MRC FOCUS2

Chemotherapy choices and doses in frail and elderly patients with advanced colorectal cancer

Matt Seymour, Tim Maughan, Harpreet Wasan, Alison Brewster, Steve Shepherd, Sinead O’Mahoney, Beth May, Lindsay Thompson, Angela Meade and Ruth Langley, on behalf of The UK NCRI Colorectal Clinical Studies Group and FOCUS2 Investigators
<table>
<thead>
<tr>
<th></th>
<th>PS 0-1</th>
<th>PS ≥ 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOCUS ('00 – '04)</td>
<td>91%</td>
<td>9%</td>
</tr>
<tr>
<td>CR06 ('96 – ’98)</td>
<td>78%</td>
<td>22%</td>
</tr>
<tr>
<td>Non-trial treated patients</td>
<td>?</td>
<td>?</td>
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</table>
what happens to all the patients who don’t go into trials?

- survey of 59 FOCUS investigators Feb ‘02
  
  - For every 10 patients entering FOCUS, they were seeing a further 17
    - most treated with chemotherapy; some not
    - usually single-agent therapy
    - often less than standard doses
FOCUS2:

- Patient Selection – who will benefit?
- Drug Selection – which drugs?
- Dose selection – how much?
advanced CRC, no prior treatment any age, PS ≤2 suitable for standard 1st-line clinical trial?

- yes
  - enter the standard trial

- no: frailty, age or both
  - enter FOCUS2
    - comprehensive health assessment
      - Chemotherapy randomisation all doses 80% of standard
        - after 6 weeks increase to 100% if no major toxicity and patient agrees
          - Outcomes: PFS, QoL
            - correlate outcomes with baseline for predictive analysis
• **Activities of daily living**
  - Nottingham: 21-point ADL scale
  - 4 subscales (mobility; kitchen; domestic; leisure)

• **Global QL**
  - EQ5D: 5-point QL scale: mobility, self-care, activity, pain, mood

• **Symptoms**
  - QLQC30 scales for fatigue, nausea/vomiting, pain, dizziness, sleep disturbance, appetite, constipation and diarrhoea
  - mean symptom score

• **Psychological**
  - HADS 14-point scale, anxiety and depression subscales

• **Physical/nutritional**
  - Timed 30-metre walk
  - arm circumference
  - weight loss
  - BMI

• **Mental/cognitive**
  - MMSE: 30-point nurse-administered test

• **Co-Morbidity**
  - Charlson: 19-point medical co-morbidity score
Randomisation: 2x2 Factorial

- FU
- OxFU
- Cap
- OxCap
Randomisation: 2x2 Factorial

Factorial Comparison 1
- **Does capecitabine give better QL improvement at 12 wks?**

- 260 patients with data 0 and 12 wks gives 90% power to detect increase from 40% to 60% with improved overall QL (2-sided $\chi^2$; 5% significance).
Randomisation: 2x2 Factorial

- FU
- OxFU
- Cap
- OxCap

Factorial Comparison 2
- **Does the addition of oxaliplatin improve PFS?**

- 460 patients will detect an increase from 50% to 65% progression-free at 6 months (90% power; 2-sided 5% significance; log rank test).
Recruitment

- 460 patients, 62 UK centres
Overall Patient Characteristics

Age
- < 70 yr  22%
- 70-75 yr  35%
- > 75 yr  43%

Performance Status
- PS=0  22%
- PS=1  49%
- PS=2  29%
Dose increase at 6 weeks

- If no significant toxicity present, a discretionary dose increase to 100% after 6 weeks...

![Bar chart showing dose increase at 6 weeks]

**Legend:**
- Green: dose increased
- Yellow: no toxicity but not increased
- Red: not increased due to toxicity
The conventional trial endpoints.....
The conventional trial endpoints.....

**Capecitabine instead of 5FU:**
- no difference in efficacy (RR, PFS, survival)
- substantial increase in toxicity (diarrh, N&V, lethargy)
- but similar global QL at 12 weeks

**Adding oxaliplatin:**
- increased efficacy (RR, PFS but not survival)
- minimal increase in toxicity (diarrhoea)
Can baseline evaluation aid decision to treat?
what do we really want to predict?

patient’s view: was treatment worthwhile?

