Modeling Cyclophosphamide’s Effect on Leukocytes

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Math Modeling in Biology 2014 Summer REU

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Agenda

- Motivation For Project
- Background Biology and Chemistry
- Model Construction
- Differential Equations
- Results
- Further Study
Background on Cyclophosphamide

- Pro-drug typically used in immune suppression and chemotherapy
- Can assist in oncolic virotherapy, the use of engineered viruses to combat cancerous cells
- Used to suppress the immune system enough so that the viruses can infect and kill the cancerous cells in the body
- Necessary to control the timing and amount of doses due to its toxicity
Pharmacodynamics of Cyclophosphamide (CY)

- Inactive until it reaches the liver and is metabolized to hydroxycyclophosphamide (HCY)
- About 70% of CY is metabolized to HCY, the rest is primarily excreted unchanged in urine
- HCY lives in equilibrium with its tautomer aldophosphamide (AP)
- AP is what kills cells at tissue level
- HCY is primarily eliminated through AP
Pharmacodynamics of Cyclophosphamide

Credit: Cyclophosphamide metabolism, liver toxicity, and mortality following hematopoietic stem cell transplantation
Model Building for CY

- Focused on CY concentrations in the liver and blood and the AP concentration in the liver and tissue
- Didn’t include HCY in the model, AP is what interacts chemically in tissues and degrades in the liver
- Assumed that a third of the amount of HCY being activated in the liver directly converted to AP
- Blood is simply a means of transport between the liver and tissues
Pharmacodynamics of Cyclophosphamide

BLOOD $\xrightarrow{k_{EC}}$ LIVER $\xrightarrow{k_1} \xrightarrow{k_2} \xrightarrow{k_{AA}}$ Tissues

$\text{Aldophosphamide}$ $\text{Cyclophosphamide}$
Differential Equations For CY Pharmacodynamics

\[
\frac{dC_B}{dt} = k_1(C_L - C_B) - C_B k_{EC} + D(t) \quad (1)
\]
\[
\frac{dC_L}{dt} = -k_1(C_L - C_B) - C_L k_{AH} \quad (2)
\]
\[
\frac{dA_L}{dt} = k_{AA} C_L - k_2(A_L - A_T) - k_{EA} A_L \quad (3)
\]
\[
\frac{dA_T}{dt} = -k_2(A_T - A_L) - \mu A_T \quad (4)
\]

\(D(t)\) is the controlled dose given every 24 hours, denoted as a piecewise function
Some Results

Dose of 5 mg/kg

Dose of 20 mg/kg
Population Dynamics of Leukocytes

- Stem cells (S), multipotent progenitor cells (MPP), common progenitor cells (CM), lymphocytes (L) and granulocytes (G)
- $S \rightarrow MPP \rightarrow CM \rightarrow L\&G$
- S and MPP also regenerate depending on L and G cell concentration
- Together L and G make up all the Leukocytes
Leukocyte Model

- \( \phi \) - feedback functions (L and G)
- \( \mu \) - death rates
- \( \lambda, r_d, r_{p'}, r_{cm} \) - rates
- \( \theta \) - fixed proportion L is made from CM
Leukocyte Model Differential Equations

\[
\frac{dS}{dt} = S \ln\left(\frac{K}{S}\right)(r_s - r_p' \phi_p'[L, G])\phi_s[L, G] - \mu_s S \quad (5)
\]

\[
\frac{dMPP}{dt} = S \ln\left(\frac{K}{S}\right)(r_s + 2r_p' \phi_p'[L, G])\phi_s[L, G] + MPP((\lambda - r_d)\phi_p[L, G] - \mu_p - \alpha_1 A_t(t)) \quad (6)
\]

\[
\frac{dCM}{dt} = MPP r_d \phi_p[L, G]\Omega_N - CM(\mu_{cm} + r_{cm} + \alpha_2 A_t(t)) \quad (7)
\]

\[
\frac{dL}{dt} = CMr_{cm}\theta \frac{10}{3003} + L(r_l - \mu_{l} - \mu_{l*}l_{vt>vth} - \alpha_3 A_t(t)) \quad (8)
\]

\[
\frac{dG}{dt} = CMr_{cm}(1 - \theta) \frac{10}{3003} + G\mu_g \quad (9)
\]
Some Issues With Interpreting this Model

- Could not find the $\alpha_3$ value
- My model doesn't work with only $\alpha_2$ & $\alpha_1$
- Because of the feedback functions, effects of the doses are extremely complicated
10 days 5 mg/kg a day

\( \alpha = 0 \)
L and G decreases 46%

\( \alpha = 0.5 \)
L decreases 68%

\( \alpha = 1 \)
L decreases 81%

\( \alpha = 2 \)
L decreases 93%
Finding Optimal Doses

My solution of differential equations as a function of a loading dose, maintenance dose, and time in Mathematica

- A loading dose is a high dose given to achieve a drastic effect quickly
  - First three days
- A maintenance dose is a lower dose to maintain that effect
  - Following seven days
Examples of Optimal Loading and Maintenance Doses depending on $\alpha_3$

<table>
<thead>
<tr>
<th>$\alpha_3$ value</th>
<th>LD</th>
<th>MD</th>
<th>$\Delta L$ 3 days</th>
<th>$\Delta L$ 10 days</th>
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<tbody>
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<td>0</td>
<td>200</td>
<td>10</td>
<td>17.3%</td>
<td>50.2%</td>
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<td>1</td>
<td>30.3%</td>
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<tr>
<td>.35</td>
<td>19</td>
<td>0</td>
<td>30.3%</td>
<td>74.5%</td>
</tr>
</tbody>
</table>
The end product
Future Work

- Taking the viral response into account
- Finding a more definitive $\alpha_3$ parameter or maybe $\alpha_1$ & $\alpha_2$ are functions rather than rates
- Fit data to my model
- Using elements of Control theory to find optimal dosage
Thanks for listening!