INCORPORATING PATIENT’S CHARACTERISTICS IN CANCER PHASE I CLINICAL TRIALS USING TIME TO DLT: ESCALATION WITH OVERDOSE CONTROL (EWOC)

Yuan Liu
Department of Biostatistics and Bioinformatics
Winship Cancer Institute
Emory University

Mourad Tighiouart, André Rogatko
Samuel Oschin Comprehensive Cancer Institute
Cedars-Sinai Medical Center

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Goals of phase I cancer clinical trial:
- Estimate the maximum tolerated dose (MTD).
- Assumption: both efficacy and toxicity increase with dose.
- Minimize overdose rate; maximize effective dose coverage

Designs:
- Rule-based approaches: 3+3 and its modifications
- Model-based approaches: CRM, EWOC, and their extensions.

EWOC-PH:
- Time to DLT
- Proportional Hazards model
- Late onset toxicity; shorten trial duration
INCORPORATING PATIENT’S CHARACTERISTICS

- A key assumption by the definition about phase I clinical trial designs
  - patient population is homogeneous in susceptibility to treatment.
  - Individualized MTD can prevent patients being overdosed or being treated under an ineffective dose.

- Model-based approaches:
  - Flexible to incorporate covariates in a Bayesian model

- Aims of this study:
  - Extend EWOC-PH to account for patient’s heterogeneity
  - Simulation study was conducted to investigate its operating characteristics.
MODEL SETTING

- Let $T_j$ be the random variables representing time to DLT up to time $\tau$, and let $\Omega_n = \{(Y_j, x_j, z_j, \delta_j); j = 1, 2, ..., n\}$ be the observed data, where $Y_j = \min(T_j, \tau)$, $\delta_j = I(T_j \leq \tau)$, and $x_j$ is the dose assigned to patient $j$, and $z_j$ is the value of covariate for patient $j$.

- The dose-toxicity relationship is described by the proportional hazards model (Cox, 1972)

\[
h(T_j | x_j, z_j) = h_0(T_j; \lambda') \exp(\beta \cdot (x_j - x_0) + \eta z_j), \quad \beta > 0
\]

- Assuming the baseline hazard is exponential distribution.

\[
h(T_j | x_j, z_j) = b \cdot \exp(\beta \cdot (x_j - x_0) + \eta z_j), \quad \beta > 0
\]

\[
L(b, \beta, \eta | \Omega_n) = \prod_{j=1}^{n} (b \cdot \exp(\beta(x_j - x_0) + \eta z_j))^\delta_j \exp(-Y_j \cdot b \cdot \exp(\beta(x_j - x_0) + \eta z_j))
\]
RE-PARAMETERIZATION

- Suppose we have a dichotomized covariate $z$ takes value of 0 and 1 that leads to personalized MTDs: $\gamma_0$ if $z = 0$ or $\gamma_1$ if $z = 1$

- Define:

  \[
  \Pr(Y \leq \tau \mid x = \gamma_i, z = i) = 1 - S(Y \mid \gamma_i, z = i) = \theta, \quad i = 0, 1
  \]

  \[
  \Pr(Y \leq \tau \mid x = x_0, z = 0) = 1 - S(Y \mid x_0, z = 0) = \rho_0
  \]

- Based on the one to one correspondence between Survival function and hazard function

  \[
  b = \frac{1}{\tau} \log(1 - \rho_0); \quad \beta = \frac{1}{\gamma_0 - x_0} \log \left( \frac{\log(1 - \theta)}{\log(1 - \rho_0)} \right); \quad \eta = \frac{\gamma_0 - \gamma_1}{\gamma_0 - x_0} \log \left( \frac{\log(1 - \theta)}{\log(1 - \rho_0)} \right)
  \]

- The likelihood function is re-parameterized in terms of $\gamma_0, \gamma_1, \text{and} \rho_0$

  \[
  L(b, \beta, \eta \mid \Omega_n) \rightarrow L(\gamma_0, \gamma_1, \rho_0 \mid \Omega_n)
  \]

- Prior distribution/posterior distribution
The first patient in each group will receive an initial dose of $x_0$ and be observed until $\tau$. If the patient has DLT before $\tau$, then we would recommend to stop the trial in the subgroup or go with a lower level dose. Otherwise, the next patient is enrolled if available.

