Adaptive Decision Making in a Lymphocyte Infusion Trial

Peter F. Thall,¹,* Lurdes Y. T. Inoue,¹ and Thomas G. Martin²

¹Department of Biostatistics, The University of Texas M. D. Anderson Cancer Center, Box 447, 1515 Holcombe Boulevard, Houston, Texas 77030, U.S.A.
²Department of Hematology/Oncology, University of California at San Francisco, Box 0324, San Francisco, California 94143, U.S.A.

*email: rex@mdanderson.org

SUMMARY. We describe an adaptive Bayesian design for a clinical trial of an experimental treatment for patients with hematologic malignancies who initially received an allogeneic bone marrow transplant but subsequently suffered a disease recurrence. Treatment consists of up to two courses of targeted immunotherapy followed by allogeneic donor lymphocyte infusion. The immunotherapy is a necessary precursor to the lymphocyte infusion, but it may cause severe liver toxicity and is certain to cause a low white blood cell count and low platelets. The primary scientific goal is to determine the infusion time that has the highest probability of treatment success, defined as the event that the patient does not suffer severe toxicity and is alive with recovered white blood cell count 50 days from the start of therapy. The method is based on a parametric model accounting for toxicity, time to white blood cell recovery, and survival time. The design includes an algorithm for between-patient immunotherapy dose de-escalation based on the toxicity data and an adaptive randomization among five possible infusion times according to their most recent posterior success probabilities. A simulation study shows that the design reliably selects the best infusion time while randomizing greater proportions of patients to superior infusion times.

KEY WORDS: Adaptive randomization; Bayesian design; Dose finding; Leukemia; Lymphocyte infusion.

1. Introduction

Patients with hematologic malignancies who have undergone allogeneic bone marrow transplantation (alloBMT) but whose disease has recurred have a very poor prognosis with conventional treatments. We describe an adaptive Bayesian design for a clinical trial of an experimental therapeutic strategy for patients who previously have received an alloBMT but who have suffered a disease recurrence more than 90 days after the transplant. Patients with acute myelogenous leukemia, advanced chronic myelogenous leukemia, or myelodysplastic syndrome will be included. Prognostically, the fact that the patient's disease has recurred after alloBMT supersedes the type of malignancy diagnosed initially. The 1-year survival rate of these relapsed patients is only about 5-10%, regardless of the type of malignancy. They also exhibit very similar response rates, of approximately 20-40%, with a variety of salvage chemotherapy regimens. The trial aims to evaluate the efficacy and safety of targeted immunotherapy followed by allogeneic donor lymphocyte infusion (DLI) while also attempting to optimize the interval between administration of targeted immunotherapy and DLI, hereafter referred to as DLI time. The duration of the DLI is only about 20 minutes. The rationale for this study stems from previous trials demonstrating that DLI can induce remissions in patients with acute and chronic leukemias relapsing after alloBMT (Antin, 1993; Collins et al., 1997). The donor T-cells can recognize antigens on the surface of the malignant cells and directly induce cell death. DLI, however, appears to be most successful in patients who have low tumor burden, known as minimal residual disease. The goal of the targeted immunotherapy is to induce minimal residual disease, thus providing the DLI with a better chance of success.

Mylotarg is an engineered monoclonal antibody attached to chaetocin, a potent cellular toxin (Bernstein, 2000). Mylotarg binds to the cell surface receptor CD33 located on immature blood progenitor cells, both normal and leukemia cells. Thus, an entry criterion for the trial is that the patient's cancer cells must express the CD33 cell surface antigen. Mylotarg has been administered to patients with relapsed acute myelogenous leukemia, with overall response rates of approximately 20-30% (Sievers et al., 1999). Its main side effects are liver dysfunction (hepatotoxicity, HT), infusion-related fevers and chills, prolonged neutropenia (low absolute neutrophil count, ANC, defined as <1000 cells/μl), and thrombocytopenia (low platelets). Severe HT is the adverse event of greatest concern with Mylotarg because it is potentially life threatening (Giles et al., 2001; Neumeister et al., 2001) and it is more likely to be severe in patients who have received prior stem cell transplantation than in those who have not. In previous clinical trials of Mylotarg, infusion-related fever and chills have been controlled through the administration of steroids prior to Mylotarg. Very few other severe adverse
events were encountered, and almost all were resolved before day 50. Although HT is the most likely adverse event, in the sequel, we include any severe toxicity that cannot be resolved therapeutically, other than low blood counts, in the definition of HT.

The average time to achieve ANC >1000 cells/µl following Mylotarg is more than 40 days. In this study, mobilized DLI will be given following Mylotarg in an attempt to hasten neutrophil recovery. Usually, donor lymphocytes are collected without giving the donor white blood cell (WBC) growth factors. This unstimulated lymphocyte collection contains mostly lymphocytes and very few immature stem cells. However, if the donor is given WBC growth factors prior to lymphocyte collection, then this (mobilized) collection will contain a much larger proportion of immature stem cells (Lane et al., 1999). Mobilized DLI is usually given to patients who receive chemotherapy for disease relapse following alloBMT. The goals of mobilized DLI are to provide lymphocytes capable of fighting leukemia and immature stem cells capable of hastening bone marrow recovery.

