Application of a Bayesian approach to treatment selection in a rare disease sub-population

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High risk multiple myeloma (HRMM)

• Multiple myeloma (MM) is a cancer that develops from cells in the bone marrow
  ~ 4500 new cases each year in the UK

• High risk = certain genetic factors associated with poor outcomes
  20-30% of MM
  Rare sub-population

• Standard treatment in newly diagnosed MM varies by practice

• Large phase III trial (Myeloma XI+) is currently evaluating treatment strategies

• Limited data available for HRMM sub-population
Designing the trial – challenges

Aim: assess whether we can improve outcomes for HRMM patients by selecting the optimum treatment strategy to take to phase III

- Rare patient population
  3 arm phase II: n~450 HRMM (~2500 MM)

- Variable standard treatment

- Differing treatment approaches requiring multiple endpoint evaluation
  Deliverability of treatment also important due to intense treatment in one arm
Designing the trial – overcoming the challenges

- Treatment selection based on multiple outcomes and multiple interim assessments for futility
- Using data from Myeloma IX/XI+ to provide almost concurrent control data

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Overcome?</th>
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<tbody>
<tr>
<td>Rare patient population</td>
<td>✓ Efficient in terms of sample size (n=120)</td>
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<tr>
<td>Variable standard treatment</td>
<td>✓ ‘Standard’ control arm as up to date as possible</td>
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<td>Differing treatment approaches requiring multiple endpoint evaluation</td>
<td>✓ Can incorporate multiple endpoints</td>
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Trial overview

**Arm A**
- Recruit 10 patients, perform interim assessment
- Stopping boundary crossed?
  - **YES**
    - DROP ARM
    - Recruit remaining patients to Arm B
  - **NO**

**Arm B**
- Recruit 10 patients, perform interim assessment
- Stopping boundary crossed?
  - **YES**
    - DROP ARM
    - Recruit remaining patients to Arm A
  - **NO**

Total n=120
STOP TRIAL
Final analysis
Endpoints

Interim analyses for futility
After every 10 patients reach 12 months post-rand
• Progression-free survival @ 12m post-rand
• Deliverability of treatment
• Minimal residual disease (MRD)
  • The small number of cancer cells remaining
  • Known to cause relapse

Final analysis
Compare each treatment arm to control prior
Compare two experimental treatment arms
• Progression-free survival at 18 months post-rand
Implementing the design

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A7, …, A14 = progressed or died by 18m

- Count data modelled using Dirichlet priors
  - Control data from MyeIX (later to be updated to MyeXI+):
    \[\text{Dir}(14, 29, 30, 15, 0, 0, 10, 50, 15, 18, 19, 13, 0, 0)\]
  - Experimental priors:
    \[a_1 + \ldots + a_{14} = 14, \text{ following the “flat prior” method suggested by Thall and Sung}\]
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- Data monitored according to endpoints
  - Compound events follow Beta distribution
  - Monitor via posterior probability
Stopping rules

Interim analyses:
• $P(\text{MRD }-\text{ve rate } > \text{control rate } + 10\%) < 0.05$
• $P(\text{Non-deliverability } > \text{control rate } + 20\%) > 0.9$
• $P(\text{Proportion progressed/died @ 12m post-rand } > \text{control rate}) > 0.9$

Final analysis:
• $P(\text{Proportion alive and progression-free at 18 months post-registration } > \text{control rate}) < 0.85$

Converted to stopping boundaries, e.g.
“At the first interim assessment, if the number of participants who are MRD negative is 1 or less (out of 10), stop for futility.”
Design performance

- Simulations performed to determine operating characteristics
- Check sample size large enough
- Assess probability of early stopping, $\pi$, under various scenarios
- Under null scenario (no change from control), $1-\pi$ is equivalent to $\alpha$
  
  5.27% in MUK nine with n=120
Summary / final thoughts

• Flexible design
  • Multiple endpoints
  • Complex data structure / interaction between endpoints
  • Updating control prior when additional data available

• MUK nine design now changed to 1 experimental arm
  • Remove deliverability endpoint (removed intense arm)
  • Re-evaluate simulations
  • Flexibility allows us to incorporate a new arm at a later date (if the opportunity arises!)

• Software freely available
  • Not all of the above are incorporated
  • R package being developed
References


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