<table>
<thead>
<tr>
<th>Q.37)</th>
<th>...how much has your chemotherapy treatment interfered with your normal daily activities?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□ not at all □ a little □ quite a bit □ very much</td>
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</table>

<table>
<thead>
<tr>
<th>Q.38)</th>
<th>Since you started chemotherapy, how worthwhile do you think your treatment has been?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□ not at all □ a little □ quite a bit □ very much</td>
</tr>
</tbody>
</table>
what do we really want to predict?

patient’s view: was treatment worthwhile?

“overall success” of treatment

clinicians’ overall assessment of benefit?

did it have an objective anti-cancer effect?

was there major toxicity?
“overall success” after 12 weeks:

**good outcome**
- clinician scores benefit
  
-and
  - patient not dissatisfied
  
-and
  - no major toxicity

**intermediate outcome**
- either
  - clinician scores no benefit, but patient satisfied and no major toxicity
  
-or
  - clinician scores benefit, but either patient dissatisfied or major toxicity

**poor outcome**
- clinician scores no benefit
  
-and either of
  - patient dissatisfied
  - major toxicity
  
(or dead)
Randomised, eligible and started treatment = **450**

- alive, 3 month progress form received = **388**
- died before 3 months = **61**
- 3 month data missing = **1**

**Clinician Assessment**

- Clinician assessment "treatment benefit" = **247**
  - Patient satisfied and no major toxicity = **183**
    - Patient not satisfied or major toxicity = **64**
  - Patient not satisfied or major toxicity = **141**
    - Patient satisfied and no major toxicity = **82**
      - Patient not satisfied or major toxicity = **59**

**Outcome**

- Good outcome = **183 (41%)**
- Intermediate outcome = **146 (32%)**
- Poor outcome = **120 (27%)**
Univariate analysis

Predictive value of each factor at baseline for good, intermediate or poor outcome at 12 weeks

<table>
<thead>
<tr>
<th>Variable</th>
<th>number with data</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex</td>
<td>449</td>
<td>0.664</td>
</tr>
<tr>
<td>age</td>
<td>449</td>
<td>0.198</td>
</tr>
<tr>
<td>WHO perf. status</td>
<td>449</td>
<td>0.0001</td>
</tr>
<tr>
<td>number of disease sites</td>
<td>449</td>
<td>0.026</td>
</tr>
<tr>
<td>“liver-only” or not</td>
<td>444</td>
<td>0.057</td>
</tr>
<tr>
<td>WBC</td>
<td>449</td>
<td>0.0001</td>
</tr>
<tr>
<td>GFR (&lt;(\geq)50ml/min)</td>
<td>438</td>
<td>0.227</td>
</tr>
<tr>
<td>albumin</td>
<td>448</td>
<td>0.036</td>
</tr>
<tr>
<td><strong>Global QoL (EQ5D)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>409</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Symptoms (QLQ-C30):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fatigue</td>
<td>412</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>nausea/vomiting</td>
<td>420</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>pain</td>
<td>416</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>dyspnoea</td>
<td>420</td>
<td>0.010</td>
</tr>
<tr>
<td>insomnia</td>
<td>418</td>
<td>0.017</td>
</tr>
<tr>
<td>anorexia</td>
<td>414</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>constipation</td>
<td>416</td>
<td>0.180</td>
</tr>
<tr>
<td>diarrhoea</td>
<td>417</td>
<td>0.830</td>
</tr>
<tr>
<td><strong>mean symptom score</strong></td>
<td>421</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Physical/nutritional:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>431</td>
<td>0.339</td>
</tr>
<tr>
<td>weight loss</td>
<td>418</td>
<td>0.127</td>
</tr>
<tr>
<td>arm circumference</td>
<td>446</td>
<td>0.066</td>
</tr>
<tr>
<td>20-metre timed walk</td>
<td>388</td>
<td>0.196</td>
</tr>
<tr>
<td><strong>Activities (Nottingham ADL):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mobility subscale</td>
<td>449</td>
<td>0.008</td>
</tr>
<tr>
<td>kitchen subscale</td>
<td>449</td>
<td>0.017</td>
</tr>
<tr>
<td>domestic subscale</td>
<td>449</td>
<td>0.004</td>
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<tr>
<td>leisure subscale</td>
<td>449</td>
<td>0.086</td>
</tr>
<tr>
<td><strong>overall ADL score:</strong></td>
<td>449</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Medical co-morbidity:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson score</td>
<td>449</td>
<td>0.313</td>
</tr>
<tr>
<td><strong>Mental health:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cognitive function (MMSE)</td>
<td>393</td>
<td>0.507</td>
</tr>
<tr>
<td>anxiety (HADS)</td>
<td>449</td>
<td>0.275</td>
</tr>
<tr>
<td>depression (HADS)</td>
<td>449</td>
<td>0.781</td>
</tr>
</tbody>
</table>
Multivariate Analysis

