Making Dreams Reality: PRRT in the Clinical Setting

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• I have no disclosures to report
Indication

Lutathera® is a radiolabeled somatostatin analog indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut neuroendocrine tumors in adults.

FDA approved 01/26/2018
Phase 3 Trial of $^{177}$Lu-Dotatate for Midgut Neuroendocrine Tumors

Trial background

• International multicenter trial
  • 41 centers in 8 countries
• 229 patients randomized in 1:1 ratio
  • 116 patients received Lu177-dotatate IV 200 mci (7.4 GBq) x 4 q8 weeks + octreotide LAR 30 mg q4 weeks for symptom control
  • 113 patients received octreotide LAR 60 mg q4 weeks
Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors

![Graphs showing progression-free survival and overall survival](image)

Treatment with 177Lu-Dotatate resulted in markedly longer progression-free survival and a significantly higher response rate than high-dose octreotide LAR among patients with advanced midgut neuroendocrine tumors.

Major findings

• Estimated rate of progression free survival:
  • At month 20: 65.2% vs 10.8%
  • Median PFS: 28 months vs. 8.4 months

• Overall survival:
  • 14 deaths vs 26 deaths, represents estimated risk of death at 60% lower in Lu177-dotatate group
  • Updated data: 80% reduction in risk of progression or death

• Response rate:
  • 18% vs 3%
Product

• 177Lu-DOTA-Tyr-Octreotate:
  • 177 Lu
    • Medium energy beta emitter
      • (Emax in KeV): 175 (12.3%) 380 (9%) 497 (78.7%)
    • Gamma emission
      • (E in KeV): 208 (11%) 113 (6%)
    • Maximum tissue penetration 2.2 mm (mean 0.67 mm)
    • Physical half life of 6.7 days
  • DOTA-Tyr-Octreotate (dotatate)
    • Somatostatin peptide analogue with complexing moiety
    • Binds with high affinity to somatostatin receptors
Treatment Criteria

- Somatostatin receptor imaging positive
  - Ga68 dotatate (NETSPOT)
  - Octreoscan
- Scoring system
  - Proposed by Krenning with regards to Octreoscan imaging
Treatment criteria

• Relative uptake score
  • 0: none
  • 1: much lower than liver
  • 2: slightly less than or equal to liver
  • 3: greater than liver
  • 4: greater than spleen
  • Use kidney if liver/spleen not evaluable
Treatment criteria

• Recommended laboratory values
  • Cr \<= 1.7 mg/dl or Cr clearance \>= 50 ml/min*
  • Hg \>= 8.0 g/dl
  • WBC \>= 2.0 K/uL
  • PLT \>= 75 K/uL
  • Tbili \<= 3 x ULN
  • Albumin \>= 3.0 g/dl (unless normal PTT)
  • Negative for pregnancy
Treatment criteria

• Discontinue long acting octreotide at least 4 weeks prior to tx
• Discontinue short acting octreotide at least 24 hours prior to tx
Treatment

• Antinausea premedication given (time 0)
• Amino acid solution, 4-6 hr duration
  • For renal protection
• 177Lu-DOTA-Tyr-Octreotate
  • Start at 0.5 hr following amino acid initiation
• Additional 1-2 hr observation in shielded room
• Discharge precaution sheet
Treatment

• Medications
  • Premedication:
    • Zofran 16 mg IV infusion
    • Emend 150 mg IV infusion
  • Prn medication:
    • Zofran 8 mg IV
    • Ativan 0.5 mg IV
    • Sandostatin 200 mcg SQ
    • Sandostatin 200 mcg/hr IV
    • dexamethasone
Treatment

- Amino acid solution
  - Administer over 4-6 hours
  - Less is more!

<table>
<thead>
<tr>
<th>Compound</th>
<th>Amount</th>
</tr>
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<tbody>
<tr>
<td>Lysine</td>
<td>25 g</td>
</tr>
<tr>
<td>Arginine</td>
<td>25 g</td>
</tr>
<tr>
<td>NaCl solution 9 mg/ml</td>
<td>1 L</td>
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Side effects

- Nausea/vomiting
  - Related to amino acid infusion
- Neuroendocrine hormonal crisis
  - 1% of patients
  - Within 48 hours of treatment
  - Blood pressure changes, flushing, hyperthermia, bronchospasm
- IV Octreotide acetate (Sandostatin): 250-500 mcg bolus and infusion (100-500 mcg/hr)
- Fluids/electrolytes, corticosteroids
MDA Experience

