Evaluation of treatment effect with paired failure times in a single arm phase 2 oncology trial

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Phase 2 Trials endpoint

• Goal of phase 2 clinical trials: to estimate activity and toxicity of new anticancer agents

• For cytotoxic agents, most used endpoints are related to the tumor shrinkage

• The problematic is different with a cytostatic agents. Need for an endpoint which takes account of that change
Example of design in a multiple progression framework

- Reference Von Hoff et al. (2010)
- Purpose: To compare the time to progression (TTP) using the experimental treatment to the TTP with the most recent regimen on which the patient had experimented progression

![Diagram showing TTP1 and TTP2 with progression events]
Growth Modulation index

- The growth modulation index is defined as the ratio between the time to progression of 2 successive lines of treatment:
  \[ GMI = \frac{TTP2}{TTP1} \]

- The natural history of most advanced tumors suggests that GMI < 1 (patients tend to progress increasingly faster on successive lines of treatment)

- In Von Hoff’s article, the trial designed to test the hypothesis that at least 15% of the patients have GMI > 1.3

- Need for correct estimate of the proportion of patients having a GMI superior to a given threshold
Aim of our work

• To propose statistical methods to estimate the proportion of patients having their GMI superior to a given threshold by handling censored observations

• To investigate design parameters which could influence the performance of these estimators
Methods

• We consider a study in which patients enter after having a first progression. Consequently, the time to progression at previous therapy (TTP\textsubscript{1}) is always observed by design.

• Statistic of interest:

\[ S_{GMI}(\delta) = P \left( \frac{TTP_2}{TTP_1} > \delta \right), \quad \delta \geq 0, \]

• \( \delta \) is an arbitrary threshold which represents the sign of activity considered clinically relevant.
Non-parametric approach

• The non-parametric approach, described in Kovalchik et al (2011), consists in using the ranks of each pair \((TTP_1, TTP_2)\) to estimate \(S_{GMI}(1)\). To handle censoring, we used midranks:

\[
TTP_{1i}: [L_{1i}; R_{1i}] \quad \text{and} \quad TTP_{2i}: [L_{2i}; R_{2i}]
\]

• \(\min_{ji}: R_{j(1)} \leq R_{j(2)} \leq \cdots \leq R_{j(min_i-1)} \leq L_{ji} \leq R_{j(min_i)} \leq \cdots \leq R_{j(2n)}\)

• \(\max_{ji}: L_{j(1)} \leq L_{j(2)} \leq \cdots \leq L_{j(max_i)} \leq R_{ji} \leq L_{j(max_i+1)} \leq \cdots \leq L_{j(2n)}\)

• Imputation of the midrank: \(M_{ji} = \frac{\min_{ji} + \max_{ji}}{2}\)

• \(\hat{S}_{GMI}(1) = \frac{1}{n} \sum_{i=1}^{n} I(M_{2i} \geq M_{1i})\)
Parametric approach

• By assuming a parametric distribution for the GMI, the probability of interest can be derived as a function of the estimated distribution parameters
• E.g., with Weibull distributed TTPs

\[ f_j(x; a, b_j | u_i) = a(u_i b_j)^{-a} x^{a-1} \exp\{-[x/(u_i b_j)]^a\} \]

the GMI has a log-logistic distribution:

\[ f(\delta; a, \kappa) = a\kappa^a \delta^{a-1} (1 + (\delta \kappa)^a)^{-2}, \delta \geq 0 \]

• Maximum likelihood estimates of the parameters can be obtained and used to derive the estimated probability of interest

\[ S_{GMI}(\delta; \hat{a}, \hat{\kappa}) = (1 + (\delta \kappa)^a)^{-1} \]
Simulation study

• Objectives: to evaluate the influence of the design parameters on the two estimators

• We varied:
  – The dependence between $TTP_1$ and $TTP_2$ (Kendall’s $\tau$)
  – The shape of the distribution of TTP
  – The relative effect of second line treatment compared to the first
  – The censoring rate