Figure 1 illustrates the treatment plan and clinically relevant patient outcomes. Therapy begins with a bolus of Mylotarg aimed at reducing the patients’ leukemic burden. The patient is then monitored for the following week for HT. If no HT is encountered, then a second dose of Mylotarg is administered. Mobilized DLI will be given at a defined interval following the second dose of Mylotarg. Patients who develop HT after the first dose of Mylotarg will not receive a second dose and will not receive scheduled DLI because one dose of Mylotarg likely will not result in prolonged neutropenia. These patients will be taken off study and may receive DLI at a later time once HT has been resolved. Patients who experience HT after the second course of Mylotarg will receive DLI as scheduled because, at that point, DLI is the only remaining therapeutic avenue and likely will hasten neutrophil recovery. Due to the effects of the first course of Mylotarg, all patients will suffer neutropenia, defined as an ANC falling below 1000, within 5 days of drug infusion. Neutrophils are white blood cells that play an important role in fighting infections. The dual therapeutic goals of the mobilized DLI are to enhance neutrophil recovery and kill remaining cancer cells. Restoring the patient’s ANC is critical because, during the period of neutropenia, the patient is highly susceptible to life-threatening bacterial and fungal infections. Treatment success is defined as the event that the patient does not suffer HT and is alive with ANC ≥1000 at day 50.

The primary scientific goal of the trial is to determine the DLI time, among five predetermined times after the Mylotarg, having the highest treatment success probability. Our design is based on a parametric Bayesian model for the probability of HT as a function of Mylotarg dose and for the times to ANC recovery and death, each as a function of infusion time and whether the patient has experienced HT. We take a model-based approach because decisions must be made adaptively during the trial based on very limited information, and this problem is especially acute early in the trial. The design has two main components: an algorithm for between-patient de-escalation among six Mylotarg dose pairs if an unacceptable high HT rate is observed and a sequentially adaptive randomization of patients among the infusion times. Depending on the interim HT data and the dose de-escalation algorithm, each patient may receive any of five possible dose combinations in the two courses. Each patient’s randomization probabilities for the five infusion times are based on their current posterior success probabilities. Thus, each patient is more likely to be infused at a time having higher current success rate, based on the most recent data from the trial. This method is used in place of balanced randomization because it yields unbiased comparisons among the infusion times while also providing each patient, with high probability, the current highest success rate. Because the therapeutic goal of the treatment being studied in this trial is to save patients for whom initial treatment has failed, it is an example of a salvage therapy.

We provide a detailed description of the patient outcomes and probability model in Section 2. The trial design is presented in Section 3, followed by a summary of a simulation study of the design in Section 4. We close with a discussion in Section 5.

2. Probability Model
2.1 Patient Outcomes
The indicator of HT in the jth Mylotarg course is denoted by 1 for j = 1, 2. Because the patient’s targeted immunotherapy is terminated if there is HT in the first course, Yj is defined only if Yj = 0, so that the three possible HT outcomes are Yj = 1, (Yj,Yj) = (0,1), and (Yj,Yj) = (0,0). We let Tj indicate HT in either course, which is either of the first two outcomes. We assume that the onset time of neutropenia, TN, is uniformly distributed on the interval from 0 to 5 days. Denoting the infusion time by ti and the time from infusion to ANC recovery by TA, the patient’s time from start of therapy to ANC recovery is t + TA and total duration of neutropenia is tN + N − TN.

The primary scientific goal of this study is to choose the best DLI time among 11, 14, 17, 20, and 23 days after the initial Mylotarg bolus. This is motivated by the potential
trade-off between giving the DLI as soon as possible after Mylotarg to hasten neutrophil recovery or potentially giving the DLI too soon after Mylotarg such that residual circulating immunotoxin can bind to the donor stem cells and further delay ANC recovery. Ideally, patients achieve ANC recovery within 14 days after DLI. Therefore, the neutropenic interval, \( t_1+T_A-T_D \), begins within 5 days of the initial Mylotarg infusion and lasts until approximately 14 days following DLI. Because the half-life of Mylotarg is approximately 60-90 hours, giving DLI soon after Mylotarg may prolong neutropenia and thus increase the risk of death due to infection. This study is designed to identify the DLI time, \( t_f \), that is associated with the shortest neutropenic interval, \( T_A \), while maintaining survival. Formally, clinical success is defined as the event that the patient does not suffer HT within the first 8 days, recovers ANC \( \geq 1000 \), and survives to day 50. Denoting the time of death by \( T_D \), the success probability of a patient infused at time \( t_f \) is \( \theta(t_f) = Pr(Y_1 = 0 \text{ and } t_f + T_A < 50 < T_D | t_f) \).

