Long Course Chemoradiation for Rectal Cancer

The transition from 5-fluorouracil to Capecitabine. A retrospective Audit of Single Centre Experience in a New Zealand Setting

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Introduction

- Incidence rates of colorectal cancer in New Zealand rank amongst the highest worldwide\(^1\)

- Complete surgical resection is the cornerstone of curative treatment

- Neoadjuvant treatment is given
  - T3/T4 tumours
  - Nodal disease
  - Distal tumours

What is long course chemoradiation?
Chemotherapy sensitizes the tumour to the effects of radiation

5 FU bolus versus infusion
Capecitabine

- Convenient and avoids a central line
- Mechanism of action may enhance tumour radiosensitivity relative to normal tissues as final step of enzymatic activation occurs within the tumour
- Effect on surrounding tissues may be decreased
- Preclinical studies show additive tumour cell inhibition with radiotherapy compared to 5FU
Capecitabine

- Two Phase 1 studies

- Dunst et al\(^2\)
  - Dosing ranged from 250 – 1250mg/m\(^2\) twice daily
  - No grade 3/4 toxicity seen at 825mg/m\(^2\)
  - DLT was hand foot syndrome

- Ngan et al\(^3\)
  - MTD was reached at dose level of 1000mg/m\(^2\) bd for 5 days throughout radiation
  - 900mg/m\(^2\) was associated with no DLTs

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Phase II/III studies

- Multiple phase II/III studies comparing Capecitabine versus 5 Fluorouracil
- Most studies used 825mg/m² twice daily (range 500-1200mg/m²)
- Shown to be non-inferior in phase III trials[^4][^5][^6]
- Comparative rates of downstaging and sphincter preservation[^4][^5][^6]
- Comparable toxicity

Pathological Complete Response

- pCR = no residual carcinoma

- Metanalysis have shown improved disease free survival and overall survival if pathological complete response is seen after neoadjuvant therapy\(^7\)

- Pathological complete response rate in these studies is 15%

Audit

- Retrospective audit of patients receiving neoadjuvant chemoradiation for rectal cancer at Wellington Hospital January 2005 – May 2011
- WBCC transitioned from 5FU to Capecitabine in 2006
- Chosen dose 875mg/m² given continuously with radiotherapy
- Examines toxicity rates and pathological complete response rates, comparing 5FU with capecitabine, in patients with rectal cancer receiving neoadjuvant chemoradiotherapy
Methods

- Information collected via review of clinical notes
  - Demographics
  - MRI stage at diagnosis
  - Treatment intent
  - Location of tumour
  - Type of treatment received
  - Type of chemotherapy
  - Grade 3-4 toxicity events (NTCAE version 3)
  - Treatment discontinuation events
  - Complete pathological response
ChemoRadiation

- 5 Fluorouracil 225mg/m^2/day infused continuously via FOLFUSOR device during radiation
- Capecitabine 875mg/m^2 twice daily continuously whilst receiving radiation
- Radiation given with standard fields over 5-6 weeks to 45 Gy with 5.4 Gy boost
246 Patients notes reviewed

112 Patients Analysed in audit

118 patients Short Course Radiation

6 Patients Adjuvant chemoradiation

3 patients neoadjuvant radiation alone

7 patients received long course chemorad with palliative intent and did not undergo surgery
## Results: Demographics

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<tr>
<th></th>
<th>Males</th>
<th>Females</th>
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<tr>
<td></td>
<td>66%</td>
<td>33%</td>
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Median Age: 63 years  range 26-86
Location

- Of patients receiving long course chemoradiation initial MRI staging revealed

<table>
<thead>
<tr>
<th>Location</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Rectosigmoid</td>
<td>8%</td>
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<tr>
<td>Upper</td>
<td>7%</td>
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<td>Mid</td>
<td>21%</td>
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<td>Low</td>
<td>64%</td>
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Stage

- T4 tumours 20%
- T3 tumours 74%
- T1/2 tumours 6%
- Node negative tumours 20%
Chemotherapy Prescription

- In those receiving neoadjuvant long course chemoradiation with curative intent

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<th>5 Fluorouracil</th>
<th>Capecitabine</th>
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<td>21 (19%)</td>
<td>91 (81%)</td>
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Chemotherapy Toxicity

- Capecitabine
  - Grade 3-4 toxicity seen in 10%
    - Of these 10% hand foot syndrome, 90% diarrhoea
- 5-Fluorouracil
  - Grade 3-4 toxicity seen in 4%
    - fatigue
  - 16% of patients had a treatment interruption
    - Average duration Capecitabine 13 days
    - Average duration 5-Fluorouracil 4 days
Treatment completion

• In patients who were treated with curative intent (n=112)

  • 1 patient receiving capecitabine did not complete radiotherapy as developed grade 4 diarrhoea

  • 1 patient did not complete neoadjuvant cape + XRT as developed a bowel obstruction. Went on to have surgery.

  • 1 patient declined to have surgery after cape + XRT

  • 1 patient died of a suspected PE during neoadjuvant cape + XRT treatment

  • 1 elderly patient developed unrelated delirium after neoadjuvant therapy and surgery was cancelled

• All other patients completed prescribed neoadjuvant radiation treatment and went on to have surgery
# Complete Pathological Response

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<td>9 %</td>
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<tr>
<td>Das et al</td>
<td>89</td>
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<tr>
<td>Dunst et al</td>
<td>69</td>
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<td>Veerasarn et al</td>
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<tr>
<td>Chau et al</td>
<td>68</td>
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<tr>
<td>Wong et al</td>
<td>18</td>
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<td>Kim et al</td>
<td>38</td>
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Conclusions

- Capecitabine 875mg/m² in conjunction with radiation has acceptable levels of toxicity and comparable rates of pathological complete response.

- Capecitabine toxicity did not interfere with ability to complete radiation or proceed to surgery.

- Pathological complete response rates from Wellington are comparable with rates from meta-analysis.
References


