Clinical trials in Molecular Radiotherapy

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Introduction

• Look at the role of clinical trials in radionuclide therapy
• Understand some of the terms used in clinical trials
• Look at two recent examples
  – Commercial trial – Alpharadin
  – Academic trial - HiLo
Why clinical trials

- Provides evidence base for clinical practice
- Provides data for toxicity and efficacy which is required for consent
- Provides evidence for re-imbursement
- Enables nuclear medicine to compete with other treatment modalities
What is needed for success

What is needed for success
What team for clinical trials

• NM doc
• Oncologist
• Study nurse
• Physicist
• NM techs
• Sponsor
• Clinical trials coordinator
ECTD

• Most studies in Europe has to follow ECTD
• Defines roles and responsibilities
• Provides a quality mark for all involved
• Ensures any medicinal product complies with GMP
• Will allow studies done in different countries to have comparable results
GMP

• Good manufacturing practice
• Ensures quality of products used in trials
• Each component must come from a GMP source
• Any product must be made to GMP with all records kept of what was used and how it was put together
The protocol

• This is the method that must be completed by all those undertaking trial
• Defines inclusion and exclusion criteria
• Defines what treatments to be given and when
• Defines what tests will be done to identify efficacy and toxicity
• Type of protocol defined by stage of trial
Types of trials

• Pre-clinical will be needed for new agents
• Phase-1 Defines maximum tolerated dose and for radio-isotopes dosimetry. In oncology normally done on patients with advanced cancers up to 25 patients
• Phase-2. Tries to define efficacy limited number of centres with fixed activity or fixed dose can be up to 100 patients
## Phase I Dose Escalation Schedule

<table>
<thead>
<tr>
<th>No of Patients</th>
<th>Treatment</th>
<th>Dose increase</th>
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<tbody>
<tr>
<td>3</td>
<td>10 mg CHT-25 + 370 MBq/m² ¹³¹I</td>
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</tr>
<tr>
<td>3</td>
<td>10 mg CHT-25 + 740 MBq/m² ¹³¹I</td>
<td>X 2</td>
</tr>
<tr>
<td>3</td>
<td>* 10 mg CHT-25 + 1480 MBq/m² ¹³¹I</td>
<td>X 2</td>
</tr>
<tr>
<td>3</td>
<td>* 10 mg CHT-25 + 2220 MBq/m² ¹³¹I</td>
<td>X 1.5</td>
</tr>
<tr>
<td>3</td>
<td>* 10 mg CHT-25 + 2960 MBq/m² ¹³¹I</td>
<td>X 1.3</td>
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* Bone Marrow Harvesting required
<table>
<thead>
<tr>
<th>Patient</th>
<th>#1</th>
<th>#2</th>
<th>#3</th>
<th>#4</th>
<th>Cumulative activity</th>
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<tbody>
<tr>
<td>1</td>
<td>370 (663)</td>
<td></td>
<td></td>
<td></td>
<td>370 (663)</td>
</tr>
<tr>
<td>2</td>
<td>370 (573)</td>
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<td></td>
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<td>370 (573)</td>
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<tr>
<td>3</td>
<td>370 (725)</td>
<td>740 (1377)</td>
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<td></td>
<td>1110 (2102)</td>
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<tr>
<td>4</td>
<td>740 (1380)</td>
<td>1480 (1868)</td>
<td>2220 (3395)</td>
<td>370 (554)</td>
<td>4810 (7197)</td>
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<tr>
<td>5</td>
<td>740 (1286)</td>
<td>1480 (2220)</td>
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<td>2220 (3506)</td>
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<tr>
<td>6</td>
<td>740 (1104)</td>
<td></td>
<td></td>
<td></td>
<td>740 (1104)</td>
</tr>
<tr>
<td>7</td>
<td>1480 (2397)</td>
<td>2220 (2560)</td>
<td>2960 (4553)</td>
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<td>6660 (10507)</td>
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<tr>
<td>8</td>
<td>740 (1093)</td>
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<td>740 (1093)</td>
</tr>
<tr>
<td>9</td>
<td>740 (1105)</td>
<td>1480 (2104)</td>
<td>2220 (3239)</td>
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<td>4440 (6448)</td>
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</tbody>
</table>