### 2.2 Regression Models

In addition to the fact that each patient receives either one or two courses of Mylotarg, the trial design includes an algorithm for Mylotarg dose de-escalation between patients, described in Section 4. Consequently, the Mylotarg doses given in courses 1 and 2, denoted \( d_1 \) and \( d_2 \), may vary between patients. We assume that the probability of HT depends on the cumulative dose of Mylotarg according to the logistic model

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

and

\[
\pi_2(d_2, \gamma) = Pr(Y_2 = 2 | Y_1 = 0, d_1, d_2, \gamma) = \logit^{-1}(\gamma_0 + \gamma_2 d_2), \tag{2}
\]

where \( \logit(p) = \log(p/(1-p)) \), \( d_2 = d_1 + d_2 \), and \( \gamma = (\gamma_0, \gamma_1) \). The linear components of \( \pi_1 \) and \( \pi_2 \) have identical parameters and differ only in terms of Mylotarg dose, reflecting the assumption that the risk of toxicity is a function of cumulative dose. Recalling that \( (Y_1, Y_2) \) take on three possible values, the overall probability that a patient has HT is \( \pi_+ = \pi_1 + (1 - \pi_1)\pi_2 \), with \( 1 - \pi_+ = (1 - \pi_1)(1 - \pi_2) \).

To reduce collinearity among the parameter estimates in the following models for regression of the means of cumulative dose, we assume an exponential distribution with mean \( t_1 \). We further assume that HT within the first 8 days, recovers ANC 21000, and survives to day 50. Denoting the time of death by \( T_D \), the success probability of a patient infused at time \( t_f \) is \( \theta(t_f) = Pr(Y_1 = 0 \text{ and } t_f + T_A < 50 < T_D | t_f) \).

### 2.3 Likelihood

Let \( \delta_0 \) denote the indicator that \( T_A \) is not right-censored either administratively or by death, with \( T_A^0 \) the observed value of \( T_A \) or its censoring time, and let \( \delta_0 \) and \( \delta_D \) be the analogous quantities for survival time. Denoting \( F(t) = Pr(T > t) \), the likelihood is given by

\[
C(Y_1, Y_2, T_A, \delta_A, T_D, \delta_D | \alpha, \beta) = \left\{ \pi_1 f_{D,1}(T_D)^{\delta_D} F_{D,1}(T_D)^{1-\delta_D} \right\} Y_1 \\
\times \left\{ (1-\pi_1)^{Y_2} (1-\pi_2)^{1-Y_2} f_A(T_A | t_f)^{\delta_A} \right. \\
\left. \times F_A(T_A | t_f)^{1-\delta_A} f_D(T_D)^{\delta_D} F_D(T_D)^{1-\delta_D} \right\}^{1-Y_1}.
\]

Because administrative censoring takes place only at \( t = 50 \), when \( Y_1 = 1 \) the event time portion of the likelihood takes one of two forms: \( f_{D,1}(T_D) \) if \( T_D < 50 \) or \( F_{D,1}(50) \) if \( T_D > 50 \). Because \( f_D \) is piecewise exponential, when \( Y_1 = 0 \), the event time portion of the likelihood takes one of the following five forms:

\[
\begin{align*}
&\left\{ f_{D,1}(T_D) \right. \\
&\times F_{D,2}(50 - t_f) \\
&\times f_{D,2}(T_D - t_f) \\
&\times F_{D,1}(t_f) F_{D,2}(50 - t_f) \quad \text{if } T_D < t_f, \\
&\times F_{D,1}(t_f) F_{D,2}(50 - t_f) \quad \text{if } t_f + T_A < 50 < T_D, \\
&\times F_{D,2}(50 - t_f) \quad \text{if } t_f + T_A < 50 < T_D, \\
&\times F_{D,1}(t_f) F_{D,2}(50 - t_f) \quad \text{if } t_f + T_A < 50 < T_D, \\
&\times F_{D,2}(50 - t_f) \quad \text{if } 50 < \min\{t_f + T_A, T_D\}.
\end{align*}
\]
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The last four rows correspond to cases in which the patient survives long enough to be infused at \( t_I \), with \( f_D(t) = \mathcal{F}_{D,1}(t_I)F_{D,2}(t - t_I) \) and \( F_D(t) = \mathcal{F}_{D,1}(t_I)\mathcal{F}_{D,2}(t - t_I) \). Thus, for Mylotarg dose schedule \((d_1, d_2)\), the 50-day success probability for a patient infused at \( t_I \) is

