Network meta-analysis of survival data using fractional polynomials; An example with first line metastatic renal cell cancer treatments

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First line targeted cancer therapies in treatment of metastatic renal cell cancer (mRCC) enabled an increment in progression-free survival (PFS) from 2 to 6 months.

An improvement in overall survival (OS) was not demonstrated in RCTs, or it was difficult to assess due to "cross-over" confounding.

Most of the evidence is available from registrational RCTs representing comparisons of a treatment of interest with previous therapeutic standard (interferon alpha).
Network meta-analysis (NMA) synthesizes direct and indirect evidence between ≥ 2 treatments linked by ≥ 2 RCTs.

Frequently NMA of survival data is based on simple adjustment of hazard ratio -> proportional hazards (PH) assumption (e.g. all published NMAs in mRCC\(^1\)).

Even survival modelling within single treatment appraisals in health economics is commonly founded on PH assumption (e.g. NICE appraisals of 32/45 of cancer drugs\(^2\)).

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2 - Nicholas R. Latimer, Medical Decision Making, Aug 2013: 743-754.
What is wrong with PH assumption?

Assuming constant ratio of hazards implies constant difference in effectiveness through time.

This is often implausible:
- if evidence comes from many different RCTs (e.g. NMA)
- if dealing with terminal disease (e.g. metastatic cancer)
- if modelling is required far beyond the RCT’s horizon (e.g. CEA)
Relaxing PH assumption can be achieved with fractional polynomials (FP) \(^1,^2\)

Contrary to PH models (effect fixed, one dimensional - HR dependent), FP models estimate the hazard/survival through several parameters

**Objective:**

The aim is **to apply FP** in NMA of PFS and OS analysis of 1st line targeted cancer therapies for mRCC and **to compare FP and PH** approach in order to identify and explain the potential differences
1. Systematic literature review

RCTs’ selection criteria:

a. A treatment examined in an RCT must be first line targeted therapy;
b. PFS and/or OS must be represented by reproducible Kaplan Meier curves accompanied by the numbers of patients at risk at least at two different time points;
c. The population examined in an RCT should be representative of the general mRCC population;
d. an RCT must be connected to the rest of RCTs in the NMA through at least one comparator (applied at the end of selection process);
2. Data extraction

- Number of patients at risk (R), number of patients experiencing event (D) and number of censored patients (C) at equal time intervals were needed.

- At our disposal were treatment specific KM curves, followed by R per different time intervals (2, 3, 4, 5, 6 or 10 months).

- W/o informationa on C -> Assume constant rate of censoring within a time interval\(^1\) -> improvements of existing method were needed for intervals not dividable by 2 (!)
3A. Survival analysis – FP model

- An FP function of second order can be utilised to estimate natural logarithm of $h$:  
  $$
  \ln (h(t)) = \beta_0 + \beta_1 t^{p1} + \beta_2 t^{p2}
  $$

- FP model with best fitting powers (DIC) from predefined set (-2, -1, -0.5, 0, 0.5, 1, 2, 3) for all RCTs is selected for further analysis of the effect ($\beta$ parameter)

- Common parametric curves can be seen as special simplified cases of FP models (e.g. Exponential: $\beta_1 = \beta_2 = 0$; without $p1$ and $p2$; Weibull: $\beta1 \neq 0$; $\beta2 = 0$; $p1=0$; without $p2$;)

Now $\beta$s can be split to represent trial specific baseline ($\mu$) and trial specific treatment effect ($\delta$):

$$
\begin{pmatrix}
\beta_{Ojk} \\
\vdots \\
\beta_{Mjk}
\end{pmatrix} = \begin{pmatrix}
\mu_{Ojb} \\
\vdots \\
\mu_{Mjb}
\end{pmatrix} + \begin{pmatrix}
\delta_{Ojb} \\
\vdots \\
\delta_{Mjb}
\end{pmatrix}
$$

- Baseline trt
- Active trt

Each treatment’s effect can be estimated through $\delta$ that is result of pooled estimates of $\delta$s specific for that treatment across included trials.

To determine the powers of best fitting FP model and to estimate the treatment effects ($\mu$s and $\delta$s), we relied on developed code$^1$ conducted 50,000 MCMC in WinBugs and R software.

3B. Survival analysis – PH model

- We fitted the most common parametric functions over hazard/survival data of a referent treatment and choose the best fitting distribution

- Tested were: Weibull, exponential, lognormal, logistic and loglogistic distributions

- Active treatments’ effects were estimated through simple adjustment of HR across all trials as recommended by Bucher et al.¹

11 publications presenting 8 RCTs were included.

8 publications reported PFS (4,709 pt) and 5 publications OS (3,818 pt).

7 compared treatments: sunitinib, pazopanib, interferon alpha (IFN), bevacizumab (beva) + IFN, temsirolimus + beva, cediranib and placebo.

2 out of 5 OS studies allowed cross-over after progression (sunitinib vs IFN and pazopanib vs PLC trials).
Results – systematic literature review

PFS

IFN

S

B+IFN

P

T+B

OS

IFN

S

B+IFN

P

T+B

Plc

Plc
Results – hazard rates OS
<table>
<thead>
<tr>
<th></th>
<th>Progression free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RCTs' estimates (mnths)</td>
<td>FP model (mnths)</td>
</tr>
<tr>
<td>IFN</td>
<td>5.0-5.4</td>
<td>4.3</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>8.2-11.0</td>
<td>12.1</td>
</tr>
<tr>
<td>Bevacizumab+IFN</td>
<td>8.5-16.8</td>
<td>10.1</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>8.4-9.2</td>
<td>10.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.8-4.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Temsirolimus+Beva</td>
<td>8.2-9.1</td>
<td>9.3</td>
</tr>
<tr>
<td>Cediranib</td>
<td>12.1</td>
<td>7.6</td>
</tr>
</tbody>
</table>
Results – PFS estimates (PH vs FP model)

PFS estimates using FP model

[Graph showing PFS estimates for different treatments: IFN, Sunitinib, Beva+IFN, IFN, Beva+Temsiro, Pazopanib, Cediranib, Placebo]
Results – OS estimates (PH vs FP model)
1. **PH assumption was violated** in NMA of PFS and OS estimations

2. Median survival estimates were almost always lower with FP vs PH model (PH overestimates ?)

3. **Sunitinib was the most effective treatment on PFS** in both models (heavily overestimated in long term by PH)

4. **Unclear effect on OS in both models** (FP – sunitinib; PH – pazopanib), impact of cross over
Future research

- Resolving issues on models’ uncertainty
- Transfering effectiveness NMA data to CEA in settings of Serbia and the Netherlands

Questions?

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