$^{211}$At and Ovarian Cancer

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Background

• Research group led by Prof. Ragnar Hultborn and Prof. Lars Jacobsson (The TAT Group)
• Collaboration since 1994 in Gothenburg
• Radiation physics
• Oncology
• Nuclear chemistry
The Gothenburg efforts

- Labeling chemistry
- In vitro studies
- Animal studies
- Clinical studies (phase I study published)

**Overall aim:**

To evaluate the efficacy and toxicity of $^{211}$At, and other $\alpha$-particle emitting nuclides.
Ovarian cancer

1–2% life time risk in European and American women.

<table>
<thead>
<tr>
<th>Metastases</th>
<th>Frequency</th>
<th>Treatment</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>30%</td>
<td>Radical surgery</td>
<td>~85%</td>
</tr>
<tr>
<td>Abdominal</td>
<td>60%</td>
<td>Debulking surgery + chemotherapy</td>
<td>~35%</td>
</tr>
<tr>
<td>Distant</td>
<td>10%</td>
<td>Chemotherapy</td>
<td>~20%</td>
</tr>
</tbody>
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A new additional therapy is needed.
Previous i.p. RIT of ovarian cancer

- Radionuclides used: $^{131}$I, $^{90}$Y ($\beta$ -emitters).

- Promising results - but a phase III study was not successful.

Low absorbed doses to microscopic tumors owing to:

- **Too long half-life** (bone-marrow dose limiting due to high blood activity).

- **Too long particle range** for microscopic tumors.
Why $^{211}\text{At}$?

- The short range of the $\alpha$-particles
  High absorbed fraction in small tumors
- The high energy (high LET)
  High abs. dose/decay, less dep. on cell cycle & oxygen
- The short half-life
  Reduces normal tissue irradiation

**Some concerns:**
- Too short range
  All tumor cells are not reached
- Normal tissue toxicity of the $\alpha$-particles
  Could decrease the therapeutic window
- Availability
  Clinical applications may be difficult
Astatine production

PET and Cyclotron Unit, Rigshospitalet, Copenhagen

\[ ^{209}\text{Bi}(\alpha,2n)^{211}\text{At} \]

Energy: 28 MeV He\(^{++}\)
Irr. time: Up to 8 h
Yield: Max 2 GBq
Frequency: 2–3 times/month

\( E_\alpha \leq 28 \text{ MeV} \)
Backing Al (30 × 27 × 5 mm)
Al (7 µm), \(^{209}\text{Bi} (18 \text{ µm})\)
Nude mice studies

**Toxicity**

**Bone marrow:** White blood cell counts - RBE


**Kidneys:** Glomerular filtration rate

*Cancer Biother Radiopharm, In press*

**Peritoneum:** Trans membrane transport

*Manuscript*

**Therapeutic efficacy**

**Local therapy: Intraperitoneal microscopic tumors**

*J Nucl Med 2006;47:1342–50*  
*Int J Radiat Oncol Biol Phys 2006;66:1228–37*  
*Nucl Med Biol 2006;33:1065–72*

**Macroscopic tumors**

Renal toxicity in nude mice

- Moderate kidney uptake.
- Tolerable mean absorbed dose to kidneys (~10 Gy).
- Renal toxicity is not critical in therapy using $^{211}$At-MX35 F(ab’)2.
Nude mice tumor model

$10^7$ OVCAR-3 cells i.p.

Macroscopic tumors 8 weeks post treatment.

Maximal tumor diameter (mm)

Time after inoculation (weeks)
Therapeutic efficacy on i.p. tumors

- **Short term**
  Dissection 2 months after therapy:
    - No macroscopic tumors
    - No microscopic tumors
    - No ascites
  Tumor free fraction (TFF)

- **Long term**
  Dissection 7 months after therapy
Microscopic tumors - Efficacy related to tumor size

Tumor free fraction (%) (400 kBq i.p.)

Microscopic tumors - Fractionated therapy, 3 in 8 days

5 weeks
\( \phi \approx 0.3 \text{ mm} \)

No gain in efficacy, but lower myelotoxicity!

Nucl Med Biol 2006;33:1065–1072
Clinical phase I study

- Women with recurrent ovarian cancer in remission after second line chemotherapy.

- No major adhesions in the peritoneal cavity.

- Informed consent.

- Nine patients included.

Logistics of the phase I study

**Preparations**

- Laparoscopy
- Peritoneal catheter insertion
- Peritoneal scintigraphy with $^{99m}$Tc
- Pretreatment with KClO$_4$ or KI (P. 6–9)

**Sampling**

- Blood (1–48h)
- I.p. fluid (1–24h)
- Urine (1–48h)
- Gamma camera (1–48 h)

**Infusion/therapy**

- 1–2 L Extraneal solution
- 33–120 MBq $^{211}$At-MX35 F(ab’)2
- 0.2 MBq $^{125}$I-HSA

**Follow up**

- Hematology
- TSH
- Creatinine
- HAMA
Pharmacokinetics in patients

Pharmacokinetics was related to the initial activity concentration (IC) of the infused $^{211}$At-MX35 F(ab’)2 solution.

**Peritoneal fluid**

$^{211}$At-MX35 F(ab’)2

$^{125}$I-HSA

**Plasma**

$^{211}$At-MX35 F(ab’)2

$^{125}$I-HSA
Pharmacokinetics in patients - thyroid uptake

The Sahlgrenska Academy
Conclusions phase I study

1. Intraperitoneal administration of $^{211}$At-MX35 F(ab’)$_2$ can most probably achieve therapeutic absorbed doses in microscopic intraperitoneal tumors, without observed or estimated toxicity.

2. Maximum tolerable absorbed dose to peritoneum in humans is not known.

The 9 patients:
- Two still without any sign of disease.
- Two with relapse, although not peritoneal.
- Five have died in their disease. Two without peritoneal relapse.
- Total: Only 3/9 have had peritoneal relapse ~4 y after therapy.

Note: The 9 patients included were all in a much more advanced stage than the intended patient population for a phase II-III study, which will be given the treatment directly after primary chemotherapy.
Motif for a phase II study

- Microscopic peritoneal tumors might be the cause of relapse
- Low radiation risk
- Feasible therapy

85 patients needed for detection of $\geq 30\%$ decrease in recurrence within 2.5 years.

Collaboration between different centers?
Future/ongoing work

• Clinical phase II study
• Possible improvements
  - Add i.v. injection
  - Smaller antibody fragments
  - Pretargeting
  - $^{213}$Bi (in collaboration with ITU, Karlsruhe)
• Other types of cancer
  - Prostate cancer, breast cancer.
Authors

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Alpha emitting radionuclides

Astatine-211
+ Good physical properties ($T_{1/2}$, daughters).
+ Chemistry under development.
+ Specific activity (antigenic sites).
+ ”Unlimited source” due to $^{209}\text{Bi}(\alpha,2n)^{211}\text{At}$.
  
  Cost: Approx. 2000 Euro per patient.
– Few production facilities, limited capacity.
Alpha emitting radionuclides cont.

Bismuth-213
+ Good physical properties ($T_{\frac{1}{2}}$, daughters).
+ Chemistry well established.
+ Generator produced.
– Limited source of Ac-225?
The TAT Group
www.TargetedAlphaTherapy.com

Thank you for your attention!