Developing Clinical Facilities for BNCT and proton radiotherapy in Birmingham

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University Hospital Birmingham

Particle Physics Group Seminar
Birmingham, November 2010
Overview of techniques and projects

- **External beam treatments**
  - X-ray therapy
  - Proton and ion beam therapy

- **Binary therapies**
  - Boron Neutron Capture Therapy
  - High Z enhanced radiotherapy

- **Systemic treatment**
  - Targeted radionuclide therapy
  - chemotherapy
Glioblastoma
Glioblastoma - clinical course

Head trauma
9M before

Mild headache

post-surgery

9M

Post-chemo-radiotherapy

Courtesy of Tetsuya Yamamoto, Tsukuba, Japan
The Tsukuba approach

Surgery → BNCT → XRT → Proton

Courtesy of Tetsuya Yamamoto, Tsukuba, Japan
Boron Neutron Capture Therapy

Ion combined range ~ 8-9µm. Cell diameter ~ 10 µm.

=> radiation damage mostly within cell
BNCT as a binary therapy

2 key steps

• Delivery of $^{10}\text{B}$ selectively to tumour cells and with a sufficiently high concentration

• Delivery of a thermal neutron fluence to the tumour cells, while delivering a non-toxic radiation dose to healthy cells
BPA-formulation – the problem

- Maximum concentration BPA-fructose ~30 mg/ml
- Clinical experience ranges 450 mg/kg/2 hours to 900 mg/kg/6 hours
  → 70 kg adult infusion volume 1.2 to 2.1 litres
- Target BPA dose 1050 mg/kg/2 hours → BPA-fructose volume 2.45 l
- Fructose not allowed for infusion in the UK

- In order to avoid any limitation imposed by tolerable fluid volume and regulatory authorities, a new BPA formulation was required.
BPA formulation – the solution?

• A range of excipients were tested for solubility and stability
  – fructose
  – glucose
  – mannitol
• The chosen product: BPA 100mg/ml in 110mg/ml mannitol
• pH of 8±0.2
• Osmotic pressure 1353 mOsm
• Thus BPA-mannitol concentration >3-fold BPA-fructose
• Avoids possible serious adverse reactions from hereditary fructose intolerance
Clinical optimisation of uptake parameters of Boronophenylalanine (BPA) for use in trials of Boron Neutron Capture Therapy (BNCT)

Trial Design

Stage 1: Route of delivery
- a) Using single dose BPA (350mg/kg over 2h) via central venous or intra-carotid artery
- b) With and without rapid (30s) Mannitol infusion (300ml 20%)

Stage 2: Dose escalation
- a) Single 750mg/kg dose over 2h
- b) Single 1050mg/kg dose over 2h
### Study Plan

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Patients</th>
<th>BPA route</th>
<th>Mannitol BBB</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>3</td>
<td>IV</td>
<td>No</td>
<td>Completed</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>3</td>
<td>IV</td>
<td>Yes</td>
<td>Completed</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>3</td>
<td>IA</td>
<td>No</td>
<td>Completed</td>
</tr>
<tr>
<td>Cohort 4</td>
<td>3</td>
<td>IA</td>
<td>Yes</td>
<td>Open - Nov 2010</td>
</tr>
</tbody>
</table>

This to be followed by dose escalation study on a further 6 patients.
Sampling

- **Blood** for $^{10}$B PK assay (-0.5h to +48h post start of Infusion)
- **Brain biopsies** for pathology & $^{10}$B assays (3h, 3.5 and 4h post infusion)
- **CSF** for $^{10}$B assay (at time of biopsies if accessible)
- **ECF** (Via Brain microdialysis) for $^{10}$B assay (0h to +48h)
- **Urine** for $^{10}$B for assay (-0.5h to +48h)
Results: Blood

Average Blood Data by Cohort

Boron Concentration (microg/g)

Cohort 1 Average
Cohort 2 Average
Cohort 3 Average

Times from infusion start (hrs)
Results: ECF

Average ECF Data by Cohort

- Cohort 1 Average
- Cohort 2 Average
- Cohort 3 Average

Boron concentration (micorg/g) vs. Time from infusion start (hrs)
Tumour cellularity

Patient 2 tumour biopsy

Patient 5 tumour biopsy
Correlation between boron uptake and Tumour cell number density

Boron uptake in tumour measured by ICP-MS [µg/g]

Cell number density

µg 10^6/g tissue, normalized

Cellularity Index
Results: adjusted for cellularity
Results: adjusted for cellularity
Results: adjusted for cellularity
Results: adjusted for cellularity
Results: adjusted for cellularity
Phenylalanine transport mechanism

