A COMPARISON OF METHODOLOGIES FOR ESTIMATING SURVIVAL IN PATIENTS TREATED WITH SECOND-GENERATION TYROSINE-KINASE INHIBITORS FOR CHRONIC MYELOID LEUKAEMIA

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ISPOR Europe 2013
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Introduction

- Chronic myeloid leukaemia (CML) is a cancer of myeloid blood cells and represents around 15-20% of all leukaemias.
- The disease has 3 phases: chronic (majority of patients), accelerated, blast (more advanced, difficult to treat).
- Imatinib, a tyrosine kinase inhibitor (TKI), was introduced in 2001 and has transformed the treatment of CML.
- Following imatinib, three 2nd-generation TKIs have so far been appraised by NICE: dasatinib, nilotinib and most recently bosutinib.

Typically in oncology, parametric curves are fitted to Kaplan-Meier data to extrapolate survival.

**Illustrative example**

- Drug A: Weibull curve
- Drug B: Kaplan-Meier data

1. Surrogate survival approach

- Assume OS dependent upon response (MCyR, CCyR, or MMR).
- Estimate OS for responders, hazard ratio for non-responders.

2. Pfizer data on file (2013)
1. Surrogate survival approach

- 2006: Analysis of >3000 patients, treated with IFN-alpha, busulfan or HU
  - Increase MOyr by 25% = increase OS by 1.8 years
  - HU: Does not alter the natural history of the disease, no MOyr expected and OS estimates range from 3 to 6 years

Illustrative example

<table>
<thead>
<tr>
<th>MOyr</th>
<th>Incremental OS over HU</th>
<th>Total OS at HU OS in...</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>7.2 yrs</td>
<td>10.2 yrs</td>
</tr>
<tr>
<td>40%</td>
<td>2.9 yrs</td>
<td>5.9 yrs</td>
</tr>
</tbody>
</table>

But estimated median survival for CML patients treated with imatinib is >25 years

Under-estimate for TKIs? – Use a mature TKI study to calibrate/validate the relationship for TKIs

2. Cumulative survival approach

OS = time on new treatment + OS on standard care (=HU)

Strengths and limitations of the cumulative and surrogate approaches

- Bosutinib was cost-effective vs HU under the surrogate approach, but not under the cumulative approach in a third-line CP CML population
- In all 3 appraisals, significant disparity in OS between approaches - why?

OS in CML – 1st line CP (TA251)

TA251 considered both cumulative and surrogate approaches:

<table>
<thead>
<tr>
<th>Cumulative approach</th>
<th>Surrogate (MCyR) approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total OS = Time on TKI (solid colour) + 3rd line HU (grey stripe = 2nd line)</td>
<td>Time on HU (grey stripe) + OS (COX)-2; Time on TKI (solid colour)</td>
</tr>
<tr>
<td>14.7</td>
<td>22.4</td>
</tr>
</tbody>
</table>

Nilotinib (with PAS) found to be cost-effective compared to imatinib under both approaches, whilst dasatinib was dominated by nilotinib

OS in CML – 2nd line CP (TA241)

TA241 considered only the surrogate approach:

<table>
<thead>
<tr>
<th>Surrogate (MCyR) approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total OS = Time on TKI (solid colour) + OS (COX)-2; Time on TKI (solid colour)</td>
</tr>
<tr>
<td>13.4</td>
</tr>
</tbody>
</table>

What results under a cumulative approach?

- Calibrate using long-term 2nd line HU data
- What assumption for Time on TKI?
- What assumption for HU OS?

- Nilotinib just cost-effective vs HU using surrogate approach (S23-E31H/GALY), but dasatinib not cost-effective vs HU
- What is impact on ICER of more conservative, cumulative approach?

OS in CML – 3rd line CP (ID495)

In the most recent CML appraisal, both approaches were considered:

Surrogate (MCyR) approach

<table>
<thead>
<tr>
<th>Cumulative approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total OS = Time on bosutinib + OS</td>
</tr>
<tr>
<td>12.8</td>
</tr>
</tbody>
</table>

What assumption for HU OS at 3rd/4th line? – 3.5 years?

Illustrative example

- Bosutinib was cost-effective vs HU under the surrogate approach, but not under the cumulative approach in a third-line CP CML population
- In all 3 appraisals, significant disparity in OS between approaches - why?

Strengths and limitations of the cumulative and surrogate approaches

- Bosutinib was cost-effective vs HU under the surrogate approach, but not under the cumulative approach in a third-line CP CML population
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Conclusion and Discussion

- The surrogate and cumulative survival approaches are associated with differing strengths and weaknesses, but both are associated with considerable uncertainty.

- The choice of cumulative vs. surrogate approach has a significant impact on the cost-effectiveness results and could change recommendations:
  - By choosing one approach over another, one set of results is preferred over another.
  - How is the choice made between the two options?

- Once an approach is taken in one disease area...
  - Should it be maintained for consistency?
  - Or replaced if superior approaches are found?

- Are there other examples (e.g., HIV) where structural assumptions have evolved within a certain disease area?
  - Should existing coverage decisions be reviewed?

Thank you!

Any questions?