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Note that this review is for educational purposes only for radiology and nuclear medicine board preparation. Any doses or treatment paradigms should be confirmed and administered according to the product labels and accepted medical society standards.

Lutetium 177 PSMA (trade name Pluvicto):

PSMA standing for prostate specific membrane antigen is one of the many misnomers in medicine in that PSMA is highly expressed in prostate cancer cells but is not strictly confined to prostate cancer cells. PSMA is expressed to some degree in various other tumors. However, PSMA is most associated clinically with prostate cancer and PSMA-based radiotherapies are currently only clinically available for prostate cancer but are being studied in current and planned future trials for other malignancies as well, to include cancers that include triple negative breast cancer. This episode focuses solely on PSMA use for prostate cancer. PSMA agents have been developed with positron and gamma emitters for imaging, and with beta or alpha particles for therapy. The agents in common current clinical use are positron emitters for PSMA PET imaging using either Fluorine 18 or Gallium 68, paired with PSMA therapeutics with Lutetium 177 with beta particles.

What is the physical half-life of Lutetium 177?
6.647 days (remember about 1 week)

True or false? Lu177 PSMA emits both beta particles and gamma rays.
True. After binding to the PSMA-binding ligand on the PSMA transmembrane protein, the Lu177 destroys the cell with beta particles, and the gamma rays allow imaging of sites of binding throughout the body for things like dosimetry, or imaging to evaluate potential extravasation at the injection site.

What is the primary route of elimination of Lu177 PSMA?
Renal excretion is the primary route of Lu177 PSMA elimination from the body.

True or false? After binding to the PSMA receptor, Lu177 PSMA is internalized into the cell.
True. Following infusion, the Lu177 PSMA binds to target receptors on the cell membrane and the radioligand is internalized into the PSMA-expressing cells. The beta particles thereafter radiate the target and adjacent cells, causing cell death through DNA damage.

What specific subset of prostate cancer patients is Lu177 PSMA currently approved for?
At least for Lu177-PSMA-617, trade name Pluvicto, therapy is for patients with PSMA-positive metastatic prostate cancer who have been treated with androgen deprivation therapy as well as taxane-based chemotherapy.

What is the current dose cycle for Pluvicto therapy?
Current approved regimens for Pluvicto are 6 separate doses each separated by 6-week intervals. If disease progression or unacceptable toxicity occurs, therapy may be discontinued, or a reduced dose may be considered for the remaining administrations. More on this later.

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Is dosing for Lu177 PSMA currently standard between patients or individualized to the patient such as with a weight-based approach?
Currently for Pluvicto, a standard dose of 7.4 GBq (200 mCi) is given intravenously unless dose reduction due to toxicity is indicated. One could ask—given how humans vary greatly in size, shape, body composition, metabolism, renal and liver function, and extent and distribution of disease, whether dosing should be individualized to the patient. I think we all know this is where we need to head, but we aren't there yet. Individualizing doses of radioligand therapies to the patient may require dosimetry to be calculated per patient. Look for this in the future, but we aren't quite there to provide this yet. However, this is of interest to many in nuclear medicine, and I hope we do see the day where therapies such as Lu177 PSMA are increasingly individually dosed to the patient. Someday, future nuclear medicine practitioners will listen back to this and probably laugh that we were giving the same dose to everybody, but you must start somewhere I suppose.

What are some of the most common adverse reactions to Lu177 PSMA?
According to the Vision trial upon which Pluvicto therapy was FDA approved for clinical use, the most common adverse reactions of any grade were fatigue (43%), dry mouth (39%), nausea (35%), anemia (32%), decreased appetite (21%) and constipation (20%).

The most common grade 3 or higher adverse reactions were anemia (13%), thrombocytopenia (8%), and fatigue (6%).

Following Lu177 PSMA (Pluvicto) treatment, how many days should one limit close contact with others and sleep in another room per manufacturer recommendations?
Restrictions following Lu177 PSMA therapy include limiting close contact within 3 feet of household contacts for 2 days, and with children or pregnant women for 7 days. One should sleep in a separate bedroom from household contacts for 3 days, from children for 7 days, and from pregnant women for 15 days. One should refrain from sexual activity for 7 days. Effective contraception is to be used during treatment and for 14 weeks after the last dose of Lu177 PSMA.

What types of symptoms indicate possible myelosuppression following Lu177 PSMA therapy?
Myelosuppression can manifest as abnormal values on complete blood counts including low hemoglobin, white blood cell counts, absolute neutrophil counts, and platelet counts. Clinical symptoms of possible myelosuppression include fatigue, pale skin, shortness of breath, bleeding or bruising more easily than normal, difficulty stopping bleeding, frequent infections, fever, sore throat, or mouth ulcers. Depending on the severity of myelosuppression treatment may need to be withheld, permanently discontinued, or given at reduced dose.