• Selectively transported across the blood brain barrier, endothelial cells and astrocytic cells by a common LAT-1 transporter system.
• LAT-1 is upregulated in tumour cells and might be expected to enhance the concentration of L amino acids particularly in tumour cells.
• Increased uptake may be dependent on:
  – Strongly dependent on duration of exposure,
  – Less strongly dependent on concentration of BPA
  – Strongly dependent on relative expression of LAT-1
LAT-1 expression in GBMs

Photomicrographs of tumour cells in GBM (A) and a metastatic tumour (B) showing the LAT-1 cells as red, PCNA (proliferating) cells as blue and the LAT-1+PCNA cells as red-blue (arrows)

Slide courtesy of A Detta
Results for counted stained cell populations in GBMs

60-90 % of tumour cells express LAT-1

A much lower proportion are proliferating

Detta and Cruickshank, Cancer Res 2009
New findings on LAT-1

Expression of LAT1 predicts risk of progression of transitional cell carcinoma of the upper urinary tract

Kuniaki Nakanishi · Sho Ogata · Hirotaka Matsuo · Yoshikatsu Kanai · Hitoshi Endou · Sadayuki Hiroi · Susumu Tominaga · Shinsuke Aida · Hiroyasu Kasamatsu · Toshiaki Kawai

![Graph showing disease-free survival](image-url)
The conventional research paradigm compared with BNCT

Conventional wisdom
- Find something (protein, pathway, signal etc) that is unique to the tumour
- Block this and the tumour stops growing
  - Problem is that tumours adapt

BNCT with BPA
- find something that the tumour is doing (LAT-1 over expression)
- Exploit this to kill the tumour
- The more the tumour does this, the better BNCT will work
Glioblastoma Multiforme
Prognosis improvement in the last 30 years

Walker et al. J Neurosurg 49 (1978) 333-343

Disease progression or recurrence through lack of local control
Neutron source is $> 1 \times 10^{12} \text{ s}^{-1}$
(1 mA proton current at 2.8 MeV)

For 40 minute treatment time, need 5 mA proton current and suitable target
Neutron generation and moderation

Neutron source is $> 1 \times 10^{12} \text{ s}^{-1}$
Li target during fabrication
Thermal neutron intensity map

Thermal neutrons per source neutron
Doses to Tumour and normal cells
Dose to Tumour cells
### Clinical Experience (Approx data to 2008)

<table>
<thead>
<tr>
<th>Facility</th>
<th>Approx. patients (compound)</th>
<th>Tumours treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan (various)</td>
<td>&gt;300 (BSH / BPA)</td>
<td>Mainly GBM</td>
</tr>
<tr>
<td>Brookhaven, NY</td>
<td>54 (BPA)</td>
<td>GBM</td>
</tr>
<tr>
<td>MIT, Boston</td>
<td>28 (BPA)</td>
<td>GBM, melanoma (extremity and brain)</td>
</tr>
<tr>
<td>Espoo, Finland</td>
<td>&gt;200 (BPA)</td>
<td>GBM, Head and Neck</td>
</tr>
<tr>
<td>Studsvik, Sweden</td>
<td>52 (BPA)</td>
<td>GBM</td>
</tr>
<tr>
<td>Pavia, Italy</td>
<td>2 (BPA)</td>
<td>Metastases in liver (ex -vivo)</td>
</tr>
<tr>
<td>Petten, Netherlands</td>
<td>34 (BSH)</td>
<td>GBM, melanoma mets in brain</td>
</tr>
<tr>
<td>Rez, Czech Republic</td>
<td>5 (BSH)</td>
<td>GBM</td>
</tr>
<tr>
<td>Barriloche, Argentina</td>
<td>7 (BPA)</td>
<td>Melanoma of skin</td>
</tr>
</tbody>
</table>
BNCT Clinical Results from Tsukuba

15 patients only

BNCT + XRT
BNCT alone
Overall Survival Time

Time to progression

BNCT for glioblastoma
Boron neutron capture therapy for newly diagnosed glioblastoma

Tetsuya Yamamoto \textsuperscript{a,*}, Kei Nakai \textsuperscript{a}, Teruyoshi Kageji \textsuperscript{b}, Hiroaki Kumada \textsuperscript{c}, Kiyoshi Endo \textsuperscript{a}, Masahide Matsuda \textsuperscript{a}, Yasushi Shibata \textsuperscript{a}, Akira Matsumura \textsuperscript{a}

