THE OUTBACK TRIAL

A Phase III trial of adjuvant chemotherapy following chemo-radiation as primary treatment for locally advanced cervical cancer compared to chemo-radiation alone

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Australia

Cervix Cancer Education Symposium, January 2017, Mexico
Treatment of locally advanced disease

- Concurrent cisplatin and radiation the standard of care for locally advanced disease for FIGO stage 1B or higher: NCI alert in 1999

- Individual patient data meta-analysis of 18 trials confirmed benefit of concurrent chemo:
  - significant improvement in 5 year OS rate: (60 to 66%)
  - significant improvement in 5 year DFS rate (50 to 58%)
  - Also improved loco-regional disease-free survival

Chemoradiotherapy for cervical cancer meta-analysis collaboration: JCO 2008
Negative prognostic factors

- Larger tumor volume: particularly >50cc
- Higher FIGO stage: clinical staging
- Uterine corpus invasion: determine on MRI
- Nodal involvement: utility of PET staging
- Smoking
- Adenocarcinoma?

Narayan et al, Int J Gynecol Ca 2009
Monk et al, Int J Gynecol Ca 2007
Waggoner et al, Gynecol Oncol 2006
Mileshkin et al, Int J Gynecol Ca 2014
Fujiwara et al, Curr Oncol Rep 2014
Which chemotherapy?

• Cisplatin 40mg/m² weekly (5-6 cycles) during chemoRT a recommended standard

• Meta-analysis also suggested similar benefit with non-platinum regimens
  • No effect of cycle length or dose intensity of cisplatin

• Options for those not suitable for cisplatin
  • Carboplatin – tolerable but may be inferior
  • 5FU – tolerable but may be inferior

Au-Yeung et al, JMIRO 2013
Lanciano et al, JCO 2005
Distant failure the most common site of first relapse

- Loco-regional failure alone is rare 17/436 (4%)
- Meta-analysis: loco-regional failure in 35%
- Disease often relapses at multiple sites

Chemoradiotherapy for cervical cancer meta-analysis collaboration: JCO 2008
Narayan et al, Int J Gynecol Ca 2007
How can we reduce distant failures?

JCO meta-analysis suggested improved survival in the 2 trials that gave 2 cycles of additional chemo (‘OUTBACK’) - may treat micromets and improve survival - Absolute 5 year OS benefit of 19%

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Chemoradiotherapy for cervical cancer meta-analysis collaboration: JCO 2008
Standard cisplatin chemoRT vs Cisplatin-Gemcitabine chemoRT followed by 2 cycles of cisplatin/gemcitabine

- 9% improvement in PFS (65 to 74%) at 3 years but at a cost of increased toxicity: HR 0.68 (P = 0.022)
- Patients only followed-up for 1 year so unable to evaluate impact on OS
- Local failure 11 vs 16% (P=NS)
- Distant failure 8 vs 16% (P = 0.005)
Subsequent questions

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Control arm</th>
<th>Cis/Gem arm</th>
<th>P value</th>
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<tbody>
<tr>
<td>≥ 1 x G3/G4 toxicity</td>
<td>46%</td>
<td>87%</td>
<td>P&lt;0.001</td>
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<tr>
<td>Hospitalized</td>
<td>11 pts</td>
<td>30 pts</td>
<td>P = 0.003</td>
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<tr>
<td>Discontinued Rx</td>
<td>1 pt (&lt; 1%)</td>
<td>18 pts (7%)</td>
<td>P&lt;0.001</td>
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<tr>
<td>Transfusion</td>
<td>28%</td>
<td>49%</td>
<td>P&lt;0.001</td>
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- How manageable is the toxicity given others couldn’t deliver and what about long-term toxicity? (9 vs 2 pts)
- What is the concurrent gemcitabine adding?
- Would further adjuvant chemo improve the results?
- Would different drugs be better / less toxic

Puget Sound Oncology, Gynecol Oncology 2006
Thomas G, JCO 2011
Recent RCT examining only concurrent treatment

- Cisplatin concurrent chemoRT
  vs
- Cisplatin/Gemcitabine concurrent chemoRT

Closed early after interim analysis suggested no potential to improve survival and increased toxicity (n=74)

Wang CC et al, Gynecol Oncol 2015
OUTBACK trial: randomized phase III study

Patients with stage IB1 & positive nodes, IB2, II, IIIB or IVA cervical cancer who have given informed consent

Eligible patients

RANDOMISE

Max 6 weeks

Arm A – Control Arm
Concurrent chemoradiation

Arm B – Intervention Arm
Concurrent chemoradiation followed by 4 cycles of Carboplatin/Paclitaxel

Follow up for a minimum of 3 years
OBJECTIVES

Primary objective: To determine if adding adjuvant chemo to standard chemo-XRT improves overall survival

- A sample size of 780 (390 per arm) will have 80% power with 95% confidence for detecting a reduction in the hazard of death of at least 30% (HR 0.68) from the control regimen (approx 10% improvement in OS at 5 years from 63% to 73%)
- Based on 3 year accrual rate and median time to recurrence of 12 months
OBJECTIVES

Secondary objectives: To determine
• Progression-free survival rates
• Acute and long-term toxicities
• Patterns of disease recurrence
• The association between RT compliance and outcomes
• Patient QOL, including psycho-sexual health

Tertiary objectives:
• To collect blood and tissue for translational studies
• To explore the association between complete metabolic response on post-treatment PET and outcomes

Cervix Cancer Education Symposium, January 2017, Mexico
Gynecologic Cancer InterGroup
Cervix Cancer Research Network: The OUTBACK trial

- Multi-centre phase III trial
- International, Cooperative group study
- Led by ANZGOG
- Coordinated at the NHMRC Clinical Trials Centre (CTC), the University of Sydney

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How OUTBACK evolved

• Originally presented at the ‘new concepts’ session at the ANZGOG meeting in 2008
• Proposed as a 40 patient phase II to assess feasibility and tolerability
• Protocol taken to ACORD trial development workshop in 2009 by fellow: Dr Carmel Pezaro
• Concurrently presented for discussion at the GCIG Cervix Consensus meeting in Manchester in 2009 and endorsed for further development as a phase III trial
TRIAL OPENED MARCH 2011

• 43 patients: 27 ANZ, 16 GOG (at 24 May 2012)
The challenges

• Persuading PHARMA to supply paclitaxel
• Multiple unsuccessful Australian grant apps despite international interest
  – PeterMac, Perpetual, Victorian Cancer Agency
  – NHMRC/Cancer Australia 2009-10, 2011
  – ‘don’t think you can do it’
• Persuading the US GOG to join
• Contracts, insurance, lawyers
• Not being able to open in India or South America
• Need to increase the sample size

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The keys to success

• Lots of early morning teleconferences and thousands of emails
• Patience and diplomacy
• Think of it like running a marathon
• A great team of helpers and supporters locally - led by Julie Martyn from the CTC
• Mentors – Martin Stockler, Danny Rischin
• Lots of international help and support
  Ted Trimble, Gillian Thomas, Bill Small
  Dave Gaffney, Kathleen Moore, Brad Monk
• Believe in yourself!
Recruitment Jan 2016: 869/900

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From little things...