Based on $\Omega_{j-1}$, the $j^{th}$ patient receives the dose so that the posterior probability of exceeding $\gamma_0$ if $z_j = 0$ or $\gamma_1$ if $z_j = 1$ is equal to a feasibility bound $\alpha$.

The feasibility bound $\alpha$ usually starts at $\alpha = 0.25$ and increases in small increments of 0.05 until $\alpha = 0.5$. 
SIMULATION PLAN

- Compare three models:
  - EWOC-PH with covariate
  - EWOC-PH without covariate
  - Separate trails for each group by EWOC-PH

- Examine the operating characteristics.
  - Bias of estimation
  - Mean Square of Error (MSE) of estimation
  - Probability of DLT
  - Probability of over dose
## Simulation Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$ - Sample size</td>
<td>36, 48</td>
</tr>
<tr>
<td>$\alpha$ - Feasibility bound</td>
<td>0.25</td>
</tr>
<tr>
<td>$\theta$ - Target probability of DLT under MTD</td>
<td>0.33</td>
</tr>
<tr>
<td>$\rho_0$ - True probability of DLT at $X_0$</td>
<td>0.10, 0.05</td>
</tr>
<tr>
<td>$(\gamma_0, \gamma_1)$ - True MTD combination when $z = 0$ and $z = 1$</td>
<td>(0.2, 0.2), (0.4, 0.4), (0.6, 0.6), (0.8, 0.8), (0.2, 0.4), (0.2, 0.6), (0.2, 0.8), (0.4, 0.6), (0.4, 0.8), (0.6, 0.8)</td>
</tr>
<tr>
<td>Allocation rate of two groups</td>
<td>1:1, 1:2</td>
</tr>
<tr>
<td>Accrual Rate</td>
<td>1, 4</td>
</tr>
</tbody>
</table>

Data generating:

$$T_j = \frac{-\log(U)}{b \cdot \exp(\beta(x_j - x_0) + \eta z_j)}$$
SIMULATION RESULTS 1
BIAS OF ESTIMATED MTD

*selected results summary for sample size = 48, accrual rate = 4, allocation rate = 0.5, and probability of DLT at $x_0 : \rho_0 = 0.05$. 
**Simulation Results 2**

MSE of estimated MTD

*selected results summary for sample size = 48, accrual rate = 4, allocation rate = 0.5, and probability of DLT at $x_0$ : $\rho_0 = 0.05$.  

*Note: The graph shows the Mean Squared Error (MSE) of estimated Maximum Tolerated Dose (MTD) for different scenarios with varying accrual rates and allocation rates.*
SIMULATION RESULTS 3

PROBABILITY OF DLT

*selected results summary for sample size = 48, accrual rate = 4, allocation rate = 0.5, and probability of DLT at $x_0 : \rho_0 = 0.05$. 

*
SIMULATION RESULTS 4
PROBABILITY OF OVER-DOSE

*selected results summary for sample size = 48, accrual rate = 4, allocation rate = 0.5, and probability of DLT at $x_0 : \rho_0 = 0.05$. 
SIMULATION RESULTS 5
COMPARE TO EWOC WITH COVARIATE

*selected results summary for sample size = 48, accrual rate = 4, allocation rate = 0.5, and probability of DLT at $x_0 : \rho_0 = 0.05$. 
SIMULATION RESULTS 6
COMPARE TO EWOC WITH COVARIATE

*selected results summary for sample size = 48, accrual rate = 4, allocation rate = 0.5, and probability of DLT at \(x_0 : \rho_0 = 0.05\).
CONCLUSION

- This study extends EWOC-PH to incorporate patient covariates. The results are similar to those from standard EWOC with covariates with an up to 30% improvement in MSE.

- When comparing to EWOC-PH without covariate design
  - In a heterogeneous patient population, our approach has more than 100% improvement in efficiency (MSE)
  - In a homogeneous patient population, our approach has only an up to 30% decrease in efficiency (MSE).

- Modeling patient heterogeneity in terms of susceptibility to treatment increases the probability that patients will be treated at safer and more efficacious doses, and estimation of personalized MTDs increases the probability that the best treatment plan will be used in subsequent phase II and III clinical trials.
THANK YOU!
QUESTIONS OR COMMENTS?