Adjusting for Treatment Switching in RCTs – Identifying, analysing and justifying appropriate methods: a case study in metastatic melanoma

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Overview

• What is treatment switching?
• Direct and indirect switching
• Treatment switching adjustment methods for direct switching
• Applying adjustment methods to the BREAK-3 trial
• Assessing the validity of the assumptions
• Indirect switching to other post-study treatments
• Conclusions
What is treatment switching?

Switching can be “direct” or “indirect”
Treatment switching adjustment methods for direct switching

- Rank preserving structural failure time (RPSFT) model

- Iterative parameter estimation (IPE) algorithm
  Branson and Whitehead (2002)

- Inverse probability of censoring weights (IPCW)

- Two-stage accelerated failure time model
Treatment switching adjustment methods for direct switching

• Rank preserving structural failure time (RPSFT) model

• Iterative parameter estimation (IPE) algorithm
  Branson and Whitehead (2002)

• Inverse probability of censoring weights (IPCW)

• Two-stage accelerated failure time model

RPSFTM and IPE make the common treatment effect assumption
Treatment switching adjustment methods for direct switching

- Rank preserving structural failure time (RPSFT) model

- Iterative parameter estimation (IPE) algorithm
  Branson and Whitehead (2002)

- Inverse probability of censoring weights (IPCW)
  Robins and Finkelstein (2000), Hernan et al. (2001), Fewell,

- Two-stage accelerated failure time model

IPCW and Two-stage method are reliant on no unmeasured confounders assumption
Treatment switching adjustment methods  
for direct switching

- Rank preserving structural failure time (RPSFT) model  

- Iterative parameter estimation (IPE) algorithm  
  Branson and Whitehead (2002)

- Inverse probability of censoring weights (IPCW)  

- **Two-stage accelerated failure time model**  
  Two-stage is reliant on the existence of a disease-related secondary baseline
Treatment switching adjustment methods for direct switching

- Rank preserving structural failure time (RPSFT) model

- Iterative parameter estimation (IPE) algorithm
  Branson and Whitehead (2002)

- Inverse probability of censoring weights (IPCW)

- Two-stage accelerated failure time model

RPSFTM, IPE and two-stage are generally applied with recensoring, but this may cause bias if the treatment effect is time-dependent.
Applying adjustment methods to the BREAK-3 trial (August 2014 data-cut)

- Dabrafenib vs DTIC chemotherapy
  187 patients randomised to dabrafenib, 63 patients randomised to DTIC

- Switching was permitted after disease progression
  37 (58.7%) DTIC group patients had switched onto dabrafenib as of August 2014

- Time from randomisation to switch
  Median time-to-switch was 93 days,
  80% of switchers had switched by approximately 169 days,
  90% of switchers had crossed over by approximately 281 days
### Adjusting for direct (DTIC to dabrafenib) switching in the BREAK-3 trial

<table>
<thead>
<tr>
<th>Description</th>
<th>HR</th>
<th>DTIC group</th>
<th>Median OS days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description Point estimate lower 95% CI Upper 95% CI</td>
<td></td>
<td>Median OS days</td>
<td></td>
</tr>
<tr>
<td>Intention to treat (ITT) analysis</td>
<td>0.81</td>
<td>0.56</td>
<td>1.16</td>
</tr>
<tr>
<td>RPSFTM `treatment group'</td>
<td>0.59</td>
<td>0.25</td>
<td>1.43</td>
</tr>
<tr>
<td>RPSFTM `treatment group' without recensoring</td>
<td>0.68</td>
<td>0.36</td>
<td>1.29</td>
</tr>
<tr>
<td>IPCW</td>
<td>0.71</td>
<td>0.31</td>
<td>1.62</td>
</tr>
<tr>
<td>Two-stage Weibull</td>
<td>0.77</td>
<td>0.50</td>
<td>1.19</td>
</tr>
<tr>
<td>Two-stage Weibull without recensoring</td>
<td>0.78</td>
<td>0.51</td>
<td>1.18</td>
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Which is the appropriate adjustment method?
Assessing the validity of assumptions

- **Common treatment effect** *(RPSFTM and IPE)*
  - Median time-to-switch was 93 days
  - Comparisons of PFS as randomised and comparisons of PFS of first and second progression for switchers indicated that switchers do benefit from switching treatment – no strong evidence to reject common treatment effect

- **No unmeasured confounders** *(IPCW and Two-stage)*
  - Data on EQ5D and EORTC was not collected beyond the June 2012 data-cut

- **Time to switch from secondary baseline** *(Two-stage)*
  - Median time from progression to switch for switching patients was 16 days
Assessing model performance

- **Counterfactual HR (RPSFTM and IPE)**
  - Counterfactual HRs were 1.00 for RPSFTM treatment group and 1.35 for IPE treatment group using a Weibull model

- **Model convergence**
  - IPE algorithm with recensoring did not converge when applied to BREAK-3
  - EORTC covariates were excluded to achieve convergence in the IPCW and Two-stage model (the EQ-5D utility score was retained)

- **Sample size and number of switchers and non-switchers**
  - 187 patients randomised to dabrafenib, 63 patients randomised to DTIC
  - 37 (58.7%) DTIC group patients switched onto dabrafenib

- **Maximum stabilised weight (IPCW)** - Highest weight was 17.99
Assessing model performance

- Extent of data loss due to recensoring (RPSFTM, IPE and Two-stage)
  - Longest follow-up time was reduced by 35% from 1236 days to 781 days
  - Data analysis indicated that the treatment effect was time-dependent

RPSFTM incorporating recensoring       RPSFTM without recensoring
Ruling out the least appropriate adjustment analyses for BREAK-3

- All adjustment analyses produced lower HRs than the ITT HR
  - IPE – model did not converge and counterfactual HR was not equal to 1
  - IPCW – small sample size, convergence issues, some missing data
  - Two-stage - convergence issues and some missing data
  - RPSFTM with recensoring – large amount of data lost which is likely to lead to bias due to the changing treatment effect over time

Preferred direct switching adjustment analysis:

RPSFTM without recensoring
Indirect switching - other post-study treatments

- BREAK-3 was further confounded by patients switching onto other post-study treatments.
  - 43 patients switched onto other small molecule therapy
  - 27 of these patients were in the dabrafenib group and 16 were in the DTIC group

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Conclusions

• All adjustment analyses produced lower HRs than the ITT HR, and hence, a larger treatment effect.

• It is necessary to assess the validity of the key assumptions and performance of each of the models in relation to the trial data, to find the most appropriate method of adjusting for treatment switching.

• Of the analyses applied to the BREAK-3 trial, we preferred the RPSFTM+two-stage adjustment analysis that adjusts for direct and indirect switching, because we believe it was necessary to attempt to adjust for indirect switching and direct switching in the BREAK-3 trial.
Thank you for your attention

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References