Repeated therapy possible at 1 month if localisation > 3% injected activity/kg + no stem cell rescue required
Incidence and CTC grade of haematological toxicity in relation to administered activity

<table>
<thead>
<tr>
<th>Administered activity (MBq per m²)</th>
<th>Treatment no.</th>
<th>Haemoglobin</th>
<th>Neutrophils</th>
<th>Lymphocytes</th>
<th>Platelets</th>
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<tbody>
<tr>
<td>370</td>
<td>4</td>
<td>G1(1),G2(2)</td>
<td>G1(1),G2(1)</td>
<td>G2(1)</td>
<td>G2(1)</td>
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<tr>
<td></td>
<td></td>
<td>G3(1)</td>
<td>G3(2)</td>
<td></td>
<td>G3(1)</td>
</tr>
<tr>
<td>740</td>
<td>6</td>
<td>G1(1),G2(5)</td>
<td>G2(1)</td>
<td></td>
<td>G1(1)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G2(1)</td>
</tr>
<tr>
<td>1480</td>
<td>4</td>
<td>G1(1),G2(2)</td>
<td>G1(2),G2(3)</td>
<td></td>
<td>G2(1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G3(4)</td>
<td>G3(4)</td>
<td></td>
<td>G3(2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G4(1)</td>
</tr>
<tr>
<td>2220</td>
<td>3</td>
<td>G2(2), G4(1)</td>
<td>G2(1), G3(1)</td>
<td></td>
<td>G3(1)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G4(2)</td>
</tr>
<tr>
<td>2960*</td>
<td>1</td>
<td>G2</td>
<td>G4</td>
<td></td>
<td>G3</td>
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<tr>
<td></td>
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</tr>
</tbody>
</table>

*DLT with toxic death due to *pneumocystis* pneumonia
FDG-PET Response in Hodgkin’s disease following 554 MBq (patient 04)

Mediastinal Lymphadenopathy
Phase II

- Can be single centre or multi-centre
- Looks at marks of efficacy
- Should not be seen as final proof
- Sets up expected response rate
- This to be used to power a proper phase III that will provide proof of efficacy
- Still monitor toxicity
Lu-177 octreotate (n=310) Kwekkeboom JCO 2008

- Carcinoid n=188
  - 1% CR, 22% PR, 17% MR, 42% SD, 20%DP
- PET non func n=72
  - 6% CR, 36% PR, 18%MR, 26% SD, 14% DP
- PET func n=19
  - 0% CR 60% PR, 20% MR, 30% DS, 10% PD
Krenning et al JCO 2005
Phase III trials

• Compare 2 types of treatment
• Can be vs placebo or vs standard treatment
• Normally multicentre
• If for registration maybe paid for by a drug company
• If to determine best practice may be funded by government or charity
• Patients assigned randomly to the two groups
• Often patient and their doctors “blinded”
Trial oversight-1

• Trial committee
  – Made up of PI of trial, centre PIs and sponsor
  – Reviews recruiting
  – No access to un-blinded data
  – Responsible for ensuring data collected though this may be via a third party
  – Publishes results
Trial oversight - 2

• Independent Drug (Trial) Monitoring Committee
  – Not involved in trial but knowledge of trial
  – Reviews un-blinded data at pre-determined time points
  – Looks for safety issue
  – Can stop trial
    • Toxicity
    • Poor recruitment
    • Proven efficacy
  – Not a co-author on final paper
Alpharadin Phase III RCT

- Set up by Algeta/Bayer
- Based at Radium Hospital, Oslo
- Commercial interest from Bayer
- Plan to set up trial in 30 countries
- Powered to show survival
- Need 900 patients 2/3 to have treatment, 1/3 placebo
- No imaging to preserve blinding
- Published NEJM July 2013 369: 213 Parker et al
Protocol

- Patient to have proven bone metastases from Ca prostate
- Could have failed therapy such as taxanes
- After consent randomised to treatment or placebo
- Only one person at each sites know if it is active drug-must not tell patient or other docs
- 30kBq/kg 4 weekly for 6 cycles if live long enough or symptoms not worse
Results OS

