Five High Quality ANZMTG Trials Are Helping Define The Role Of Radiotherapy In Melanoma

Gerald Fogarty
The Australasian Melanoma Conference 2016
Hosted by Melanoma Institute Australia
28 – 29 October 2016, Sofitel Wentworth Hotel, Sydney
PRIMARY
Primary site Trial 1
1. ANZMTG 02.12 RADICAL Trial

- A randomised controlled multicentre trial of imiquimod versus radiotherapy for lentigo maligna (LM)
- Lead PI: Dr Pascale Guitera, Melanoma Institute Australia, Sydney, NSW, AU
- Patient focused Youtube video – enter Radical trial into You Tube search box
Primary site Trial 2

2. ANZMTG 01.09 RTN2

- A phase III trial of postoperative radiation therapy following wide excision of neurotropic melanoma of the head and neck

- PI: Dr Matthew Foote, Princess Alexandra Hospital, QLD, AU

- Open at MDAH, MSKCC
ANZMTG 01.09 RTN2 – Trial Schema

Localised Neurotropic Melanoma of Head and Neck

Surgical Excision (1cm margin)

RANDOMISATION

Adjuvant Radiotherapy (48 Gy in 20 F)

Observation

Follow up schedule

- All patients followed up for 5 years
- If lesion recurs locally, re-excise, re-stage and continue on F/U
ANZMTG 01.09 RTN2 – Trial Endpoints

• **Primary**
  - Time to in-field relapse

• **Secondary**
  - Progression-free survival
  - Overall survival
  - Patterns of relapse
  - Late toxicity
  - Quality of life
ANZMTG 01.09 RTN2 – Current accrual and sites

- Australian Sites (14 sites) + Memorial Sloan Kettering Cancer Centre, NYC, US
- Need 100 pts
- 38 patients randomised
- 2 from MSK
- 1 MDAH

Ethics underway at the following sites:
- Norfolk and Norwich University Hospital, UK
REGIONAL
Regional Trial 1
ANZMTG / TROG Melanoma Nodal Trial

• Adjuvant radiotherapy improves nodal field control in melanoma patients after lymphadenectomy
• PI: Professor Michael Henderson, Peter MacCallum Cancer Centre, VIC, AU
ANZMTG 01.02 – Trial Schema

Eligibility
• Completely resected, palpable, nodal metastatic melanoma

Stratification
Institution
Nodal Region
Number of positive nodes
Metastatic node size
Extent of extra-nodal spread

RANDOMISATION

Adjuvant RT (48 Gy in 20 F)  Observation
ANZMTG 01.02 – Trial Endpoints

• **Primary:**
  o Regional nodal field relapse (as a first relapse)

• **Secondary:**
  o Relapse free survival
  o Overall survival
  o Pattern of relapse
  o Late RT toxicity (including lymphoedema)
  o Quality of life
ANZMTG 01.02 – Time to lymph node field relapse
Microscopic melanoma is radiosensitive!!

HR (ART:OBS) = 0.47, P = 0.005

<table>
<thead>
<tr>
<th>Years from randomisation</th>
<th>Number at risk ART</th>
<th>Number at risk OBS</th>
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<tbody>
<tr>
<td>0</td>
<td>122</td>
<td>126</td>
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<tr>
<td>1</td>
<td>66</td>
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<tr>
<td>7</td>
<td>0</td>
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</tbody>
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### Late Effects

**Grade 2 – 4 (ART v OBS)**

only sub cut fibrosis signif

<table>
<thead>
<tr>
<th>Condition</th>
<th>H + N</th>
<th>Axilla</th>
<th>Groin</th>
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<tbody>
<tr>
<td><strong>Subcutaneous Tissue Fibrosis</strong></td>
<td>49% v 27% *&lt;br&gt; p = 0.042</td>
<td>60% v 34% *&lt;br&gt; p = 0.045</td>
<td>60% v 34% *&lt;br&gt; p = 0.045</td>
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<tr>
<td><strong>Chronic Pain</strong></td>
<td>24% v 17%</td>
<td>23% v 31%</td>
<td>23% v 31%</td>
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<tr>
<td><strong>Nerve Damage</strong></td>
<td>19% v 15%</td>
<td>26% v 19%</td>
<td>26% v 19%</td>
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<tr>
<td><strong>Joint Discomfort (RT field)</strong></td>
<td>21% v 12%</td>
<td>13% v 13%</td>
<td>13% v 13%</td>
</tr>
<tr>
<td><strong>Other Morbidity</strong></td>
<td>21% v 20%</td>
<td>39% v 29%</td>
<td>39% v 39%</td>
</tr>
</tbody>
</table>
Lymphoedema Leg