• First standard of care administration 7/26/2018
• As of 2/24/2019, 43 patients received at least one treatment
• No significant nausea or vomiting
  • All patients ate during the day
  • Handful of patients required prn antinausea medication
• No neuroendocrine crises
  • One patient required Sandostatin SQ about 3 hours following tx for flushing
  • Two patients required Sandostatin SQ at end of day for diarrhea
Side effects

• Thrombocytopenia:
  • All grades/grade 3 or 4 - 53%/1%
    • Grade 1 (75K - 150K)
    • Grade 2 (50K – 75K)
    • Grade 3 (25K – 50K)
    • Grade 4 (< 25K)

• Recommendations:
  • Withhold until grade 0-1, discontinue if delay of 16 wks or longer
  • Resume at 100 mci for subsequent treatment
  • If no recurrence, administer at 200 mci for next therapy
  • Recurrent grade 2 or higher, discontinue
MDA Experience

• Of the 43 patients receiving at least one treatment:
  • 5 patients initiated treatment with grade 1 thrombocytopenia (122-147K)
  • One patient on hold for 4\(^{th}\) tx
    • Trend: 122---117---93---65
  • One patient received 2 tx, others 1 tx only
    • Patient with 1 tx had prior splenic embolization
  • 8 patients developed grade 1 thrombocytopenia during treatment
    • One patient dropped below 100K before 4\(^{th}\) tx
  • One additional patient with normal platelets initially experienced notable toxicity
    • 246---73 (delay to recovery)---166---62 (delay with recheck)---47 (grade 3)
Side effects

• Anemia
  • Grade 1 (<LLN - 10 g/dL)
  • Grade 2 (<10 g/dl - 8 g/dL)
  • Grade 3 (<8 g/dl - 6.5 g/dL)
  • Grade 4 (<6.5 g/dL)

• Leukopenia
  • Grade 1: (<LLN - 3 K/uL)
  • Grade 2: (<3 K/uL – 2 K/uL)
  • Grade 3: (<2 K/uL – 1 K/uL)
  • Grade 4: (<1 K/uL)
Side effects

• Anemia/Leukopenia
  • All grades/grades 3 or 4: (81%/0%) and (26%/3%)
• Recommendations:
  • Withhold until grade 0-2
  • Discontinue if delay of 16 wks or more
  • Resume at 100 mci (if no recurrence, next treatment at 200mci)
  • Discontinue with grade 3 or higher recurrence
MDA Experience

• Of the 43 patients receiving at least one treatment:
  • 27 patients initiated treatment at grade 1 anemia, 5 at grade 2
    • One patient experienced grade 3 (7.7 g/dL) but unusual circumstance
    • 2 patients improved from grade 2 to grade 1, other grade 2 patients one tx only
    • 3 patients declined from grade 1 to grade 2 with recovery
    • 2 patients declined from grade 0 to grade 1
    • 2 patients improved from grade 1 to grade 0
  • 3 patients initiated treatment at grade 1 leukopenia, one at grade 2
    • The one grade 2 patient held steady through 4 cycles
    • Of the 3 initial grade 1 patients, one steady through 2 tx, others only one tx so far
    • 8 patients declined from grade 0 to grade 1
    • 4 patients declined from grade 0 to grade 2 (all started at lower end of grade 0)
MDA Experience: hematologic toxicity

• 2 patients with treatment delay or cancellation because of low platelets
  • Update 3/18- 2 additional delayed patients
• NO treatment delays or activity reductions because of anemia or leukopenia
Side effects

• Renal toxicity
• Defined as (package insert)
  • Creatinine clearance less than 40 mL/min
  • 40% increase in baseline serum creatinine
  • 40% decrease in baseline creatinine clearance
• What we use
  • eGFR vs creatinine clearance
  • eGFR limit of 40 mL/min/1.73 sq. m
  • Treating patients below the limit at initial activity of 100 mci
MDA experience

• No patient experienced treatment limiting decline in renal function
  • Greatest creatinine increase was 20% (to max of 1.08)
  • Greatest eGFR drop was 18% (from 49 to low of 40)
  • Update 3/18: patient with 37% creatinine increase (to 1.05) and 32% eGFR decline (to 63)
  • Multiple patients had absolute increase in eGFR

• 2 patients treated with baseline significant renal compromise
  • Initial treatment reduction to 100 mci
  • Patient with baseline eGFR of 35, steady after one tx
  • Patient with baseline eGFR of 33, steady after one tx
MDA Experience: renal toxicity

