Intra-Tumoral Infusion of P-32 Radiolabeled Microspheres for Localized Radiotherapy of Pancreatic Tumors

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Financial Disclosure

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Oncosil™ (Oncosil Medical Ltd.)

**Single-use brachytherapy device**

- indicated for treatment of locally advanced unresectable pancreatic cancer (LAPC)
- in combination with gemcitabine-based chemotherapy
- Approved in: EU, UK, Hong Kong, Singapore, Malaysia, New Zealand, Switzerland
- Clinical trials in the US completed
Oncosil

Silicon nanoporous microparticles (on the order of 30 µm, but variable)

• Highly-doped with phosphorous ($^{31}\text{P}$)
• Exposed to neutrons (nuclear reactor): $^{31}\text{P}(n,\gamma)^{32}\text{P}$
**Phosphorus-32**

- Pure $\beta^-$ emitter
- $E_{avg} = 0.695$ MeV, $E_{max} = 1.711$ MeV
- Half-Life: 14.27 days
- $\beta^-$ range (mm): 2.76 ($E_{avg}$), 8.14 ($E_{max}$)
  
- $\sim$100% (macroscopic) local energy deposition
  
  (1.11E-13 Gy-kg/Bq-s)

Oncosil Prescription

100 Gy (±20%)  

- Assumptions  
  - 100% local energy absorption and uniform dose (i.e., uniform microparticle distribution throughout tumor)  
  - $^{32}$P physical decay only (i.e., no biologic clearance)  
  - 1.03 g/cc  
  - Tumor volume: 14 to 113 cc (shortest diameter: 2 cm, longest diameter: 6 cm)  

\[
100 \text{ Gy} = 1.11 \times 10^{-4} \text{ Gy-g/MBq-s} \times \text{MBq}_{\text{inj}} \int_0^\infty e^{-\lambda t} \, dt / M_{\text{tumor}}(\text{g}); \quad \lambda = 5.62 \times 10^{-7} \text{ s}^{-1}
\]

\[
\text{MBq}_{\text{inj}} = 0.5215 \times V_{\text{tumor}}(\text{cc}) = 100 \times V_{\text{tumor}} \times 1.03 \times 5.62 \times 10^{-7} / 1.11 \times 10^{-4}
\]

- $^{32}$P concentration in diluent: 6.6 MBq/ml ($V_{\text{Oncosil}} = \text{MBq}_{\text{inj}} / 6.6$)  
  - $V_{\text{Oncosil}} = 8\%$ of $V_{\text{tumor}}$ ($\text{[MBq}_{\text{inj}} / 6.6] / V_{\text{tumor}} = 0.079$ rounded off to 0.08)
Oncosil Preparation

250 MBq $^{32}$P calibrated on reference day (0)

Day of implantation (Di): -2 to +7

Diluent ml: $7.0e^{ln(2)Di/14.27}$

$V_{\text{Oncosil}} = 0.08 \times V_{\text{tumor}}$

$V_{\text{tumor}} = 14$ to $113$ cc

$V_{\text{Oncosil}} = 1.1$ to $9$ ml
**Oncosil Implantation (EUS-guided)**

- echoendoscope (EES) guided to stomach or duodenum (whichever provides best access to the tumor)
- 22 gauge EUS guided FNA needle loaded into EES biopsy channel and advanced through gastric wall and into the tumor
- 3-way Luer lock tap and Oncosil syringe attached to FNA needle
- Slow infusion (visualized with EUS), followed by saline flush (1.5 ml)
- With EES in stomach, 3.5 ml saline flush
- EES + needle withdrawn, tip rinsed with water (50 ml) over radioactive waste bag, needle placed in radioactive waste container

Image courtesy of Oncosil Medical Ltd.
Oncosil Implantation: Example Images

pre-Tx contrast CT of tumor

endoscopic US pre-infusion

endoscopic US post-infusion (Oncosil “blush”)

Oncosil Post-Therapy Imaging

Secondary bremsstrahlung x-ray

- $^{32}$P is a pure beta emitter (no photon emissions)
- Manufacturer-recommended imaging
  - Post-implant time points: $\leq$ 4 hours and 7 days
  - Energy window: 75 keV±30% (52.5 – 97.5 keV)
  - Collimation: medium energy
  - Whole body planar (WB): 10 cm/min
  - SPECT: 90–120 views/360°, 30 sec/view, 128x128 matrix
  - CT: site’s standard-of-care for SPECT/CT
- Tumor activity between time points should:
  - decrease over time according to $^{32}$P T½ (14.27 d)
  - not redistribute (i.e., biodistribution should not change)
Oncosil Post-Therapy Imaging

4-h post-implant

WB anterior  posterior
SPECT transverse slice  coronal slice

7-d post-implant
Oncosil Bremsstrahlung Imaging Limitations

- $^{32}$P activity in the WB and SPECT images is a tiny “island” in an “ocean” of background (i.e., there is a complete lack of anatomical information and, thus, localization)