\textsuperscript{a}Department of Neurosurgery, University of Tsukuba, Tsukuba City, Japan
\textsuperscript{b}Department of Neurosurgery, Tokushima University, Japan
\textsuperscript{c}Department of Research Reactor and Tandem Accelerator, Japan Atomic Energy Agency, Japan

Radiotherapy and Oncology 91 (2009) 80–84
Glioblastoma Multiforme
Prognosis improvement in the last 30 years

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Disease progression or recurrence through lack of local control
Collaborations and Acknowledgements

UHB Trust: Prof Alun Beddoe, Drs Cecile Wojnecki and Richard Hugtenburg (now Swansea Uni), Dr Spyros Manolopoulos (ex STFC)

University of Birmingham: Profs David Parker and Garth Cruickshank, Drs Monty Charles and Andy Mill

University of Oxford: Dr Mark Hill, Prof Bleddyn Jones

PhD students: Zamir Ghani, Ben Phoenix

Funding bodies, EPSRC, CR-UK, UHB Charities
Critical steps in developing a clinical facility

• Complete P-K study and demonstrate a good understanding of BPA uptake mechanisms
• Improve the power and reliability of our neutron source (STR+FC CLASP proposal)
• Finalise the safety-case for MHRA and respond to queries as appropriate (approx 2 years)
• Funder and legal approvals for clinical trial
• Information paper for UHB Chief Exec in preparation (submission in Spring 2011)
• Formal partnership between UB and UHB?
Proposed Developments

- **Ion Source**: Upgrade power supplies and diagnostics. Re-tune to be a better source of mass-1 protons.
- **Beam Transport System**: Refine to minimize proton losses on apertures etc.
- **Target Cooling System**: Improve via binary ice approach.
Final thoughts (on BNCT)

- Binary therapies such as BNCT are aimed specifically at tumours which exhibit a high degree of infiltration into the surrounding healthy tissues.
- BNCT is still at a very early stage of development (patient numbers < 1000).
- They require input from a wide range of scientific disciplines.
- BNCT with BPA appears to offer potential as a therapeutic modality for glioblastoma.
- New data may identify high LAT-1 expression as a marker of a resistant sub-group of tumours.

- BNCT is ripe for investment and provides a great opportunity for the UK to take a lead.
- Can we afford to miss this opportunity? (as we did with particle therapy)
The Birmingham BNCT team

UHB Trust
• Profs Alun Beddow and Bleddyn Jones (now Oxford), Drs Cecile Wojnecki and Richard Hugtenburg (now Swansea Uni), Dr Allah Detta.

University of Birmingham
• Profs David Parker and Garth Cruickshank, Drs Monty Charles and Andy Mill

University of Oxford
• Dr Mark Hill (Prof John Hopewell)

CR-UK Pharmacokinetic Study
• Contributions from Strathclyde, Newcastle, Manchester and CR-UK

PhD students
• Zamir Ghani and Ben Phoenix (plus approx 10 previous PhDs)
Protons
Birmingham
Care is best at the centre
PROTONS

% DOSE

Single field

Depth

2 opposed fields

Depth

3 co-planar fields

Depth

X-Rays

%DOSE

Single field

Depth

2 opposed fields

Depth

3 co-planar fields

Depth

Slide Courtesy of Prof Bleddyn Jones
Proton therapy in UK: we already have it!

- World First: hospital based proton therapy at Clatterbridge, Liverpool, [converted fast neutron therapy facility].
- >1400 patients with ocular melanoma; local control >98%.
- First example of 3D treatment planning in UK
- Unsung success story of British Oncology.
- 62 MeV protons so eye tumours only
Paul Scherrer Institute

- Swiss National Research Lab
- Long-standing investment in proton therapy
- Major expansion in progress, with new cyclotron (250 MeV) and new treatment room
The Siemens synchrotron system
Proton Gantry – scale of a person
Optimal environment... continues to evolve
Proposed facility: Treatment Floor
One possible Configuration: First Floor

- 2 x Virtual MDT rooms
- Hot-desk space
Second Floor

Paediatric Unit, managed by BCH
UK scene – latest news..

- 3 Trusts (UCLH, Christie and Birmingham) are “helping the DH with the development of their outline business case for the spending review”
- The choice appears to be between 2 or 3 centres.
- For patients and pathways, 3 is very much better than 2
- If there are 2, they will be London and Manchester
- If there is a 3rd, it will be in Birmingham