\[
\theta(t_I) = \{1 - \pi_1 (d_1)\}\mathcal{F}_{A}(50 - t_I \mid t_I) \\
x \sum_{y_2=0}^{1} \pi_2 (d_+) y_2 \{1 - \pi_2 (d_+)\}^{1-y_2} \\
\times \mathcal{F}_{D,1}(t_I, y_2) \mathcal{F}_{D,2}(50 - t_I, y_2 \mid t_I) \\
= \{1 - \pi_1 (d_1)\}\mathcal{F}_{A}(50 - t_I \mid t_I) \\
x \sum \pi_2 (d_+) \exp \{-t_I e^{-(\alpha_0 + \alpha_1)} \\
\times \{1 - \pi_2 (d_+)\} \exp \{-t_I e^{-(\alpha_0 + \alpha_1)} \} \\
\times \exp \{-t_I e^{-\alpha_0} - (50 - t_I) e^{-(\alpha_2 + \alpha_3 + \alpha_4 x_f^2 + \alpha_1)} \} \},
\]

where

\[
\mathcal{F}_{A}(50 - t_I \mid t_I) = 1 - \exp\{-(50 - t_I) e^{-(\alpha_0 + \alpha_1)} + \alpha_3 x_f + \alpha_4 x_f^2 + \alpha_1 + \alpha_2 \}
\]

\( \pi_2 (d) = \logit^{-1}(\gamma_0 + \gamma_d d) \). The quantities \( \{\theta(t_I), t_I = 11, 14, 17, 20, 23\} \), will provide the basis for adaptively randomizing patients among the five infusion times throughout the trial.

2.4 Prior Distributions

When using Bayesian adaptive decision rules in small-scale clinical trials, the priors may have a substantive effect on the decisions early in the trial when relatively little data are available, i.e., in clinical trials including decisions based on small amounts of data, no prior is truly noninformative. In the present setting, assuming a highly dispersed prior on a given parameter will have particular consequences with regard to the doses assigned to the patients earlier in the trial as well as on the decision of whether to stop the trial early if unacceptably high rates of either toxicity or death are observed.

We assume a priori that each of the parameter vectors \( \beta, \alpha, \) and \( \gamma \) is multivariate normal. We apply a slightly modified version of the method of Bedrick, Christensen, and Johnson (1996) for specifying priors in a generalized linear regression model setting. The Bedrick et al. method begins with specification of a multivariate prior having dimension \( p \) equal to that of the parameter vector, based on \( p \) distinct covariate vectors, in the natural domain corresponding to the phenomenon described by the parameter. This distribution is then transformed to obtain the prior on the parameter vector. Here, the natural domains corresponding to \( \beta, \alpha, \) and \( \gamma \) that we employ are, respectively, the mean time to ANC recovery, mean probability of surviving 50 days, and HT probability.

Because the third author of this paper (TM) is a physician specializing in BMT and is a coinvestigator in the DLI trial, the numerical values of the priors are based on his clinical experience and prior beliefs regarding the patient outcomes in the trial.

We denote the mean and variance of \( \alpha_j \) by \( \mu_{\alpha_j} \) and \( \sigma_{\alpha_j}^2 \), and \( \text{cov}(\alpha_j, \alpha_k) = \sigma_{\alpha_j,\alpha_k} \), with the prior parameters of the \( \beta_j \)'s and \( \gamma_j \)'s denoted similarly. Because \( \beta \) is three dimensional, we first specified the prior mean and a 90% credibility interval (CI) for the mean time to ANC recovery, \( \mu_A(t_I, \beta) \), at each of three distinct infusion times. These are summarized in Table 1, part a. The rationale for these numerical prior parameters is that the earliest possible time to neutrophil recovery following DLI is approximately 8 days and the typical range is between 8 and 15 days. By \( t = 23 \) days, the Mylotarg should clear the patient's bloodstream and standard neutrophil recovery would be expected following DLI administration, i.e., recovery in 8-15 days. At \( t = 17 \) days, there is greater uncertainty about the amount of residual circulating Mylotarg, with greater amounts associated with a delay in neutrophil recovery. This motivates the larger, 8-20 day, 90% CI. At \( t = 11 \) days, there certainly will be circulating Mylotarg and neutrophil recovery may be delayed slightly or significantly, hence the wider CI.

We used this prior information to determine the means of the linear terms \( \eta_A(x_I, \beta) = \beta_0 + \beta_1 x_I + \beta_2 x_I^2 \) algebraically for \( x_I = -2, 0, \) and 2 and then used the credibility intervals to solve for the variance of each entry of \( \eta_A(x_I, \beta) = (\eta_A(-2, \beta), \eta_A(0, \beta), \eta_A(2, \beta)). \) Because \( \beta \) is a one-to-one linear function of \( \eta_A(x_I, \beta) \), applying the usual transformation theorem for multivariate normals then yielded the three-dimensional normal distribution of \( \beta \).
For $\alpha$, we first determined the prior of $\alpha_0$ from the mean probability 0.02 of death without HT within the first 11 days and the probability 0.90 that the probability of this event will be less than 10%. Formally, we assumed that

