Astatine-211 alpha particle radioimmunotherapy in Ovarian carcinoma; Phase-I outcome

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For the TAT-group, (www.TAT.gu.se)

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Ovarian Cancer

Stage 1: limited to the ovaries
Stage 2: limited spread to pelvis
Stage 3: spread through abdomen
Stage 4: spread to distant organs

Advanced disease at diagnosis. Approx. 60% stadium > III

- High rate of intra abdominal recurrences
- Death from ovarian cancer most often occurs from progression of abdominal disease.
Maximum cytoreductive surgery AND Post op. (pre op) platinumbased chemotherapy

- Cis-platinum superior to non-platinum chemo
- Carboplatin equal to cis-platinum
- Ptaltinum based combo superior to platinum monotherapy
Lymphadenectomy in Ovarian Neoplasms (LION)
647 pts (st IIB-IV) randomized (1:1) +/- removal of retroperitoneal pelvic and paraortic lymphnodes

- High relapse rate-
  - ~50% in 2 years relapse
- NO benefit in OS or in PFS despite 56% of pts had metastatic lymphnodes!

Indicating that Chemotherapy can eradicate metastatic spread to affected lymphnodes

But fails to eradicate non vascularized i.p. deposits
Enhanced local therapy can decrease recurrences but at high toxicity for patients

**External radiation therapy**
WAR, whole abdominal radiation therapy

Total abdominal dose of > or /=36 Gy associated with a longer overall survival

Toxicity  Acute: diarraea, nausea, fatigue, hematol
Longterm toxicity: basal pnemonia, Liver damage, bowle obstruction

**Intra peritoneal chemotherapy**

- OS: median increase approx. 67 mts vs 50mts
- More toxic:
- GI, Hematological, renal, fatigue
- **Not Standard**
Intraperitoneal Radioactive Phosphorus ($^{32}$P) Versus Observation After Negative Second-Look Laparotomy for Stage III Ovarian Carcinoma: A Randomized Trial of the Gynecologic Oncology Group

Phase III Trial of Intraperitoneal Therapy With Yttrium-90–Labeled HMFG1 Murine Monoclonal Antibody in Patients With Epithelial Ovarian Cancer After a Surgically Defined Complete Remission


## Theoretical considerations

**Model Results** from Using 1.7 L of Intraperitoneally Infused Radiolabeled mAbs in Osmotic Agent

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Fraction of mAbs radiolabeled</th>
<th>Administered activity (MBq)</th>
<th>% Decays per cell (%)</th>
<th>Bone marrow</th>
<th>Peritoneal fluid</th>
<th>Tumor (from cell-bound mAbs)</th>
<th>Tumor (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{177}$Lu</td>
<td>1/270</td>
<td>3,900</td>
<td>2,561</td>
<td>0.94</td>
<td>17</td>
<td>0.43</td>
<td>0.34 0.30</td>
</tr>
<tr>
<td>$^{90}$Y</td>
<td>1/270</td>
<td>1,100</td>
<td>2,580</td>
<td>0.61</td>
<td>25</td>
<td>0.13</td>
<td>0.12 0.12</td>
</tr>
<tr>
<td>$^{86}$Rb</td>
<td>1/270</td>
<td>6,300</td>
<td>2,561</td>
<td>1.02</td>
<td>68</td>
<td>0.22</td>
<td>0.18 0.17</td>
</tr>
<tr>
<td>$^{211}$At</td>
<td>1/200</td>
<td>3,300</td>
<td>2,602</td>
<td>0.14</td>
<td>24</td>
<td>0.24</td>
<td>0.23 0.26</td>
</tr>
<tr>
<td>$^{212}$Bi</td>
<td>1/200</td>
<td>3,000</td>
<td>953</td>
<td>0.02</td>
<td>43</td>
<td>0.71</td>
<td>0.80 0.93</td>
</tr>
<tr>
<td>$^{212}$Pb</td>
<td>1/200</td>
<td>300</td>
<td>2,956</td>
<td>0.36</td>
<td>37</td>
<td>2.44</td>
<td>2.83 2.88</td>
</tr>
</tbody>
</table>

**RBE** = relative biological effect; **D** = diameter.

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**Biokinetic Modeling and Dosimetry for Optimizing Intraperitoneal Radioimmunotherapy of Ovarian Cancer Microtumors**

Stig Palm¹, Tom Bäck¹, Börje Haraldsson², Lars Jacobsson¹, Sture Lindgren¹ and Per Albertsson³

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Dr S. Palm  
Dr T. Bäck  
Dr L. Jacobsson
Cyclotron production of At-211

Scanditronix MC32 NI cyclotron at Rigshospitalet in Copenhagen
Installed 1986

Nuclear reaction:
$^{209}$Bi$(\alpha,2n)^{211}$At

Dr H. Jensen

Target

$E_a = 29 \pm 1$ MeV

Al ($\sim 7 \mu m$), $^{209}$Bi ($\sim 18 \mu m$)

