A Donor Lymphocyte Infusion Trial: Adaptively Optimizing Infusion Times

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Joint work with
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OUTLINE:

• INTRODUCTION

• PROBABILITY MODEL

• PRIOR ELICITATION

• TRIAL CONDUCT

• SIMULATION STUDY

• DISCUSSION
A General Fact About Experimental Design

An Experiment Cannot be “Optimally” Designed Until After it Has Been Conducted
A General Fact About Statistical Models

All Statistical Models are Incorrect,
But
Some are Less Incorrect than Others
Clinical Trials

• A Clinical Trial is a Medical Experiment With Human Subjects

• It has Two Purposes:
  - Treat the patients in the trial
  - Obtain scientifically useful information for developing new or improved treatments for future patients
Patients in the DLI Trial:

- Presented with hematologic malignancies
  - Acute myelogenous leukemia
  - Advanced chronic myelogenous leukemia
  - Myelodysplastic syndromes
- Had allogeneic bone marrow transplantation (tx)
- Suffered disease recurrence (>90 days after tx)
One-year survival rate:

5 to 10%

Response rate to “salvage” chemo regimens:

20 to 40%
Therapeutic Rationale

**Mylotarg**: A monoclonal antibody attached to a cellular toxin. The antibody binds to the CD33 surface receptor on blood stem (immature, progenitor) cells

**Aim**: Use Mylotarg to kill leukemia cells (although it will also kill normal cells), thus reduce the tumor burden, then infuse donor lymphocytes, which can recognize surface antigens on the leukemia cells & kill them
Therapeutic Problem

- If the lymphocytes are infused too soon, the Mylotarg may kill them.
- If the lymphocytes are infused too late, the patient may die of infection.
Death

Onset of Neutropenia

ANC Recovery

0 5 8 11 14 17 20 23 50 Days

First mylotarg bolus
Second mylotarg bolus
Donor lymphocyte infusion

Last follow-up
Scientific Aims of the DLI Trial:

• Evaluate efficacy and safety of targeted immunotherapy followed by allogeneic donor lymphocyte infusion
• Find a safe 2-course Mylotarg dose
• Optimize the interval between administration of targeted immunotherapy (Mylotarg) and lymphocyte infusion
PROBABILITY
MODEL
Probability of Hepatotoxicity (HT):

- Given first Mylotarg course: Logistic function of course 1 dose
- Given second Mylotarg course: Logistic function of the total dose in the two courses
- Parameterized by $\gamma = (\gamma_0, \gamma_1)$
Probability of Hepatotoxicity (HT):

Given first Mylotarg course:

\[
\pi_1(d_1, \gamma) = \Pr(Y_1 = 1 \mid d_1, \gamma) = \logit^{-1}(\gamma_0 + \gamma_1 d_1)
\]

Given second Mylotarg course:

\[
\pi_2(d_+, \gamma) = \Pr(Y_2 = 1 \mid Y_1 = 0, d_1, d_2, \gamma) = \logit^{-1}(\gamma_0 + \gamma_1 d_+)
\]

where \(\logit(p) = \log\{p/(1-p)\}\), \(d_+ = d_1 + d_2\), and \(\gamma = (\gamma_0, \gamma_1)\).
Time from Infusion to ANC recovery ($T_A$):

- $T_A$ follows an **Exponential** distribution with mean that is a quadratic function of infusion time

- Parameterized by $\beta = (\beta_0, \beta_1, \beta_2)$

$ANC = \text{Absolute Neutrophil Count}$
Time from Infusion to ANC recovery ($T_A$):

Exponential distribution with mean:

$$\mu_A(t_I, \beta) = \exp(\beta_0 + \beta_1 x_I + \beta_2 x_I^2)$$

$$f_A(t \mid t_I, \beta) = \mu_A^{-1} \exp\left\{-\frac{(t - t_I)}{\mu_A}\right\}$$

$$x_I = \frac{(t_I - 17)}{3}$$

for $t_I = 11, 14, 17, 20, 23$ days
Survival Time \((T_D)\):

\(T_D\) follows a **piecewise Exponential** distribution with mean \(\mu_D\) that

- Is a Linear function of \(I\{\text{Toxicity}\}\) before infusion

- Is a Quadratic function of infusion time

- Parameterized by \(\alpha = (\alpha_0, \alpha_1, \alpha_2, \alpha_3, \alpha_4)\)
Survival Time ($T_D$):

Before infusion:

$$
\mu_{D,1}(Y_+, \alpha) = \exp(\alpha_0 + \alpha_1 Y_+)
$$

After infusion:

$$
\mu_{D,2}(t_I, Y_+, \alpha) = \exp(\alpha_2 + \alpha_3 x_I + \alpha_4 x_I^2 + \alpha_1 Y_+)
$$

$$
 f_D(t \mid t_I, \alpha) = \begin{cases} 
  \mu_{D,1}^{-1} \exp(-t/\mu_{D,1}) \\
  \exp(-t_I/\mu_{D,1}) \mu_{D,2}^{-1} \exp\left\{ -(t - t_I)/\mu_{D,2} \right\}
\end{cases}
$$
Administrative censoring at t=50