$$1 - \exp(-11c^{-\mu_{\alpha_0}}) = 0.02,$$

which yields $\mu_{\alpha_0}$ and

$$Pr\{1 - \exp(-11c^{-\mu_{\alpha_0}}) < 0.10\} = 0.90,$$

which then gives $\sigma_{\alpha_0}$ under normality. The prior of $\alpha_{-0} = (\alpha_1, \alpha_2, \alpha_3, \alpha_4)$ was then determined analogously to that of $\beta$. Because $\alpha_{-0}$ has four elements, the mean and variance of the linear term $\eta_D(x_1, Y_+; \alpha_{-0}) = \alpha_2 + \alpha_3 x_1 + \alpha_4 x_1^2 + \alpha_1 Y_+$ characterizing the survival distribution of a patient infused at $t_f$ is required for each of four distinct values of the vector $(x_1, Y_+)$. We thus elicited the conditional probability of death before day 50 given that the patient survived to be infused, which is

$$Pr(T_D < 50 \mid T_D > t_f) = 1 - \exp\left(-\left(\frac{50 - t_f}{c}\right) e^{-\left(\alpha_2 + \alpha_3 x_1 + \alpha_4 x_1^2 + \alpha_1 Y_+\right)}\right) \quad (11)$$

under the piecewise exponential model. This prior is summarized in Table 1, part b. The rationale for these numerical prior parameters is that, in previous DLI studies, the mortality rates at 60-90 days post-DLI have been approximately 30%, with deaths due to infection and disease recurrence. Mylotarg may cause more neutropenia and more infection, hence higher mortality, but it also may decrease mortality by preventing disease relapse. At $t_f = 11$ or 23 days, the total duration of neutropenia may be longer than for $t_f = 17$ days. Therefore, estimated mortality will be lowest for a $t_f$ of 17 days versus 11 or 23 days. Given this, if HT occurs, then mortality is expected to increase.

For the prior on $\gamma$, the mean HT probabilities and 90% CIs, summarized in Table 1, part c, correspond to Mylotarg doses of 9 mg/m$^2$ in each of two courses. The prior corresponds to this dose level since it has been used in previous trials not involving DLI. As above, we began with the assumption that $\eta_{HT}(9, \gamma) = \gamma_0 + \gamma_1 9$ has mean logit(0.05) and $\eta_{HT}(18, \gamma) = \gamma_0 + \gamma_1 18$ has mean logit(0.10), used the credibility intervals to solve for the variances of these two linear terms, and applied the transformation theorem to obtain the bivariate normal distribution of $(\gamma_0, \gamma_1)$. The rationale for the numerical prior in Table 1, part c, is that, in the phase I and II trials utilizing Mylotarg at a total dose of 18 mg given in two courses, the incidence of HT in patients with relapsed AML following allogeneic transplantation was 16%, with half of these cases fatal. This motivated the starting dose here of 8 mg in two courses. The prior mean probabilities of HT of 2.5% after 4 mg and 10% after 8 mg are based on the above experience at the higher dose. The larger CI for 8 mg at $(d_1, d_2) = (4, 4)$ reflects the greater uncertainty over two courses of therapy.

2.5 Posterior Distributions

Based on the assumed model and priors, neither the joint posterior distribution of all the parameters nor the full conditionals are available analytically. Moreover, numerical evaluation of the posterior distribution is not feasible given the high dimension of the parameter vector. Estimation, however, can proceed using Markov chain Monte Carlo (MCMC) methods, which construct a Markov chain having stationary distribution that is the posterior distribution of interest. After an initial burn-in to reach the stationary distribution, sampled values of the chain are used to estimate the posterior. One of the key elements for using this approach is the algorithm used for constructing the chain. We used the Gibbs sampler algorithm (Geman and Geman, 1984), in which samples are taken from all univariate full conditional distributions. While not available analytically, the full conditionals are log concave so that sampling can proceed by using the adaptive rejection sampling (ARS) algorithm (Gilks and Wild, 1992). This algorithm is based on the fact that any concave function can be bounded from above and from below by piecewise hulls constructed by using tangents and chords between points that are evaluated in the density’s domain. Because the rejection probability decreases with the number of sampled values, this algorithm is quite efficient.

To evaluate the performance of the ARS algorithm within the Gibbs sampler, we initially ran parallel chains with different starting points and assessed convergence of the chains using the software CODA (Best, Cowles, and Vines, 1995). This preliminary analysis indicated that the chains converged when using a burn-in of 500 iterations and an additional 1000 iterations for computing the randomization probabilities defined in equation (15). A discussion of implementation aspects of MCMC methods is given by Gilks, Richardson, and Spiegelhalter (1996). For actual trial conduct, a larger posterior sample size may be used to improve precision of the posterior estimates.