Mean + 2SE
Differs by 7.3%
P = 0.014
Interpretation

• Positive trial – 2 previous in US failed to accrue
• Reasonable to omit RT until recurrence in groin
• Non significant worsening of survival in ART group - “RT shortens survival” – Pts not referred – a great injustice
• ? Preoperative administration to avoid surgery in some patients (~ 25%) – REFORM trial
Where to now in the age of targeted therapy?

- Can the new systemic therapies achieve the same result as an adjuvant radiotherapy after surgery?

- With improved survival after systemic therapy it is more important to optimise regional control?

- Does regional control eventually translate into improved survival?

- RCT?
DISTANT METS
Distant mets trial 1
1. ANZMTG 02.14 CombiRT

- PI: Dr Tim Wang, radiation oncologist, Westmead Hospital, NSW, AU
- Phase 1 – Pall RT escalation trial
- To evaluate safety and tolerability of combination of dabrafenib, trametinib and “palliative” radiotherapy.
- Dose escalation - 8Gy/1#; 20/5; 30/10; 40/16
- Primary - Assess patient’s pain using visual analog scale (VAS).
- Accrual target = 30 patients over 12 months
- 4 on study
BRAIN METS

• Particular problem in Melanoma
• Cause morbidity – can bleed
• Cause mortality
• New drugs effective in brain
• Role of Sx and RT in brain?
2. ANZMTG 01.07 WBRTMel Trial

- Whole Brain Radiotherapy following local treatment of intracranial metastases of melanoma - A randomised phase III trial

First single histology WBRT trial

Lead PI: Professor Gerald Fogarty, St Vincent’s+Mater Hospitals Sydney and Melanoma Institute Australia
Trial Design

- **Follow up schedule** (every 8 weeks / MRIs every 12 weeks)
  - Patients followed up for life; data collected includes: intra extra cranial disease burden, performance status, QOL, NCF, health economics.

- **Neurocognitive Function and Quality of Life Components**
  - Patients will be excluded from the NCF and QOL aspects of the study if their fluency (oral and written) is less than a year 8 standard.
Study Status

- Primary endpoint – distant brain failure at 12 months on MRI
- Many secondary
- Cooperative study with TROG, OCTO
- Hippocampal sparing allowed
- 200 patients randomised to date – 20 to go!
- 60 from Oslo from Dr Kari Jacobsen
- 25 sites open and recruiting
- Patient focused Youtube video – enter WBRT Melanoma into search box
- [http://www.youtube.com/watch?v=7gxrA7vNWPE](http://www.youtube.com/watch?v=7gxrA7vNWPE)
Interim Analysis 12 months after 100th pt

- Occurred 12 months after randomisation of 100th patient
- Trial Management Committee supported the recommendation and recruitment is ongoing.
Risk of melanoma mets in hippocampus

• Review of 77 WBRT trial eligible patients, 115 mets
• median distance to the nearest hippocampus was 37.2 mm
• No mets within hippocampus
• 4 pts (5.2%) within the 5mm hippocampal low dose region

Hong & Fogarty et al. Radiotherapy & Oncology 2014
Whole Brain RT with hippocampal sparing and simultaneous boost to oligo-metastasis is possible with normal linac in real time
Controversy!

- 2014 ASTRO “Choosing wisely” – don’t add WBRT after local treatment of Brain mets
- Stopping accrual to WBRT trials – significant problem has been addressed in international presentations and publications
ANZMTG 5 RT Trials Summary

PRIMARY SITE
1. ANZMTG 02.12 RADICAL – RCT- RT v Imiquimod in LM
2. ANZMTG 01.09 RTN2 – RCT - PORT v Obs in H+N Neurotropic Mel

REGIONAL
1. ANZMTG 01.02/TROG 02.01 – RCT – PORT in regional control of nodal melanoma

DISTANT METS
1. ANZMTG 02.14 CombiRT – Ph 1 Pall RT + BRAF/MEK

BRAIN METS
1. ANZMTG 01.07 RCT - WBRTMel Trial - WBRT v Obs 1-3 MBMs
Thank you!

Questions