If $Y_1=0$:

$$f_{D,1}(T_D) \text{ if } T_D < t_I,$$

$$f_A(T_A \mid t_I) F_{D,1}(t_I) F_{D,2}(50-t_I) \text{ if } t_I + T_A < 50 < T_D,$$

$$f_A(T_A \mid t_I) F_{D,1}(t_I) f_{D,2}(T_D-t_I) \text{ if } t_I + T_A < T_D < 50,$$

$$F_A(50-t_I \mid t_I) F_{D,1}(t_I) F_{D,2}(50-t_I) \text{ if } 50 < \min\{t_I + T_A, T_D\}$$

$$F_A(T_D-t_I \mid t_I) F_{D,1}(t_I) f_{D,2}(T_D-t_I) \text{ if } t_I < T_D < \min\{t_I + T_A, 50\}$$

If $Y_1=1$:

$$f_{D,1}(T_D) \text{ if } T_D < 50$$

$$F_{D,1}(50) \text{ if } T_D > 50$$
\[ \mathcal{L}(Y_1, Y_2, T_A, \delta_A, T_D, \delta_D \mid \alpha, \beta, \gamma) = \]

\[ = \left\{ \pi_1 f_D,1(T_D)^{\delta_D} \mathcal{F}_{D,1}(T_D^0)^{1-\delta_D} \right\}^{Y_1} \times \]

\[ \left\{ (1 - \pi_1) \pi_2^{Y_2} (1 - \pi_2)^{1-Y_2} f_A(T_A \mid t_I)^{\delta_A} \mathcal{F}_A(T_A^0 \mid t_I)^{1-\delta_A} \]

\[ f_D(T_D)^{\delta_D} \mathcal{F}_D(T_D^0)^{1-\delta_D} \right\}^{1-Y_1} \]
Success probabilities for a patient infused at $t_1$:

1) Depend on $\text{Prob}\{\text{toxicity}\}$, time to white cell recovery, & survival time

2) Are computed for the possible infusion times $\{11, 14, 17, 20, 23\}$ days

3) Are the basis for adaptively randomizing patients among the five infusion times.
\[ \theta(t_I) = \{1 - \pi_1(d_1)\} F_A(50 - t_I \mid t_I) \times \sum_{y_2=0}^{1} \pi_2(d_+)^{y_2} \{1 - \pi_2(d_+)\}^{1-y_2} \mathcal{F}_{D,1}(t_I, y_2) \mathcal{F}_{D,2}(50 - t_I, y_2 \mid t_I) \]
The “More Correct” Model that We Didn’t Use

ANC > 1000

Start Rx

Death

TA

TD|A

T0
\[ T_D = T_0 \text{ if } T_0 < T_A \]

\[ T_A + T_{D|A} \text{ if } T_0 > T_A \]

\[ P(T_0) \& P(T_A + T_{D|A}) \text{ NOT the same} \]

Model Both \[ P(T_0) \& P(T_A, T_{D|A}) \]

But …Too Many Parameters !!
Prior Distributions:

A modified version of Bedrick, Christensen and Johnson (1996):

1) Elicit the priors on the natural domains: Prob\{Toxicity\}, Prob\{ANC recovery\}, & Prob\{Survival\}
2) Transform to obtain priors on (β, α, γ)
Prior mean time to ANC recovery:

\[ \mu_A(t_I, \beta) = \exp(\beta_0 + \beta_1 x_I + \beta_2 x_I^2) \]

<table>
<thead>
<tr>
<th>( t_I )</th>
<th>( x_I )</th>
<th>Mean</th>
<th>90% c.i.</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>-2</td>
<td>20</td>
<td>10 – 30</td>
</tr>
<tr>
<td>17</td>
<td>0</td>
<td>10</td>
<td>8 – 20</td>
</tr>
<tr>
<td>23</td>
<td>2</td>
<td>10</td>
<td>8 – 15</td>
</tr>
</tbody>
</table>
Prior probability of **Death** before day 50 given survival to infusion:

\[ 1 - \exp \left\{ -(50 - t_I) e^{-(\alpha_2 + \alpha_3 x_I + \alpha_4 x_I^2 + \alpha_1 Y_+)} \right\} \]

<table>
<thead>
<tr>
<th>$t_I$</th>
<th>$x_I$</th>
<th>$Y_+$</th>
<th>Mean</th>
<th>90% c.i.</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>-2</td>
<td>0</td>
<td>0.30</td>
<td>.10 – .50</td>
</tr>
<tr>
<td>11</td>
<td>-2</td>
<td>1</td>
<td>0.50</td>
<td>.20 – .80</td>
</tr>
<tr>
<td>17</td>
<td>0</td>
<td>0</td>
<td>0.25</td>
<td>.10 – .40</td>
</tr>
<tr>
<td>23</td>
<td>2</td>
<td>0</td>
<td>0.30</td>
<td>.10 – .50</td>
</tr>
</tbody>
</table>
Prior mean hepatoxicity probability:

\[ \mathbb{E} \{ \logit^{-1}(\gamma_0 + \gamma_1 d_+) \} \]