3. Trial Conduct

The Mylotarg dose de-escalation algorithm is based on the following definitions. Based on the clinical judgment that toxicity rates of 25% in the first course and 30% in the second course would be acceptable, we defined the course 1 Mylotarg dose $d_1$ to be unacceptably toxic if

$$Pr(\tau_1(d_1) > 0.25 \mid data) > 0.95 \quad (12)$$

and the two-course pair $(d_1, d_2)$ to be unacceptably toxic if

$$Pr(\tau_2(d_1) > 0.30 \mid data) > 0.95. \quad (13)$$

The dose de-escalation algorithm is given in Figure 2, where $H_1$ is the event that $d_1$ is unacceptably toxic, regardless of $H_2$. The algorithm is as follows:

- **STOP**: If $H_1$ occurs, then the trial is stopped.
- **2 + 0**: If $H_2$ occurs, then the trial is stopped.
- **2 + 2**: If $H_1$ occurs, then the trial is continued with $d_2 = 2$.
- **4 + 0**: If both $H_1$ and $H_2$ occur, then the trial is continued with $d_2 = 4$.

**Figure 2.** The Mylotarg between-patient dose de-escalation algorithm. "4+2" denotes 4 mg/m$^2$ in course 1 and 2 mg/m$^2$ in course 2, etc., $H_1 = [d_1 \text{ unacceptably toxic}, H_2 = [(d_1, d_2) \text{ unacceptably toxic but } d_1 \text{ acceptable}]. If either $H_1$ or $H_2$ occurs after the third level, then the trial is stopped.
Figure 3 illustrates the relationship between the immunotherapy and DLI, the possible patient outcomes, and the adaptive decision rules. Arrow 1 in the figure refers to the reliance of the adaptive randomization probabilities for infusion time on the posterior success probabilities, which in turn incorporate both the ANC recovery time and survival time data. Arrow 2 refers to the fact that the patient's therapy is terminated without DLI if HT occurs in course 1. Arrow 3 refers to the use of the HT data by the dose de-escalation algorithm.

Based on historical experience at the M. D. Anderson Cancer Center, an accrual rate of about two patients per month is anticipated. The trial has a maximum sample size of 60 patients and a 30-month maximum duration, allowing the possibility that the trial may be stopped early due to an excessively high toxicity rate. In contrast with the extensive time spent simulating the trial as part of the design process, during actual trial conduct, only a few minutes are required to update the posterior and compute the probabilities (12)-(14) used as decision criteria. Thus, each new patient's assigned Mylotarg doses and DLI time or the decision to terminate the trial entirely are available immediately at the patient's accrual time.

4. Simulation Study

Because interim decisions typically have important ethical, scientific, and economic consequences, while developing a new clinical trial design, it is important for the statisticians and physicians to closely study both the properties of the design and the particular decisions that will be made under specific clinical scenarios. If any aspect of the design is undesirable, then the design parameters or model components should be modified appropriately before the design is actually used to conduct the trial. The adaptive decisions made during the DLI trial rely on the posterior distributions of the probabilities \( \pi_1(d_1) \) and \( \pi_2(d_2) \) of HT, the mean time to ANC recovery, \( \mu_A(t_I, Y_+), \) and mean survival time, \( \mu_D(t_I, Y_+). \) The aim of the simulation study was to evaluate the behavior of the design under different possible qualitative and quantitative forms of these functions. Designing such a simulation study for the DLI trial is not straightforward, however, because the number of possible shapes of \( \mu_A \) and \( \mu_D \) as functions of \( t_I \) is quite large. In order to evaluate the design under a reasonable array of possible combinations of toxicity, ANC recovery, and survival time, we proceeded as follows.

We first evaluated only the dose de-escalation algorithm in terms of HT while ignoring the rest of the trial's structure. The aim was to first calibrate the probability cutoffs used in the toxicity criteria (12) and (13) and the overall maximum sample size, based on the behavior of the dose de-escalation algorithm. Initially, an algorithm substantially more complex than that given in Figure 2 was considered, beginning with \((d_1, d_2) = (9,9)\) and involving up to five possible dose changes. We simulated this algorithm with a maximum of 50 patients under five cases with \((\pi_1(9), \pi_2(18))\) varying from \((0.65, 0.10)\) to \((0.50, 0.55).\) For each case, we solved for \(\gamma_0\) and \(\gamma_1\) and used these as fixed values in the simulations to accommodate the varying doses resulting from the de-escalation. These preliminary simulations showed that, even with the acceptable toxicity probabilities \(\pi_1(9) = 0.25\) and \(\pi_2(18) = 0.30,\) on average, 16 patients suffered HT in the first course and so
only 34 remained to be infused. Based on these numerical results and the additional medical consideration that starting with \((d_1, d_2) = (9, 9)\) might be overly risky, it was decided to modify the design. Accordingly, it began with \((d_1, d_2) = (4, 4)\) rather than \((9, 9)\), the Mylotarg dose de-escalation algorithm was simplified to that described in Figure 1, and the maximum sample size was increased from 50 to 60.