Besides monitoring a patient's complete blood count, what other laboratory tests need to be monitored with Lu177 PSMA treatment?
Kidney function laboratory tests including serum creatinine need to be monitored before and during treatment with Lu177 PSMA. Liver function tests also need to be monitored with Lu177 PSMA therapy.

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True or false? Lu177 PSMA therapy may cause infertility in males.
True. Radiation exposure to the testes during Lu177 PSMA therapy may be sufficient to cause temporary or permanent infertility.

What are options for Lu177 PSMA therapy dosage modification if an adverse reaction occurs?
In the case of adverse reactions, the dose interval may be increased from every 6 weeks to every 10 weeks, per the manufacturer of Pluvicto, to allow time for recovery between doses. Furthermore, the standard dose of 7.4 Gbq (200 mCi) may be reduced on a single occasion by 20% to 5.9 Gbq (160 mci), and if the dose is lowered it should not be increased again in the future. If a treatment delay due to an adverse reaction persists for over 4 weeks, or if the patient would require a further dose reduction due to an adverse reaction, Lu177 PSMA therapy should be discontinued.

Note that specific guidance from the manufacturer exists on management of adverse reactions that should be referred to in clinical use. In general, adverse reactions such as myelosuppression, renal toxicity, dry mouth, gastrointestinal toxicity, fatigue, electrolyte or metabolic abnormalities, liver enzyme elevation or other non-hematologic toxicity that is refractory to longer dose intervals as a first intervention for more minor severity grades and dose reduction for higher grade adverse reactions, require that treatment is permanently discontinued.

Radium 223 Dichloride (trade name Xofigo):

What is the current clinical indication for Radium 223 dichloride therapy?
Radium 223 dichloride is currently used for targeted treatment of symptomatic bone metastases from castration-resistant prostate cancer. Note that unlike Lu177 PSMA, Ra223 dichloride is not intended to treat soft tissue metastases and a typical candidate for Ra223 dichloride will have no visceral metastatic disease. Remember that Radium 223 dichloride mostly localizes to the bone and is therefore appropriate to treat symptomatic bone metastases primarily.

What type of therapeutic particle is emitted by Ra223 dichloride?
Ra223 dichloride emits alpha particles.

What are imaging criteria to qualify for treatment with Ra223 dichloride?
In short, at least 2 bone metastases should be identified on imaging and there should be no evidence of visceral metastases. Any metastatic lymph node must be below 3 cm in short axis measurement.

What is the dose and dosing schedule for Ra223 dichloride?
Unlike Lu177 PSMA where everybody receives the same dose regardless of body size, dosing of Ra223 dichloride is weight based. The exact dose is likely beyond the scope of board exams, but I would remember it is weight based. Ra223 dichloride is administered intravenously once every 4 weeks for 6 injections for a standard treatment course.

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What are acceptable lab values to proceed with Ra223 dichloride therapy?
For initial treatment:
Absolute neutrophil count (ANC) > 1.5×10^9/L
platelets ≥ 100×10^9/L
hemoglobin ≥ 10.0 g/dL

For subsequent treatments:
ANC > 1.0×10^9/L,
platelets > 50×10^9/L
No set parameters for hemoglobin

If hemoglobin declines while on radium-223 therapy, a transfusion of red blood cells may be considered. Note that lab values are stricter for the first dose as you want to make sure there is good bone marrow reserve before you initiate Ra223 dichloride therapy. Please confirm all lab parameters with the manufacturer and institutional protocols. For board exam purposes, the numbers I've listed should be helpful. Note that alkaline phosphatase (ALP) and PSA values may both be helpful to track response to Ra223 dichloride treatment, and both may be considered at baseline and after treatment for monitoring response.

True or false? There is a possibility of dose modification if adverse reactions occur following Ra223 dichloride therapy.
True. Ra223 dichloride treatment may be delayed up to 6 to 8 weeks after the last administration to allow for improved recovery of treatment-related cytopenia between doses. If blood counts do not sufficiently improve within 6 to 8 weeks of the prior dose despite supportive care, treatment should be discontinued.

True or false? Ra223 dichloride is mostly excreted in the urine.
False. Ra223 dichloride has more fecal than urinary excretion. Note that most of the dose goes to the bone, and for what is left over fecal excretion is the dominant route of elimination.

A few final thoughts: Ra223 dichloride hit the market first and found utility for treating prostate bone metastases following a clinical trial that not only showed improvement in patient symptoms and skeletal related events (such as fractures) but also a small improvement in survival for patients who had had prior prostate cancer therapies (therefore sick patients).

Lu177 PSMA is the newer agent that has been shown to extend survival as well and is indicated for treatment of soft tissue and bone disease. Think Ra223 dichloride for bone treatment and Lu177 PSMA for treatment of both bone (perhaps limited) and soft tissue disease.

Also, remember that Ra223 dichloride does not have a paired diagnostic imaging agent, and therefore is not a theranostic agent as this denotes paired imaging and therapeutic agents, such as F18 PSMA which allows for PET imaging of therapeutic targets and Lu177 PSMA which allows for targeted therapy.