• The statistical properties were evaluated in terms of mean bias, average standard error and empirical standard error
Data generation

• Generation of a frailty term: $u_i \sim \text{Gamma}$

• Generation of TTP from Weibull distribution

$$f_j(x; a, b_j | u_i) = a(u_i b_j)^{-a} x^{a-1} \exp\left\{-\frac{x}{(u_i b_j)^a}\right\}, \quad j = 1, 2$$

with $b_1 = e \ast b_2$

• Generation of censoring
  (10% and 40% of censored observations)
Result of simulation (1)

Probability \( \hat{S}_{GMI}(\delta = 1) \) of GMI being greater than 1 estimated in the simulation study via the parametric (black) and non-parametric (red) methods. Normally approximate 95% confidence intervals using the empirical standard error.
Probability $\hat{S}_{GMI}(\delta = 1)$ of GMI being greater than 1 estimated in the simulation study via the parametric (black) and non-parametric (red) methods. Normally approximate 95% confidence intervals using the empirical standard error.
Probability $\hat{S}_{GMI}(\delta = 1)$ of GMI being greater than 1 estimated in the simulation study via the parametric (black) and non-parametric (red) methods. Normally approximate 95% confidence intervals using the empirical standard error.
Application

- The FFCD 2000-05 trial was a randomized trial conducted by the French Federation of Digestive Oncology, which included 410 patients with advanced colorectal cancer.

- Estimation of the dependence between $TTP_1$ and $TTP_2$ (Kendall’s $\tau$) by modeling the risks of progression by shared frailty models.
Dependence between $PFS_1$ and $PFS_2$

- Estimation of the Kendall’s $\tau$ for the 4 situations by modeling the risks of progression by shared frailty models

$$ h_{ij}(t|u_i) = h_{0j}(t)u_i\exp(x_{ij}^T\beta) $$

- Gamma distribution assumed for the frailty term
- Weibull distribution assumed for the baseline hazard function

<table>
<thead>
<tr>
<th>Arm</th>
<th>Situation</th>
<th>Kendall’s $\tau$</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>1</td>
<td>0.195</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.152</td>
</tr>
<tr>
<td>S</td>
<td>2</td>
<td>0.142</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.225</td>
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</table>
Estimation of \( \hat{S}_{GMI}(1) \)

Survival function estimate of the growth modulation index (situation 1 on the left, situation 4 on the right) via the Kaplan-Meier method and via a log-logistic distribution. The gray area is the 95% confidence band for the Kaplan-Meier estimate.
Estimation of $\hat{S}_{GMI}(1)$

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Estimator</th>
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<tbody>
<tr>
<td>Line 1</td>
<td>Line 2</td>
</tr>
<tr>
<td>Arm C</td>
<td></td>
</tr>
<tr>
<td><strong>Situation 1</strong></td>
<td>FOLFOX</td>
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<tr>
<td><strong>Situation 3</strong></td>
<td>FOLFIRI</td>
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<tr>
<td>Arm S</td>
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</tr>
<tr>
<td><strong>Situation 2</strong></td>
<td>LV5FU2</td>
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<tr>
<td><strong>Situation 4</strong></td>
<td>FOLFOX</td>
</tr>
</tbody>
</table>

Estimation of $S_{GMI}(\delta = 1) = P(GMI > 1)$ for the four situations in the FFCD 2000-05 trial
Discussion

• Few published clinical trials using the GMI as a criterion of activity
  – Rather low correlation of the paired time-to-progression
  – At least in some of them, this may be due to the heterogeneity of the first-line treatment or to the localization of the tumor

• In phase II trials, progressions are generally assessed at fixed times, What about the effect of interval censoring on these methods?

• An increasing number of clinical trials and the EMA admits its use to compare two successive therapies
Bibliography (1)


Bibliography (2)