Overall Survival

Hazard ratio, 0.70 (95% CI, 0.58–0.83)  
P<0.001

Radium-223  
(median overall survival, 14.9 mo)

Placebo  
(median overall survival, 11.3 mo)

Survival (%) vs. Months since Randomization
New bone pain

Time to First Symptomatic Skeletal Event

Hazard ratio, 0.66 (95% CI, 0.52–0.83)
P<0.001

Radium-223
(median time to first symptomatic skeletal event, 15.6 mo)

Placebo
(median time to first symptomatic skeletal event, 9.8 mo)
A different approach

• The treatment of thyroid cancer has been in the realm of nuclear medicine since 1940s
• I-131 remains the most widely used radioisotope in cancer 70 years later
• General plan total thyroidectomy then use I-131 to destroy all remaining thyroid tissue and then monitor patient using TBG
• Normally use 100mCi (3.7GBq I-131)
Thyroid cancer – question 1

• rTSH used instead of T4 withdrawal when imaging patients with low activity I-131 or I-123

• Been shown to produce images as good as T4 withdrawal

• Though often used before therapy no clinical trial and not licenced

• Was rTSH as good as withdrawal
Prospective randomized clinical trial to evaluate the optimal dose of 131 I for remnant ablation in patients with differentiated thyroid carcinoma.
Question 2-How much I-131

- Though I-131 not expensive
- Activity too high to allow patients to be treated as an out-patient
- The main cost of treatment is the in-patient care
- Also the higher the activity the increased chance of side effects such as dry mouth
- Study from India suggested 1.1GBq is sufficient
How to set up an RCT

• Two questions
  – Would 1.1GBq be as good as 3.7GBq in ablating the thyroid
  – Could rTSH be used to replace T4 withdrawl
• Company that makes rTSH may be interested in funding part of study
• None of the companies making I-131 interested in selling LESS I-131
HiLo

• Put together proposal for a trial to compare 4 groups
  – 1.1GBq using T4 withdrawal
  – 1.1GBq using rTSH
  – 3.7GBq using T4 withdrawal
  – 3.7GBq using rTSH
  – Power calculation needed 109-110 patients per group
Results days in hospital

- Low-dose radioiodine
- High-dose radioiodine

<table>
<thead>
<tr>
<th>No. of Days in Hospital Isolation</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>≥4</td>
<td>10</td>
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# Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Comparison 1</th>
<th>Comparison 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-Dose Radioiodine</td>
<td>High-Dose Radioiodine</td>
</tr>
<tr>
<td>Ablation success based on diagnostic scan alone — no./total no. (%)</td>
<td>198/214 (92.5)</td>
<td>197/207 (95.2)</td>
</tr>
<tr>
<td>Risk difference (95% CI) — percentage points</td>
<td>-2.7 (-7.2 to 1.9)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Ablation success based on thyroglobulin alone — no./total no. (%)</td>
<td>159/186 (85.5)</td>
<td>153/173 (88.4)</td>
</tr>
<tr>
<td>Risk difference (95% CI) — percentage points</td>
<td>-2.9 (-9.9 to 4.0)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>Ablation success based on both diagnostic scan and thyroglobulin — no./total no. (%)</td>
<td>182/214 (85.0)</td>
<td>184/207 (88.9)</td>
</tr>
<tr>
<td>Risk difference (95% CI) — percentage points†</td>
<td>-3.8 (-10.2 to 2.6)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>Risk difference on sensitivity analyses‡</td>
<td>-4.9 (-11.2 to 1.4)</td>
<td></td>
</tr>
</tbody>
</table>
So what now

• Results confirmed by similar French and Taiwanese trails
• Now in UK using 1.1GBq I-131 ablation for low risk patients
• However, as stated the results may be very dependent on the surgeon used. In France and UK very centralised
• However, does show a phase III trial can be done by everyone and save money
Conclusion

• Well run RCT can provide useful answers
• Can be run by companies
• Also can be run by groups of Doctors
• Can result in changes to practice that can help patients
• Respected by other doctors