Clinical Applications of Theranostics

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Disclosures

None
Role of Nuclear Medicine Physicians in Theranostics
History

• I-131
  • First radiopharmaceutical utilized for radiotherapy
  • Almost 80 years ago
    • Saul Hertz at Mass General for therapy of Hyperthyroidism
    • Jan 1st 1941

• Since then, continued strong use of I-131
  • Hyperthyroidism
  • Thyroid Cancer
  • Lymphoma
  • Pheochromocytomas/Paragangliomas
  • Research use for AML
Growth of Therapeutic Radiopharmaceuticals

- Yt-90
- Sa-153: Beta emitters
- St-90
- Ra-223: Alpha emitter
- Lu-177: Beta emitter (Gamma for imaging)
Ga/Lu Paired utilization

• Benefits to single utilization therapy
• Many more to paired utilization
  • Ability to image exactly what gets treated (front end)
    • Appropriate staging
      • Avid vs. non avid disease
    • Ability to titrate dose via dosimetry
      • Radiation limiting
  • Ability to visualize treated disease (back end)
    • Confirmation of appropriate therapy
• Pulls experience from I-131
Nuclear Medicine Physician Role

• Training in administration of radiopharmaceuticals through residency/fellowship
• NRC guidelines for AU approval
• Team approach
  • Technologist
  • Radiation Safety
  • Medical Physics
  • Nursing
Theranostics and Neuroendocrine Malignancies

Ga-68 Dotatate
Lu-177 Dotatate
**Mechanism of Action**

**Ga-68**
- Half life of 68 minutes
- Positron emission

**Dotatate**
- Binds to somatostatin receptors on the surface membranes of Neuroendocrine tumors, with a preferentially high affinity for type 2 somatostatin receptors.
- Most normal tissue demonstrates low amount of these receptors
Protocol

- Radiopharmaceutical dose of 5 mCi (adult).
- Circulation time of approximately 60 minutes following intravenous injection.
- CT and PET images obtained from top of head through mid thigh.
Biodistribution

• Intense
  • Spleen
  • Adrenal Glands
  • Pituitary Gland

• Moderate/variable
  • Pancreas
  • Liver
  • Thyroid
  • Kidneys
  • Salivary Glands
Interpretation

• Uptake is a sign of somatostatin receptor presence, NOT presence of malignancy
  • Negative exam may still have significant disease burden
• Most useful application of this exam is to assess appropriateness of therapy with Lu-177
• Generally qualitative analysis
  • Not overly concerned with SUV values
• Due to intense variable uptake, different windows utilized
  • Liver
  • Spleen/Adrenal Glands
Ga-68 Dotatate PET/CT Scan
Ga-68 Dotatate PET/CT
Lu-177 Dotatate

- Targeted therapy for somatostatin receptor positive malignancies
  - Needs screening exam with diagnostic agent that targets somatostatin receptors
  - Ideally PET
  - Alternatively planar and SPECT with In-111 pentetreotide

- Up to 4 cycles
  - Two month gap between cycles
Dose Modification

- Dose Reduction (100 mCi)
  - Thrombocytopenia
  - Anemia
  - Neutropenia

- Dose cancellation
  - Renal toxicity
  - Hepatic Toxicity
Preparation

• Discontinue long acting somatostatin analogs for a minimum of 4 weeks prior to Lutathera

• Short acting somatostatin analogs should be held for at least 24 hours prior to therapy

• 30 mg long acting octreotide administered shortly following each therapeutic administration (between 4 and 24 hours)
  • Also administered following completion of therapy every 4 weeks for 18 months or until progression.
Side Effects

• Renal failure
• Hepatic Failure
• Bowel Obstruction
• Carcinoid Crisis
• Nausea/Vomiting
  • Amino Acids
Radiation Exposure Considerations

• Found minimal exposure to others after 24 hours
• Patients told to limit prolonged contact with others for 24 hours, then to go back to normal activity
• Pregnancy restrictions for up to 7 months following final therapy
Logistical Considerations

• Amino acids started 30 minutes prior to therapy and continued for 4 hours
• Lutathera administered over 21 minutes
• Method of IV administration
  • Syringe Pump
  • Gravity Method
Post-therapy imaging

• Assess adequacy of therapy
• Can be compared to pre-therapy imaging
Lu-177 Dotatate Post-Therapy Scan
Efficacy of Lu-177 Dotatate

- Associated with an approximately 80% reduction in mortality or tumor progression.
- Reduction in deterioration of global health status
- Improvement in progression free survival when large lesion or elevated alk phos seen at baseline

Theranostics and Prostate Cancer

Ga-68 PSMA
Lu-177 PSMA
Mechanism of Action

Ga-68
- Half life of 68 minutes
- Positron emission

PSMA
- Transmembrane protein primarily present in all prostatic tissues.
- Seen amongst various malignancies, but most notably in prostate cancer
- Increased expression in de-differentiated, metastatic, or hormone refractory disease
- Also can be used as a prognosticator for disease outcome
Ga-68 PSMA-11

