Planning a Bayesian early-phase phase I/II study for human vaccines in HER2 carcinomas

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Introduction (1)

- DNA vaccination can be envisaged as an efficient new way of preventing the slow progression of carcinogenesis in humans (Lollini et al. 2006)
- Cancer vaccines are much safer than cytotoxic agents (Hoos et al. 2007)
Introduction (2)

Type of early phase drug development trial designs (Piantadosi 1997; Zohar et al. 2007)

- Phase I: trial design that has as a primary objective identifying the maximum tolerated dose (MTD) to administer
- Phase II: trial design with safety and efficacy estimation as a primary objective
- Phase I/II: aims to locate the most successful dose (MSD) i.e. the dose that maximizes the probability of observing a therapeutic response without toxicity
Commonly used phase I/II dose-finding designs use a Bayesian approach in order to determine the MSD. In this context, Bayesian inference requires incorporation of prior information on the dose-toxicity and dose-success relationships (Legezda 2001; Chaloner 2001).
Introduction (4)

- Elicitation is the process of formulating a person’s knowledge and beliefs about one or more unknown quantities of interest into a probability distribution for those quantities (Garthwaite et al. 2005).

- An elicitation is done well if the distribution that is derived accurately represents the experts’ knowledge, regardless of how good this knowledge is.
Introduction (5)

Motivation for eliciting prior beliefs in clinical trials: (Chaloner and Rhame 2001)
- Design and sample size
- Monitoring
- Bayesian methods
- Hindsight
Objectives

The aims of this study were:

- to elicit prior probability distribution from physician’s opinion about the available dose levels planned for phase I/II dose-finding clinical trials on human DNA vaccine in HER2 tumours

- to assess via simulations the impact of the choice of prior on the recommended dose level at the end of the trial
Materials and Methods (1)

The elicitation process in four stages (O’Hagan 1998; Garthwaite et al 2005)

- Setup
- Elicit
- Fit
- Assess Adequacy
Materials and Methods (2)

Prior elicitation process:

1. Expert’s selection and identification of the aspects of the problem to elicit:
   
   13 researchers and physician selected
   
   initial guesses about toxicity and efficacy probability of the treatment per dose level (direct method)

2. Interaction with the experts:
   
   Questionnaire sent to the experts with a short cover letter
   
   They were asked not do discuss their answers with one another
Materials and Methods (3)

3. Fit of probability distributions to the expert’s summaries:

- Different priors for each dose level according to the choice of the percentile of the dose-toxicity distribution of the expert’s opinion
  - enthusiastic prior 1 – the 10th p
  - enthusiastic prior 2 – the 25th p
  - informative prior – median p
  - skeptical prior 1 – the 75th p
  - skeptical prior 2 – the 90th p
Materials and Methods (4)

4. Assessing the adequacy of the elicitation:

Simulation study of 5000 independent dose-finding clinical trials. We investigated 100 different scenarios (each under the five different priors separately) in terms of dose-toxicity and dose-success relationship.
Materials and Methods (5)

A phase I/II allocation scheme using an hybrid design (Ivanova 2003) was chosen:

- nonparametric response-adaptive design for the dose allocation scheme (up-and-down approach)

- estimation of the dose–toxicity relationship made using the Bayesian parametric modelling proposed for the continual reassessment method (O’Quigley et al 1990).
Materials and Methods (6)

Dose space: $\Omega_d = \{d_1, \ldots, d_k\}$

$\Gamma$ = maximal toxicity target

Binary indicators for toxicity ($Y=1$ if toxicity, $Y=0$ otherwise) and response ($V=1$ if response, $V=0$ otherwise)

$Q(d)$ = probability of toxicity at dose $d$

$P(d)$ = probability of response without toxicity at dose $d$

MSD: dose $d^*$ such that $P(d^*) = \max_{d \in \{d_1, \ldots, d_k\} \& Q(d) \leq \Gamma} P(d)$
Materials and Methods (7)

Allocation scheme:

Assuming that the most recent subject was treated with dose $d_j$, the dose level to be assigned to the next patient is:

- Dose $d_{j-1}$ if the most recent subject had toxicity
- Dose $d_j$ if the most recent subject had response with no toxicity
- Dose $d_{j+1}$ if the most recent subject had no response and no toxicity
Materials and Methods (8)

The allocation scheme is adjusted by monitoring $Q(d)$.