• No concerns about renal compromise during tx
• Consideration of treatment for patients with impaired baseline function
Side effects

- Hepatotoxicity
- Defined as
  - Bilirubin > 3 x ULN (1.2 mg/dL at our institution)
  - Albumin < 3.0 g/dL with a decreased prothrombin ratio of < 70%
MDA experience

• Hyperbilirubinemia
  • 5 patients started treatment above ULN
    • 3 had decline, one too early, one with initial decline then increase (1.5 initially, tx 4 cancelled with bili of 2.4, platelets 65)
    • One patient with toxicity after one tx
      • Bili rose from 1.2 to 4.4 (albumin drop from 3.3 to 2.4)

• Low albumin
  • 2 patients initiated on tx with albumin < 3.0
  • 2 patients with initial values above 3.0 with decline and increasing ascites
MDA Experience: hepatic toxicity

• Mildly elevated baseline bilirubin- proceed with caution
• Concern about elevation of bilirubin during tx
• Low starting albumin is problematic
• Progressive decline in albumin as a red flag
Laboratory assessment

• Package insert does not specify timing of lab draws
• On trial, patients had assessment at day before therapy and at 4 and 6 weeks after each treatment
• We do one assessment at 4-5 weeks after each treatment
  • Ability to avoid last minute cancellations
  • Potential to delay therapy for considerable changes and/or borderline results
  • Waiting until 6 weeks post could make ordering rushed
Side effects

• Myelodysplastic syndrome
  • NETTER-1: 2.7% with median 24 month f/u
  • ERASMUS: 2% with > 4 year median f/u
• Acute leukemia
  • ERASMUS: 0.5%
Radiation considerations

• Renal excretion
  • Approximately 50% in first 6 hr
  • One week of renal precautions
• Can measure exposure rate at 1 m
  • MDA observations were all well below 5 mR/hr
• Patient specific instructions
Response

- 29 patients received at least 1 treatment with follow up imaging at least one month later
- 7 patients received 4 treatments (none at time point for 3 months post final treatment imaging)
- No patients with frank disease progression
- 15 patients show some anatomic evidence of response (52%)
- 2 patients with mixed findings
  - One completed 4 cycles, overall decreased burden with breakthrough site
  - One completed 2 cycles, overall decreased burden but mixed liver changes
Cautionary tales
• 53 yo female with metastatic neuroendocrine tumor of pancreatic primary
• Prior therapy included SSA, everolimus, extended left hepatectomy, whole brain XRT
• Ga68 dotatate PET/CT 4/2018 and CT 9/2018 showing progression in liver
• Lutathera treatment approved for 10/2018
• Liver biopsy performed demonstrating metastatic breast cancer
• Patient history of right breast cancer diagnosed in 2013 treated with chemotherapy, mastectomy, and XRT
• Last treatment for breast cancer 12/2015
• 37 yo male with metastatic neuroendocrine tumor of pancreatic primary. Hospice vs PRRT
• Prior therapy included cap/tem, FAS, bevacizumab, everolimus, sunitinib, protocol therapy, PRRT (2013)
• Pretx labs:
  • WBC 10 K/uL
  • Hgb 11.4 gm/dL
  • Plt 415 K/uL
  • Albumin 4.1 gm/dL
  • Cr 0.68 mg/dL with eGFR 121 mL/min/sq. m
  • Bili 0.4 mg/dL
• Presents day 1 post therapy with
  • Compromised vision right eye
  • Tongue deviation
  • Dysphagia
• 69 yo female with metastatic neuroendocrine tumor of small bowel primary. Hospice vs PRRT
• Prior therapy included octreotide, protocol therapy, everolimus
• Several prior bowel obstructions, including need for surgery
• Pretx labs:
  • WBC 7.9 K/uL
  • Hgb 8.8 gm/dL (10.4 gm/dL at scheduling)
  • Plt 389 K/uL
  • Albumin 2.0 gm/dL (3.2 gm/dL at scheduling)
  • Cr 1.1 mg/dL with eGFR 51 mL/min/1.73 sq. m
  • Bili 0.7 mg/dL
• Admitted one week post first treatment with bowel obstruction
Take home thoughts

• Lutathera works...but it’s not candy

• Recommendations:
  • Careful assessment of patients with a multidisciplinary approach
    • Can try higher risk cases but keep patients in the loop
  • Follow those labs, especially platelets and albumin
    • Watch out for continued downward trends without recovery
  • Consider imaging post treatment
    • Confirm biodistribution
    • New baseline
    • Decision making for further treatment