<table>
<thead>
<tr>
<th>Dose</th>
<th>(d_+)</th>
<th>Mean</th>
<th>90% c.i.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(d_1 = 4)</td>
<td>4</td>
<td>0.025</td>
<td>0.00 – 0.20</td>
</tr>
<tr>
<td>((d_1, d_2) = (4, 4))</td>
<td>8</td>
<td>0.10</td>
<td>0.00 – 0.60</td>
</tr>
</tbody>
</table>
Posterior Distributions:

Joint posterior distribution not available in analytical form

MCMC methods

Gibbs Sampler Algorithm
Adaptive Rejection Sampling
TRIAL

CONDUCT
Mylotarg Dose De-Escalation Algorithm:

• $H_1$: Dose $d_1$ is unacceptably toxic if

$$\Pr (\pi_1 (d_1) > .25 \mid data) > .95$$

• $H_2$: Doses $(d_1, d_2)$ are unacceptably toxic if

$$\Pr (\pi_2 (d_+) > .30 \mid data) > .95.$$
Between-Patient Mylotarg Dose De-Escalation Algorithm

4 + 4

H₁  H₂

2 + 2  4 + 2

H₁  H₂  H₁  H₂

STOP  2 + 0  2 + 2  4 + 0
Adaptive Randomization Algorithm

Thompson (1933) considered two binomial probabilities, $\theta_A$ and $\theta_B$, following beta priors, representing the success probabilities of two treatments, A and B.

Based on binomial data, he proposed **Adaptively Randomizing** patients between A and B: Assign a patient to B with probability $\rho_B = \text{pr}(\theta_A < \theta_B \mid \text{data})$ and to A with probability $\rho_A = 1 - \rho_B$. 
Adaptive Randomization Algorithm

Berry & Eick (1995) numerically compared

- Thompson’s method
- Robust Bayes, maximizing total # successes in the trial + a future patient horizon
- Bather’s *strange* 1985 method
- Play-the winner (Zelen, 1969)

For n=100 + horizon of 100 to 1000,

**Thompson ~ Robust Bayes**

w.r.t. total # treatment successes
Adaptive Randomization Algorithm

A Generalization of Thompson (1933):

Each new patient is randomized to infusion time $t_j$ with probability

$$\rho_j(data) = \Pr\{\theta(t_j) = \max_{1 \leq k \leq 5} \theta(t_k) \mid data\},$$

$$j = 1, 2, 3, 4, 5.$$
SIMULATION STUDY
Preliminary Simulations

• **Many preliminary simulations** were conducted to study & modify the design, working closely with the physician, Tom Martin

• A more complex dose de-escalation algorithm, with a higher starting dose, was initially considered

• Data from Fred Hutchinson Cancer Center caused us to adopt a much lower Mylotarg starting dose

• After calibrating the toxicity (safety) monitoring rules *per se*, we studied the overall design
As infusion day $t_I$ varies between \{11, 14, 17, 20, 23\}, we considered:

- 3 cases for $\mu_I(t_I, \beta) =$ mean time to recover ANC > 1000
- 3 cases for $\Pr(T_D < 50 \text{ days } | \text{ No HT}) =$ Probability of death within 50 days, if no liver toxicity

A total of $3 \times 3 = 9$ Clinical Scenarios
<table>
<thead>
<tr>
<th>Case</th>
<th>Day of infusion</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>14</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Mean # days to ANC $\geq$ 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$A_1$</td>
<td>25</td>
<td>21.25</td>
<td>17.50</td>
<td>13.75</td>
<td>10</td>
</tr>
<tr>
<td>$A_2$</td>
<td>10</td>
<td>13.75</td>
<td>17.50</td>
<td>21.25</td>
<td>25</td>
</tr>
<tr>
<td>$A_3$</td>
<td>25</td>
<td>20</td>
<td>15</td>
<td>20</td>
<td>25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case</th>
<th>Pr (Death before day 50</th>
<th>No HT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_1$</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>$D_2$</td>
<td>0.25</td>
<td>0.20</td>
</tr>
<tr>
<td>$D_3$</td>
<td>0.40</td>
<td>0.35</td>
</tr>
<tr>
<td>Scenario</td>
<td>Pr (50-day Success)</td>
<td>Not infused</td>
</tr>
<tr>
<td>----------</td>
<td>---------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>A1,D3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pr (Selected)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td># patients treated</td>
<td></td>
</tr>
<tr>
<td>A2,D1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pr (Selected)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td># patients treated</td>
<td></td>
</tr>
<tr>
<td>A3,D2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pr (Selected)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td># patients treated</td>
<td></td>
</tr>
</tbody>
</table>
Features of DLI Trial Design

• An adaptive Bayesian statistical design: The data are monitored & the prior updated continuously throughout the trial

• Uses multiple discrete & continuous outcomes

• Therapy is *adaptive within each patient*

• The design is *adaptive between patients*

• Nominally a “Phase I/II” trial