Dose–toxicity relationship:

$$Q(d_j) = \alpha_j^a$$

$(\alpha_1, \ldots, \alpha_k)$: reflects elicited prior beliefs

$a$: parameter with prior density taken to be $g(a) = e^{-a}$
Materials and Methods (9)

After each patient’s response, posterior toxicity probabilities at each dose are updated using Bayesian methods.

\[ d^{**} : \text{maximum dose-level such that } P(d^{**}) \leq \Gamma \]

Next patient assigned to the dose \( \min(d^{**}, d_{\text{allocation scheme}}) \)
Materials and Methods (10)

Stopping: decision taken based on the Sequential Probability Ratio Test (Wald 1947; O’Quigley 2001) to stop the trial for efficacy or futility
Results (1)

Response distribution according to the expert’s opinion by dose level.
Results (2)

Toxicity distribution according to the expert’s opinion by dose level.
Results (3)

Prior dose-toxicity relationships defined according to the expert’s dose-toxicity distribution.
### Results (4)

<table>
<thead>
<tr>
<th>PRIOR (DOSE-TOXICITY)</th>
<th>MSD-1</th>
<th>MSD</th>
<th>MSD+1</th>
<th>Median sample size at stopping (Q1-Q3)</th>
<th>Mean % observed toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enthusiastic prior 1:</strong>&lt;br&gt;0.001, 0.01, 0.05, 0.15, 0.2, 0.25</td>
<td>0.19</td>
<td>0.69</td>
<td>0.06</td>
<td>42 (36-54)</td>
<td>10.8</td>
</tr>
<tr>
<td><strong>Enthusiastic prior 2:</strong>&lt;br&gt;0.01, 0.05, 0.1, 0.2, 0.25, 0.3</td>
<td>0.21</td>
<td>0.65</td>
<td>0.09</td>
<td>44 (37-54)</td>
<td>11.6</td>
</tr>
<tr>
<td><strong>Informative prior:</strong>&lt;br&gt;0.01, 0.05, 0.1, 0.2, 0.3, 0.4</td>
<td>0.24</td>
<td>0.59</td>
<td>0.12</td>
<td>30 (28-34)</td>
<td>8.1</td>
</tr>
<tr>
<td><strong>Skeptical prior 1:</strong>&lt;br&gt;0.1, 0.12, 0.25, 0.4, 0.5, 0.7</td>
<td>0.21</td>
<td>0.63</td>
<td>0.07</td>
<td>38 (33-50)</td>
<td>9.3</td>
</tr>
<tr>
<td><strong>Skeptical prior 2:</strong>&lt;br&gt;0.1, 0.2, 0.37, 0.48, 0.7, 0.99</td>
<td>0.26</td>
<td>0.58</td>
<td>0.07</td>
<td>40 (33-49)</td>
<td>8.4</td>
</tr>
</tbody>
</table>
Results (5)

- The rate of finding the true MSD is not higher than 70%.
- Enthusiastic prior 1 always gave the higher percentage of correct selection (mean MSQ=0.006)
- Enthusiastic prior 2 always gave the higher median sample size at stopping.
- The informative prior gave the lower percentage of correct selection with the lower median sample size.
Conclusion

• Introducing subjectivity into a scientific process by using expert opinion is a controversial issue.

• Caution must be taken when using predefined questionnaires since appropriate training for the clinicians to properly understand what exactly is expected from them is required.

• Including in a trial protocol a detailed section on the conduct of the elicitation process and the resulting assessments could be a first step to make the use of assessed distributions acceptable.