We simulated the entire trial under this design, as follows. From the prior on \(\gamma\) (Table 1, part c), the fixed toxicity probabilities used for the simulations corresponded to \(\tau_1(4) = 0.025\) and \(\tau_2(8) = 0.10\). We solved these two equations for \(\gamma_0\) and \(\gamma_1\) and simulated \(Y\) using the toxicity probabilities determined by these values throughout. To obtain fixed values of the baseline death rate \(\mu_D(t_1, Y+)\), we solved for fixed values of \(\alpha_0\) and \(\alpha_1\) based on their prior means. Recall that \(\Pr(T_D < 11 \mid Y = 0) = 1 - \exp(-11e^{-\alpha_0})\), so the prior mean 0.02 for this probability gives fixed \(\alpha_0 = 6.3\) for the simulation. Similarly, using the means in the first two rows of Table 1, part b, give fixed value \(\alpha_1 = -0.6644\). These values give death rates of 0.0178 for patients with HT and 0.0091 for patients without HT. The simulations assumed these two death rates throughout for a patient never infused, and for infused patients the postinfusion mean survival time was multiplied by \(\exp(\alpha_1) = 0.51\) if the patient had HT.

The remaining fixed parameter values needed for the simulations are those determining how \(\mu_A\) and the 50-day survival probability each vary as functions of \(t_1\). Rather than specifying these in terms of fixed values of \(a_2, a_3, a_4, a_5, a_6\), and \(b\), we specified three non-model-based cases of each function in terms of their numerical values at each \(t_1\). These are given in Table 2. Cases \(A_1, A_2,\) and \(A_3\) for \(\mu_A\) are functions that decrease, increase, and form a U shape with \(t_1\), respectively. Similarly, cases \(D_1, D_2,\) and \(D_3\) for the probability of death before day 50 are initially flat and then increasing, U shaped, and decreasing with \(t_1\), respectively. Each scenario thus consists of a combination \((A_i, D_j)\) from Table 2, with the fixed values of \(\gamma, \alpha_0,\) and \(\alpha_1\) as described above. The cases \(A_1\) and \(D_1\) with decreasing functions correspond to the case where Mylotarg is unlikely to destroy infused donor cells and hence neutropenia increases with \(t_1\). The cases \(A_2\) and \(D_1\) with increasing functions correspond to the case where Mylotarg kills a substantial number of donor cells, hence neutropenia decreases with \(t_1\). The U-shaped functions \(A_3\) and \(D_2\) correspond to the case where Mylotarg kills donor cells but increasing \(t_1\) prolongs neutropenia; hence, there is an optimal intermediate infusion time.

Initial exploratory simulations with 100 repetitions of the trial took roughly 2 days for one scenario on a personal computer (PC) with a Pentium III processor. In order to simulate 1000 trials under each scenario, we used parallel processing that distributed the computations for each simulation over 35 PCs. Using this approach, on average, it took roughly 12 hours to simulate each scenario. Because there was some redundancy among the nine scenarios in terms of their 50-day survival probability curve \((t_1, \theta(t_1))\), in Table 3, we summarize results for the balanced incomplete block subdesign consisting of the three cases \((A_1, D_3),\) \((A_2, D_1),\) and \((A_3, D_2)\). Results for the other six cases were substantively very similar to those in Table 3.

---

**Table 2**

Simulation cases for varying mean time to ANC recovery and probability of death before day 50 if infused at \(t_1\) and no HT

<table>
<thead>
<tr>
<th>Case</th>
<th>11</th>
<th>14</th>
<th>17</th>
<th>20</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Number of Days to ANC (\geq 1000)</td>
<td></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>
<tr>
<td>(D_1)</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.30</td>
<td>0.35</td>
</tr>
<tr>
<td>(D_2)</td>
<td>0.25</td>
<td>0.20</td>
<td>0.15</td>
<td>0.20</td>
<td>0.25</td>
</tr>
<tr>
<td>(D_3)</td>
<td>0.40</td>
<td>0.35</td>
<td>0.30</td>
<td>0.25</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Under scenario \((A_1, D_3)\), \(\theta(t_1)\) increases monotonically from 0.43 at \(t_1 = 11\) to 0.69 at \(t_1 = 23\). The selection probability, \(SP(t_1)\), is very nearly monotone increasing in \(t_1\), with \(SP(23) = 0.56\) for the optimal day \(t_1 = 23\). Moreover, on average, the adaptive randomization treats more patients at the more desirable infusion times. The success probabilities under scenario \((A_2, D_1)\) decrease monotonically with infusion day, from 0.67 at \(t_1 = 11\) to 0.39 at \(t_1 = 23\). Again, in this case, \(SP(t_1)\) follows this monotone pattern, aside from a very small increase at \(t_1 = 23\). Given the small difference in the two largest success probabilities, \(\theta(11) = 0.67\) and \(\theta(14) = 0.64\), under this scenario, the fact that \(t_1 = 11\) and 14 are selected with respective probabilities 0.50 and 0.26 is quite encouraging. Under scenario \((A_3, D_2)\), \(SP(t_1)\) increases to a maximum of 0.70 at \(t_1 = 17\) and then decreases. Both \(SP(t_1)\) and the numbers of patients infused follow this pattern, with \(SP(17) = 0.54\) for the optimal day \(t_1 = 17\). These results indicate that the quadratic functions of infusion time in the log-mean ANC recovery rate and the log-mean death rate do a very effective job of recognizing nonlinear rates in terms of the Bayesian adaptive randomization based on the posteriors of the \(\theta(t_1)\)’s. Given that the adaptive randomization must rely on very small amounts of data early in the trial, the method behaves remarkably well.