Backings:
Al (30 x 27 x 5mm)
• **Murine MX-35** (Sloan-Kettering Institute)
• Recognize, membrane sodium transporter (NaPi2b)
• F(ab’)\_2 fragments in Phase I study
• >90% of human epithelial ovarian cancers
Adjuvant therapy (also adjunct or adjunctive therapy)

Is therapy given in addition to main therapy (generally surgery)

Patient is free from detectable disease
  - but have a statistical risk of recurrence

A proportion of treated patients are already cured
  - and only subjected to the risk(s) of treatment
The study

A phase-I biodistribution and pharmacokinetic study

INCLUSION CRITERIA

- Histological confirmed ovarian adenocarcinoma
- Intra peritoneal recurrence following platinum/taxane based chemotherapy
- Treated by secondline to complete or good partial remission
- Normal baseline blood, liver, kidney, thyroid laboratory results
- Performance status of 2 or better
- Written informed consent prior to trial procedures.

EXCLUSION CRITERIA

- Active parenchymal disease, (i.e. FIGO IV)
- Presence of symptomatic extra abdominal met
- Significant heart disease /arrythmias
- Concomittant serious illnesses, infection, bleeding
- Chronic inflammatory disease
- Treated with chemo or immunotherapy within 4w
- Previously recieved a murine antibody

Dr Håkan Andersson
Logistics of the therapy

$^{211}$At activity - from production to injection

**Preparations**
- Laparoscopy
- Peritoneal catheter insertion
- Peritoneal scintigraphy with $^{99m}$Tc
- Pretreatment with KClO$_4$ or KI (Patient 6-9)

**Infusion**
- 1-2 L Extraneal solution
- 34-355 MBq $^{211}$At-MX35F(ab’)$_2$

**Sampling**
- Blood (1-48h)
- I.p.fluid (1-24h)
- Urine (1-48h)
- Gamma camera (1-48 h)
Study period Dec 2005 - Jan 2011
Amendment: 1st inclusion of thyroid blocking 2nd for improved radiochemistry.
CTC v2 Toxicity in ITT population with catheter (n=17)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal discomfort/pain</td>
<td>13</td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Skin (infection, ulcers, wound, p. poor healing)</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Abdominal swelling</td>
<td>6</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leakage</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm/shoulder pain</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
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<tr>
<td>Constipation</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertigo</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding in i.p. catheter</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Edema</td>
<td>2</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fever</td>
<td>1</td>
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<td></td>
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<tr>
<td>Small intestine perforation</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Absorbed doses. mGy/(MBq/L)

- Peritoneum: $15.6 \pm 1.0$
- Red bone marrow: $0.14 \pm 0.04$
- Urinary bladder wall: $0.77 \pm 0.19$
- Unblocked thyroid: $24.7 \pm 11.1$
- Blocked thyroid: $1.4 \pm 1.6$

No adverse effects were observed in laboratory parameters.
### Clinical outcomes

<table>
<thead>
<tr>
<th>Time to progression post-(^{211}\text{At}) (months)</th>
<th>Survival (years)</th>
<th>Time on chemo post-(^{211}\text{At}) (months)</th>
<th>Nb of lines(^8) post-(^{211}\text{At})</th>
<th>Admin. total activity (MBq)</th>
<th>Activity concentration MBq/L</th>
<th>Approx. Specific Activity (nb (^{211}\text{At}/\text{mAb}))</th>
<th>Effective dose (Sv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.1</td>
<td>1.7</td>
<td>6.5</td>
<td>2</td>
<td>34</td>
<td>22</td>
<td>1/2400</td>
<td>0.3</td>
</tr>
<tr>
<td>4.0(^*)</td>
<td>4.1</td>
<td>43</td>
<td>6</td>
<td>48</td>
<td>24</td>
<td>1/1400</td>
<td>0.3</td>
</tr>
<tr>
<td>54.1</td>
<td>12.3(^*)</td>
<td>28</td>
<td>6</td>
<td>40</td>
<td>20</td>
<td>1/1800</td>
<td>0.3</td>
</tr>
<tr>
<td>5.1</td>
<td>5.7</td>
<td>46</td>
<td>10</td>
<td>42</td>
<td>21</td>
<td>1/700</td>
<td>0.3</td>
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<tr>
<td>N.A(^*)</td>
<td>12.1(^*)</td>
<td>92</td>
<td>46</td>
<td>1/2100</td>
<td>0.6</td>
<td>1/1800</td>
<td>0.6</td>
</tr>
<tr>
<td>3.3(^*)</td>
<td>2.6</td>
<td>22</td>
<td>4</td>
<td>103</td>
<td>47</td>
<td>1/1500</td>
<td>1.3</td>
</tr>
<tr>
<td>4.0</td>
<td>2.3</td>
<td>26</td>
<td>6</td>
<td>119</td>
<td>101</td>
<td>1/2300</td>
<td>0.9</td>
</tr>
<tr>
<td>3.0</td>
<td>2.7</td>
<td>21</td>
<td>5</td>
<td>83</td>
<td>73</td>
<td>1/2900</td>
<td>0.7</td>
</tr>
<tr>
<td>41.3(^*)</td>
<td>9.6(^*)</td>
<td>22</td>
<td>5</td>
<td>65</td>
<td>53</td>
<td>1/500</td>
<td>2.3</td>
</tr>
<tr>
<td>5.0(^*)</td>
<td>2.9</td>
<td>14</td>
<td>2</td>
<td>297</td>
<td>180</td>
<td>1/200</td>
<td>2.6</td>
</tr>
<tr>
<td>3.7(^*)</td>
<td>1.6</td>
<td>14</td>
<td>3</td>
<td>333</td>
<td>203</td>
<td>1/2200</td>
<td>2.8</td>
</tr>
<tr>
<td>9.61</td>
<td>4.8</td>
<td>36</td>
<td>6</td>
<td>355</td>
<td>215</td>
<td>1/200</td>
<td>2.8</td>
</tr>
</tbody>
</table>