- Patient (e.g., breathing) motion
  - during WB and SPECT scanning, between the SPECT and CT scans, and during the CT scan

- Image registration is difficult and questionable
  - Single, small “island” in the SPECT, versus tumor + rest of pancreas (similar HU values) + a lot of other anatomy in the CT
  - Motion between SPECT and CT

- The SPECT images are low-count, and non-quantitative (i.e., counts, not Bq or Bq/ml)

A better method of imaging the Oncosil microparticle distribution is needed
Oncosil – our experience

OncoPac-1 Pilot Study

In combination with gemcitabine or gemcitabine+nab-paclitaxel in subjects with unresectable LAPC

<table>
<thead>
<tr>
<th>Patient</th>
<th>Baseline Tumor Volume</th>
<th>Survival Post-Oncosil</th>
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</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>23.2 cc</td>
<td>~1.5 y</td>
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<tr>
<td>Patient 2</td>
<td>31.5 cc</td>
<td>~6 m</td>
</tr>
<tr>
<td>Patient 3</td>
<td>8.44 cc</td>
<td>unknown (returned to S. Africa post-Tx)</td>
</tr>
<tr>
<td>Patient 4</td>
<td>52.5 cc</td>
<td>~2 y</td>
</tr>
</tbody>
</table>
Oncosil – our experience

Patient 2 (31.5 cc)

Patient 3 (8.44 cc)

Patient 4 (52.5 cc)
Oncosil – our experience

Week 0 volume is pre-treatment baseline
Oncosil – outcomes

PanCO international, multi-center, single-arm pilot study (3/2017 - 6/2018)

• 42 patients with unresectable LAPC (Australia, Belgium, UK)
• Oncosil with Gemcitabine+Nab-Paclitaxel (34) or FOLFIRINOX (8)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
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<tbody>
<tr>
<td>Median Baseline Tumor Volume</td>
<td>24.35 cc (range: 7.9–68.7)</td>
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<tr>
<td>Partial Response</td>
<td>13 (31%)</td>
</tr>
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<td>Stable Disease</td>
<td>29 (69%)</td>
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<tr>
<td>Overall Response Rate</td>
<td>13 (31%)</td>
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<td>Local Disease Control at 16 weeks</td>
<td>38 (91%)</td>
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<tr>
<td>Median Progression-Free Survival</td>
<td>9.3 months (32.3% 1-year rate)</td>
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<tr>
<td>Median Overall Survival</td>
<td>16.0 months (64.0% 1-year rate)</td>
</tr>
<tr>
<td>Median tumor volume change from baseline</td>
<td>-52% (range: +11% to -90%)</td>
</tr>
</tbody>
</table>

Ross P et al. Abstract O-1, ESMO World Congress on Gastrointestinal Cancer 2020
Oncosil – outcomes

PanCO vs. state-of-the-art standard-of-care (literature review)

- SoC therapy: chemo (CT) or induction chemo (ICT) + consolidated chemoradio (CCRT)

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<tr>
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<th>PanCO</th>
<th>CT</th>
<th>ICT+CCRT</th>
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<tbody>
<tr>
<td>Median PFS in months [95% CI]</td>
<td>9.3 [7.2, 12.2]</td>
<td>6.6 [6.2, 7.8] (27 trials) p=0.010</td>
<td>9.1 [7.6, 9.3] (16 trials) p=0.227</td>
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<tr>
<td>Median OS in months [95% CI]</td>
<td>16.0 [11.1, nc]</td>
<td>12.7 [11.9, 13.6] (34 trials) p&lt;0.001</td>
<td>12.6 [12.2, 14.0] (20 trials) p&lt;0.001</td>
</tr>
<tr>
<td>One-year % survival [95% CI]</td>
<td>64.0 [47.5, 76.5]</td>
<td>50.4 [45.3, 55.5] (34 trials) p=0.013</td>
<td>55.2 [49.4, 60.9] (20 trials) p&lt;0.001</td>
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Allerdice S et al. Abstract P-260, ESMO World Congress on Gastrointestinal Cancer 2020
Oncosil – summary

• A novel, direct-infusion unsealed brachytherapy device for unresectable LAPC
• Feasibility of EUS-guided delivery has been demonstrated
• In combination with gemcitabine+nab-paclitaxel or FOLFIRINOX
  • appears to confer additional benefit compared to SoC CT alone and ICT+CCRT
• Limitations
  • Uniform distribution, and, thus, uniform dose, is assumed (not the case in reality)
    • Dose distribution corresponding to “uniform 100 Gy” will vary from tumor to tumor
  • Aside from live EUS, visualization of implant localization is difficult
    • “hot spot” SPECT/CT insufficient (weak bremsstrahlung signal, SPECT-CT misregistration)
    • method allowing actual particle distribution visualization (and voxel dosimetry?) is needed
References


Oncosil Medical Ltd. Web site (https://www.oncosil.com/) (links to scientific meeting posters and publications found there)
Thank you!

Questions?

Contact: werwin@mdanderson.org