A Possible Theranostic Approach to Treating Metastatic Neuroblastoma

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Disclosures

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Neuroblastoma

- The second most common solid malignancy in children
- Small number of patients
  - 650 to 700 new cases/y in the US*
- Average age at first presentation – 19 months
- Frequently diagnosed at later stages (stage 3-4)
- Early treatments are effective, but patients frequently (>75%) relapse with widespread metastatic disease
- Survival rate of patients with relapsed disease is extremely low
- Can we improve their prognosis?

*http://www.cncfhope.org/CNCF_FAQs
SSTR2

- Present on up to 90% of NB tumors
- Octreotide derivative
- High binding affinity
- Peptide
- $^{68}$Ga-DOTATATE (NETSPOT) approved for imaging adult somatostatin-receptor positive neuroendocrine tumors
  - Not extensively evaluated in neuroblastoma
- $^{177}$Lu-DOTATATE (Lutathera) approved for treating adult somatostatin-receptor positive neuroendocrine tumors
  - Not extensively evaluated in neuroblastoma
Radiolabeled Peptides in Neuroblastoma

SSTR2 Receptor

Why look beyond $^{68}$Ga-DOTATATE (NETSPOT) and $^{177}$Lu-DOTATATE (Lutathera)?

$^{68}$Ga-DOTATATE

- High cost of the $^{68}$Ge/$^{68}$Ga generator
- Availability of the $^{68}$Ge/$^{68}$Ga generator
- Low resolution of $^{68}$Ga images
- Short half-life of $^{68}$Ga limits the ability to do dosimetry calculations

$^{177}$Lu-DOTATATE

- Not a matched pair with $^{68}$Ga-DOTATATE
PET/CT (left) and PET (right) scans of patient with intestinal NET and multiple metastases.

More lesions are seen in intestinal region with $^{64}$Cu-DOTATATE than with $^{68}$Ga-DOTATOC.

Imaging: $^{68}$Ga versus $^{64}$Cu

$^{68}$Ga
- $T_{1/2} = 68$ min
- $\beta^+$ Yield: 88.9%
- $\beta^+$ mean = 836 keV
- Positron range: 4 mm
- Production – $^{68}$Ge/$^{68}$Ga generator, cyclotron
- Shippable? No

$^{64}$Cu
- $T_{1/2} = 12.7$ h
- $\beta^+$ Yield: 17.6%
- $\beta^+$ mean = 278 keV
- Positron range: 1 mm
- Production – cyclotron
- Shippable? Yes
- Very labile
**"Better" Chelator for Copper**

*Cu-DOTA*

- Cu doesn’t fit within the core
- *pba* tail for binding to proteins
- Easy to make $^{64/67}$Cu complex
  - (acetate buffer, RT)
- Cu(II) lost from complex *in vivo*

*Cu-MeCOSar*

- Derivative of diamsar
- -COOH tail for binding to proteins
- Easy to make $^{64/67}$Cu complex
  - (acetate buffer, RT)
- Forms very stable Cu(II) complexes

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Donnelly *et al.*, *Dalton Trans.*, **2014**, 43, 1386
What are the optimal properties for a therapeutic radionuclide?

- $\beta^-$ (or $\alpha$) emitter
- What is the “optimal” $\beta^-$ energy?
- No/minimal extraneous emissions
- Half-life?
- Imagable gamma?
- Cost/availability
Therapy: $^{67}\text{Cu}$ vs. $^{177}\text{Lu}$

$^{67}\text{Cu}$
- $T_{1/2} = 2.6 \text{ d}$
- $\beta^-$ Yield: 100%
- $\beta^-$ mean = 141 keV
- $\beta^-$ range: 0.7 mm
- Gamma: 91 keV (7%), 93 keV (16%), 185 keV (49%)
- Production:
  - $^{68}\text{Zn}(p,2p)^{67}\text{Cu}$ (1.9 TBq/mg)
  - $^{68}\text{Zn}(\gamma,p)^{67}\text{Cu}$ (15 TBq/mg)

$^{177}\text{Lu}$
- $T_{1/2} = 6.6 \text{ d}$
- $\beta^-$ Yield: 100%
- $\beta^-$ mean = 134 keV
- $\beta^-$ range: 0.7 mm
- Gammas: 123 keV (6%), 208 keV (10%)
- Production:
  - $^{176}\text{Lu}(n,\gamma)^{177}\text{Lu}$ (1.1 TBq/mg)
  - $^{176}\text{Yb}(n,\gamma)^{177}\text{Yb}$, $^{177}\text{Yb} \rightarrow ^{177}\text{Lu} + \beta^-$ (3 TBq/mg)
1. Does $^{64/67}\text{Cu-SARTATE}$ accumulate in NB liver metastases?

2. Is treatment with $^{67}\text{Cu-SARTATE}$ as effective as treatment with $^{177}\text{Lu-DOTATATE}$?

3. If we treat the disease early enough, can we prevent the development of metastases?
   - Prophylactic Radiotherapy
Dorsal incision – Expose the spleen
Inject $10^6$ IMR32 (human) NB tumor cells
Wait 2 min.
Perform splenectomy
Close incision
1-2 mm mets are present ~2 weeks after inoculation
Imaging with $^{64}\text{Cu}$-SARTATE

- Validate that the tumors have become established
- 3 weeks post-inoculation

Autoradiography and histology
Therapy

• Treat with $^{67}$Cu-SARTATE
• Single treatment
• 4 weeks post-inoculation
  • Two different doses
    • 9.35 MBq (250 μCi)
    • 18.5 MBq (500 μCi)
• 2 weeks post-inoculation
  • Single dose (18.5 MBq)
Survival After Initiation of Therapy
4 Week Tumor growth

Survival After Initiation of Therapy
2 Week Tumor growth

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<thead>
<tr>
<th>4-Week Incubation</th>
<th>2-Week Incubation</th>
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<tbody>
<tr>
<td><strong>67Cu-SARTATE Dose</strong></td>
<td><strong>67Cu-SARTATE Dose</strong></td>
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<tr>
<td>0 MBq (Control)</td>
<td>0 MBq (Control)</td>
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<tr>
<td>9.25 MBq</td>
<td>18.5 MBq</td>
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<tr>
<td>18.5 MBq</td>
<td>0 MBq</td>
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<thead>
<tr>
<th>Mean Survival (d)</th>
<th>Mean Survival (d)</th>
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<tr>
<td>14.6±8.5</td>
<td>43.0±8.1</td>
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<tr>
<td>9.5±1.6</td>
<td>55.6±9.1</td>
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<td>15.6±4.0</td>
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\[ p = 0.064 \quad p = 0.012 \]

Conclusions

• Can image small (<1 mm) liver mets with $^{64}$Cu-SARTATE
• $^{67}$Cu-SARTATE extends life in mice with smaller tumors (2 weeks)
• $^{67}$Cu-SARTATE is more effective for treating smaller tumors (2 weeks) than larger tumors (4 weeks)

Questions

• What about $^{177}$Lu-DOTATATE vs. $^{67}$Cu-SARTATE in metastases?
• Are higher doses of $^{67}$Cu-SARTATE even more effective in the smaller tumors?
• Are $\alpha$ emitters more effective than $\beta^-$ emitters for these very small lesions?
• Are antibodies better vectors than peptides?
• Is treatment more effective if started earlier, with smaller tumors?
  • Can we prevent the growth of mets? (prophylactic radionuclide therapy)
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Thank you for your attention!