion. Effective birth control should be used during and for at least 4 months for males and 7 months for females following the final infusion.

During treatment patients should be monitored for evidence of neuroendocrine tumor release including flushing, diarrhea, hypotension, and bronchoconstriction, and symptoms should be treated with fluids, corticosteroids, electrolytes and possible IV somatostatin, as clinically indicated. Patients also need to be monitored for evidence of hypersensitivity reactions including anaphylaxis during and for at least 2 hours after completion of infusion. If hematologic or other toxicity occurs such as renal or hepatic toxicity, treatment many need to be withheld or restarted at a lower dose.

*This information is for educational purposes only, intended for board preparation purposes. Please refer to institutional guidelines, society guidelines, and the FDA label for any question on clinical use of Lu177-Dotatate or other nuclear medicine therapies.