**Notes:**
- \(^*\) indicates response to first line of chemotherapy.
- \(^\dagger\) indicates no further chemotherapy.
- \(^\ddagger\) indicates response to post-therapy chemotherapy.

**Additional Data:**

**Single cell dose (Gy):**
- \(200\mu\text{m sphere}\): 4.5, 7.0, 5.5, 9.9, 6.0, 6.9, 9.2, 6.0, 4.7, 24.6, 45.1, 52.2
- \(300\mu\text{m sphere}\): 4.5, 7.0, 5.5, 9.9, 6.0, 6.9, 9.2, 6.0, 4.7, 24.6, 45.1, 52.2

**200\mu\text{m sphere}**
- 10Gy isodepth (\(\mu\text{m}\))
- Vol(\%) >10Gy
- \(10Gy\) isodepth (\(\mu\text{m}\))
- Vol(\%) >10Gy

<table>
<thead>
<tr>
<th>Duration of response after last chemo before (^{211}\text{At})-treatment</th>
<th>Duration of response after chemotherapy and (^{211}\text{At})-treatment</th>
<th>Duration of response on first treatment post</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\sim160)</td>
<td>(\sim160)</td>
<td>(\sim160)</td>
</tr>
</tbody>
</table>

**Duration of response:**
- \(\sim160\) days for each stage of treatment.

**Effective dose (Sv):**
- 0.3, 0.3, 0.3, 0.3, 0.6, 0.6, 1.3, 0.9, 0.7, 2.3, 2.6, 2.8
Summary

Low radiation related toxicity and low dose to critical organs
Procedure related symptoms mainly grade 1 and 2, including one grade IV intestinal perforation

No signs of diminished tolerability to following therapy
No signs of thyroid dysfunction and normal TSH, T4 values
Still effective dose above 2 Sv

Individual calculated absorbed doses
- to sphere of 200µm diameter 9/12 pts >10Gy
- to single cell only the last three pts >10Gy, (specific activity)
Take home message

Aiming to eradicate subclinical disease following standard therapy i.e. an adjuvant therapy.

We now know
- Logistics, production, chemistry and treatment are feasible (>3hrs from cyclotron)
- Low acute toxicity and seemingly longterm tolerability (NB small nb of pts)
- Absorbed doses (by modeling) to potential target clusters that cover single cells up to approx 100-150µm radius size of non-vascular clusters, (using high Spec activity)

The dilemma of choosing treatment activity in a randomised effect-finding study:

We can not use imaging or biopsy to evaluate effect.
Statistical gain.
-with a portion of patients already cured and thus subjected only to risk

Activity chosen need balancing of projected risk vs theoretical gain
Intraperitoneal $\alpha$-Particle Radioimmunotherapy of Ovarian Cancer Patients: Pharmacokinetics and Dosimetry of $^{211}$At-MX35 F(ab$'$)$_2$—A Phase I Study

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Physics Contribution

Absorbed Doses and Risk Estimates of $^{211}$At-MX35 F(ab$'$)$_2$ in Intraperitoneal Therapy of Ovarian Cancer Patients

Elin Cederkrantz, PhD,$^*$ Håkan Andersson, MD, PhD,$^1$ Peter Bernhardt, PhD,$^*$ Tom Bäck, PhD,$^*$ Ragnar Hultborn, MD, PhD,$^1$ Lars Jacobsson, PhD,$^*$ Holger Jensen, PhD,$^1$ Sture Lindegren, PhD,$^*$ Michael Ljungberg, PhD,$^*$ Tobias Magnander, MSc,$^*$ Stig Palm, PhD,$^*$ and Per Albertsson, MD, PhD$^1$
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  - Ragnar Hultborn, MD, professor emeritus
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