Our elicited prior is informative. While a thorough analysis of the design’s sensitivity to the prior is beyond the scope of this article, it is useful to examine how the operating characteristics change in a specific case. To do this, we (1) decreased the mean and 95% CI of \(\mu_A(11)\) from \((20, 10-30)\) to the more optimistic values \((15, 5-25)\), (2) increased the mean and 95% CI of \(\mu_A(17)\) from \((10, 8-20)\) to the less optimistic values \((15, 13-25)\), and (3) increased the mean and 95% CI of the probability of death before day 50, given survival to infusion, for \(t_1 = 11\) to \((0.40, 0.10-0.00)\) when \(Y_+ = 0\) and to \((0.60, 0.25-0.90)\) when \(Y_+ = 1\). The effects of these changes are to shorten both mean ANC recovery time and survival time for patients with the earliest infusion day, \(t_1 = 11\). With these changes, under scenario \((A_1, D_3)\), the mean selection probabilities are \(SP = \{SP(11), \ldots, SP(23)\} = (0.07, 0.02, 0.11, 0.17, 0.63)\) and the mean numbers of patients infused are \(N = \{N(11), \ldots, N(23)\} = (7.9, 3.3, 12.1,\)
slightly while SP(23) and N(23) increase compared with the
6.5). In all three scenarios, both SP(17) and N(17) decrease
the best DLI time still has the highest values of
values in Table 3 for the actual prior. The general behavior of
the design persists under all three scenarios, however, in that
the best DLI time still has the highest values of SP and N.
It thus appears that the method is sensitive to the prior, at
least for changes of the magnitude considered, but that it still
behaves as desired.

5. Discussion
We have proposed an adaptive statistical design for conduct-
ing a clinical trial of an innovative therapeutic strategy in
a group of cancer patients with very poor prognosis. Each
patient’s outcome is the vector \((Y, T_A, \delta_A, T_B, \delta_D)\),
with several possible configurations of these variables observable
depending on whether \(Y_1 = 0\) or 1 and the values of \(T_A\)
and \(T_D\). The therapeutic strategy is adaptive within each patient
in that no further therapy is given if \(Y_1 = 1\). The design
is adaptive between patients in that each patient’s Mylotarg
doses and infusion time are determined based on the data
from previous patients in the trial. This may be considered
a phase I/II trial (Thall and Russell, 1998) in the sense that
it includes dose finding and evaluation of both adverse and
desirable outcomes. While the design described here has been
tailored to the particular application at hand, the dose-finding
and adaptive randomization methods could be applied, with
suitable modification, to design future trials having similar
goals.

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Résumé
Cet article décrit un plan adaptatif bayésien, conçu pour l’es-
sai clinique d’un traitement expérimental destiné à des pa-
tients atteints d’affectations tumorales hématologiques et ac-
cusant, après une greffe de moelle osseuse allogénique, une
récidive. Le traitement consiste en une ou deux immunothéra-
rpie-ciblées, suivies par une transfusion de lymphocytes. Si
l’on sait que l’immunothérapie est un préalable nécessaire à
la transfusion, on sait aussi qu’elle peut produire des tox-
icités hépatiques sévères, et qu’elle provoque à coup sûr des
diminations importantes des globules blancs et des plaquettes.
L’objectif scientifique primordial est ici de déterminer le délai
optimal (mesuré à partir de l’immunothérapie) pour procéder
da la transfusion, afin que celle-ci ait les meilleures chances
de succès (on définit un succès par le fait que le patient, 50
jours après le début de la thérapie, ait non seulement survécu,
mais qu’il n’ait subi aucune atteinte hépatique sévère, tout
en ayant par ailleurs recouvré une quantité normale de glob-
ules blancs). Notre méthode utilise un modèle paramétrique
prenant en compte la survie, la toxicité hépatique et le temps
de recouvrement d’une quantité normale de globules blancs.
Le plan expérimental repose d’une part sur un algorithme
comparant, à partir de données de toxicité hépatique, la déses-
calade des doses de l’immunothérapie d’un patient à l’autre; il
repose d’autre part, sur une randomisation adaptative de cinq
délais possibles pour la transfusion, randomisation effectuée
en fonction des dernières estimations a posteriori des taux de
succe de liés à chacun des cinq délais. Une simulation démontre
que c’est avec une certaine fiabilité que ce plan sélectionne
le meilleur délai après immunothérapie; de surcroît, la pro-
portion des patients randomisés sur les délais les moins bons
s’avère relativement faible.

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