- Several low molecular weight ligands for human PSMA (linked with a chelator for Ga-68) currently available for imaging purposes with PET/CT
- PSMA-11 available on public access
- High affinity for most to human PSMA with internalization into prostate cancer cells
- Biodistribution correlates well to cellular expression of PSMA
- No direct head to head comparison of different ligands
Biodistribution

- Lacrimal and salivary glands
- Liver
- Spleen
- Small and large bowel
- Kidney
  - Tracer predominantly cleared through renal system
  - Small amount through hepatobiliary system
Protocol

- No specific preparation prior to injection of radiopharmaceutical
- Aggressive hydration during uptake time =/- Lasix administration
- 60 minute injection to scan time
  - Increased detection of small lesions with delayed uptake up to 3-4 hours following injection
  - Decay of radiopharmaceutical
- Voiding recommended immediately prior to acquisition of imaging
  - False positives from ureteral uptake
  - False negatives from halo effects
- Scanning performed caudal-cranial to reduce effects of tracer excretion
Current Experience

• Localization of tumor in recurrent prostate cancer
  • PSA between .2 and 10 ng/mL
  • Higher sensitivities in shorter PSA doubling times when compared to higher initial Gleason scores

• Primary staging in high risk malignancy prior to therapy
  • Used for potential visualization of radiologically occult lymph node metastases
  • Potential higher accuracy in detecting bone metastases
Emerging Indications

- Staging prior to and through PSMA radiotherapy
  - Degree of uptake indicates appropriateness of therapy
- Targeted biopsy following previous negative biopsy with high suspicion of malignancy
- Monitoring of systemic treatment in metastatic prostate cancer
  - Awaiting comparison studies to bone scans and other traditional forms of imaging
Correlation with intensity of uptake with Gleason Score

• 141 patients with known prostate cancer s/p prostatectomy
• Evaluation of max SUV of prostate, with care taken to exclude the bladder
• Mean Max SUV significantly higher for grade 3 + 4 + 5 (18.9) versus 1+2 (7.2)
• Could potentially be utilized in the future to target sites of biopsy in appropriate patients

Limitations

• Hepatic activity
• False positives in a variety of non-prostate malignancies
  • Colon
  • Esophageal
  • Thyroid
  • Lung
  • Renal cell
  • Brain
• Celiac ganglia of autonomic nervous system
  • Retroperitoneal lymph nodes
Lu-177 PSMA

• Currently not approved by the FDA outside of clinical trial purposes
• Can be considered within the constructs of a trial
  • Patients with metastatic castrate resistant prostate cancer as late line therapy
  • PSMA expression at tumor sites must be confirmed
    • PSMA tagged PET agent (also not currently FDA approved)
      • F-18
      • Ga-68
Radiation Dose and Stability

• Highest radiation dose to parotid glands, kidneys, and bone marrow
• Bone marrow was the lowest of three doses
• Dose is stable in saline for up to 48 hours and remains stable in blood, with predominant renal excretion (over 50%), without degradation
Conditions prior to therapy

• Bone marrow reserve
• Appropriate renal function
• Appropriate hepatic function
• Discontinuation of potentially myelosuppressive therapy for over 6 weeks

Protocol

• 4-6 cycles administered in trials without adverse renal effects or greater than grade 2 salivary effects
  • Still significant xerostomia
  • Symptomatic and significant oral intake alteration (eg, copious water, other lubricants, diet limited to purees and/or soft moist foods)
• 8-12 weeks between cycles
  • Allows adequate evaluation of potential bone marrow suppression
  • CBC every 2-4 weeks between cycles
  • Majority of side effect reported related to hematologic adverse events
During administration

- Icepacks to salivary glands for 30 min prior to 4 hours following Lu-177 PSMA administration
- +/- antiemetics
- +/- corticosteroids
- Foley for 48 hours for radiation safety
- Dose 6-7.4 GBq Lu-177 PSMA
  - Slow bolus over 30 seconds
  - 1000mL NaCl or Ringers
- Can be administered in an outpatient area
Following administration

- Within 6 hours dose rate to public decreases significantly
- Can be administered in an outpatient area
- Foley should stay in for 48 hours following administration of dose for radiation precautions
- Imaging to demonstrate appropriate deposition of therapeutic dose
Theranostic Pair with PSMA

Clinical Investigations:
Increased degree of activity within the prostate as well as additional visualization of abdominal nodes in Ga-68 PSMA when compared to F-18 Fluciclovine

Multifocal lymph node activity seen on Ga-68 PSMA when compared to F-18 Fluciclovine

The End

Thank You!