- Backward stepwise ordinal logistic regression

- starting variables in model:
  - WHO PS; number of disease sites; liver-only vs not; WBC; ALB; age; EQ5D; mean symptom score; overall ADL

- model with 4 variables gives good prediction of outcome:

<table>
<thead>
<tr>
<th>variable</th>
<th>Co-efficient</th>
<th>z</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean symptom score</td>
<td>-0.0282</td>
<td>-3.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBC</td>
<td>-0.0731</td>
<td>-2.57</td>
<td>0.010</td>
</tr>
<tr>
<td>liver-only vs not</td>
<td>-0.3988</td>
<td>-1.81</td>
<td>0.071</td>
</tr>
<tr>
<td>WHO performance status</td>
<td>-0.1923</td>
<td>-1.34</td>
<td>0.181</td>
</tr>
</tbody>
</table>

Number of obs = 417; LR chi$^2$ = 42.45; prob >chi$^2$ = 0.0000
Sym score = 5%
WBC = 5 x 10^9/l
liver-only mets
WHO PS = 0

Sym score = 8%
WBC = 5 x 10^9/l
lung + LN mets
WHO PS = 1

Sym score = 50%
WBC = 11 x 10^9/l
liver + LN mets
WHO PS = 0

Sym score = 45%
WBC = 18 x 10^9/l
pelvic disease
WHO PS = 2

Sym score = 60%
WBC = 20 x 10^9/l
liver + other mets
WHO PS = 2

Sym score = 60%
WBC = 20 x 10^9/l
liver + other mets
WHO PS = 2
Effect of treatment allocation

If treatment allocation included in multivariate model

<table>
<thead>
<tr>
<th>variable</th>
<th>Co-efficient</th>
<th>z</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean symptom score</td>
<td>-0.0285</td>
<td>-3.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBC</td>
<td>-0.0832</td>
<td>-2.89</td>
<td>0.004</td>
</tr>
<tr>
<td>liver-only vs not</td>
<td>-0.3918</td>
<td>-1.75</td>
<td>0.081</td>
</tr>
<tr>
<td>WHO performance status</td>
<td>-0.1826</td>
<td>-1.26</td>
<td>0.208</td>
</tr>
<tr>
<td>Allocated oxaliplatin vs not</td>
<td>0.5840</td>
<td>3.10</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Number of obs = 417; LR chi² = 53.78; prob > chi² = 0.0000*
This analysis is preliminary...

- The next steps:
  
  - cross-validation of these findings with other trials
  
  - other outcome measures:
    - who will/will not tolerate full-dose treatment?
Conclusions

• Elderly and frail advanced CRC patients:
  
  • Can successfully be studied in a large RCT
  
  • The strategy of starting at 80% standard doses appears successful.
Conclusions

• **Baseline assessment using a range of tools:**

  • Is feasible in this population

  • Added to standard prognostic variables in predicting the overall success of treatment

  • Requires further analysis and validation, but could potentially aid decision-making:
    • when to use chemotherapy or not
    • choice of drugs or doses.
Acknowledgements

**Trial Management Group:**
- Tim Maughan
- Harpreet Wasan
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- Stephen Shepherd
- Sinead O’Mahoney

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- Lindsay Thompson
- Beth May

Staff of all participating centres...