Mathematical models of chronic lymphocytic leukemia

• Introduction to CLL
• Ibrutinib therapy – understanding the kinetics
• Calculating personalized treatments

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Intro to CLL

• most common type of leukemia

• accumulation of small B lymphocytes with mature appearance

• most patients are diagnosed without symptoms during routine blood tests

• Upon diagnosis, a “wait and see” approach is followed.

• Treatment only initiated if certain conditions are met
  => Rai and Binet staging; blood counts, doubling times of cells, etc

• Over the last years, patients are treated with a combination of chemotherapy (e.g. fluradabine, cyclophosphamide) and antibody therapy (rituximab)
Cells of origin

Resting B cell becomes activated by pathogen

Activated B cell proliferates and secretes antibody
Cells of origin

"unmutated" worse prognosis

"mutated" better prognosis
del 13q: Deletion of long arm of chromosome 13, is the most common abnormality (50%). Best prognosis, some never need treatment

Trisomy 12: 20-25% of patients, have intermediate prognosis

del 11q: Deletion of long arm of chromosome 11, relatively poor prognosis, because deletion targets the ATM gene. Occurs in 5-10% of cases

del 17p: deletion of part of short arm of chromosome 17. Poorest prognosis because it inactivates p53. (5-10% of cases)
Kinetics & Therapy of CLL

- Growth kinetics before treatment
- Kinetics during targeted therapy
Growth kinetics

- growth tends to be exponential in the long term
- you can feed heavy water to patients to label cells
- dynamics of label uptake and dilution allows you to estimate the division rate of cells
- knowing the overall growth rate and the division rate of cells allows us to estimate the death rate of cells.

- Messmer et al 2005
- Our own work in progress

about 0.5% of cells die per day
Therapy

up to 2014, the standard was “chemo-immunotherapy” => good results, except for more virulent disease types, e.g. del 17p

this is still the case, but things are changing

Targeted treatment approaches are emerging.
Ibrutinib

- Previously called PCI-32765
- First Bruton tyrosine kinase (BTK) inhibitor
- Acts via specific binding to a cysteine residue in the BTK kinase domain
- Inhibits BTK phosphorylation and its enzymatic activity
- Clinically active through:
  - Induction of cell death
  - Inhibition of proliferation
  - Inhibition of tissue homing

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Treatment response to Ibrutinib

Kinetics of chronic lymphocytic leukemia (CLL) cells in tissues and blood during therapy with the BTK inhibitor Ibrutinib

Dominik Wodarz, Naveen Garg, Natalia L. Komarova, Ohad Benjamini, Michael J. Keating, William G. Wierda, Hagop Kantarjian, Danielle James, Susan O'Brien and Jan A. Burger
CLL response to Ibrutinib (treatment start at day 0)

Every patient shows a temporary phase of **lymphocytosis**, where the number of CLL cells in blood increases up to a peak, before eventually declining.
Compartments

Tissues, such as lymph nodes, spleen, bone marrow

Blood

Action, i.e. division and growth, most cells here => Microenvironment

No action small fraction of tumor
Ibrutinib

Tissues, such as lymph nodes, spleen, bone marrow

Action, i.e. division and growth, most cells here => Microenvironment

Blood

No action small fraction of tumor
Question

What does this lymphocytosis mean?

Cells in the blood only tip of iceberg

Most action occurs in tissues (lymph nodes, spleen, bone marrow)

Ibrutinib disrupts tissue microenvironment, thus cells re-distribute to blood

Do most cells simply shift between compartments? => drug not very effective

Do most tissue cells die and only a minority redistribute? => drug effective
We considered a two-compartment model for CLL dynamics:
Mathematical model

Treatment:

Tissue

Blood

division

redistribution

homing

death
Mathematical model

\[ m = \text{rate of redistribution} \]
\[ d_1 = \text{CLL cell death rate in tissue} \]
\[ d_2 = \text{CLL cell death rate in blood} \]
\[ c = \text{factor to account for the observation that CLL cells stabilize at low levels in the long term} \]
\[ \alpha = m + d_1 \]

**idea:** fit model to treatment data and estimate the parameters
Model

**Aims:**

- estimate crucial parameters
- calculate the percentage of pre-treatment tissue tumor burden that redistributes into the blood
Model

Relative number of cells redistributed from tissue to blood:

\[ Z(t) = \frac{\int_0^t m x(t') \, dt'}{x_0} = \frac{m}{\alpha x_0} \left( (x_0 - C_x)(1 - e^{-\alpha t}) + \alpha C_x t \right). \]  \hspace{1cm} (11)

This quantity is a composite of two characteristic times of decay: the first term measures the decay-time of CLL lymphocytes in tissues (and it is defined by both redistribution and death processes), and the second term measures the decay time in blood, defined uniquely by the death rate \( d_2 \).

Tumor stabilizes due to parameter \( c \) this phase is not interesting. Here \( Z \) grows linearly in time because of remaining equilibrium level of CLL cells in tissue.
Model fitting

Model contains 2 variables:

- cells in tissues

\[
\frac{dx}{dt} = -mx - d_1 (x - c)
\]

- cells in blood => absolute lymphocyte counts

\[
\frac{dy}{dt} = mx - d_2 y
\]
Model fitting

Model contains 2 variables:

- cells in tissues
- cells in blood => absolute lymphocyte counts

\[
\frac{dx}{dt} = -mx - d_1(x - c) \\
\frac{dy}{dt} = mx - d_2y
\]
Fitting

The solution reads

\[ x(t) = C_x + (x_0 - C_x)e^{-\alpha t}, \]
\[ y(t) = \frac{mx_0}{d_2 - \alpha}e^{-\alpha t} + \left(y_0 - \frac{mx_0}{d_2 - \alpha} - C_y\right)e^{-d_2t} + C_y. \]

(9) \hspace{1cm} (10)

It turns out that apart from the solution just described, there is always a second solution which yields exactly the same fit, with

\[ \hat{\alpha} = d_2, \quad \hat{d}_2 = \alpha, \]
\[ \hat{C}_y = C_y, \quad \hat{y}_0 = y_0, \quad \hat{m}x_0 = mx_0 + (y_0 - C_y)(d_2 - \alpha). \]

(12) \hspace{1cm} (13)

This duality of solution does not allow one to determine the parameters
Solution

We need to know the number of CLL cells in tissue at least at two time points.
Solution

We need to know the number of CLL cells in tissue at least at two time points

Use radiological data available for a subset of patients to estimate the number of CLL cells in tissue
Solution

We need to know the number of CLL cells in tissue at least at one time point

Use radiological data available for a subset of patients to estimate the number of CLL cells in tissue

The volume of lymphoid tissues and the spleen was quantified by computed tomography (CT) scans, and this was used to estimate the number of CLL cells in the tissues
Volumetric Analysis

Volumetric analyses of CLL lymph node and spleen manifestation (A) before and (B) during therapy with ibrutinib.

Depicted are CT images from a representative CLL patient from our series with superimposed reconstruction of main areas of CLL involvement, highlighted in color. The volumes of the axillary (red), intra-abdominal (blue), inguinal (purple) and spleen (green, yellow) disease manifestations are displayed next to each involved area.

Volumetric analysis done for 3 time points: one before treatment, two during treatment
Model fitting

Model contains 2 variables:

- cells in tissues
- cells in blood => absolute lymphocyte counts

\[
\frac{dx}{dt} = -mx - d_1(x - c) \\
\frac{dy}{dt} = mx - d_2y
\]
Fitting
Parameter Estimates

\[ d_2 = \text{death rate of CLL cells in blood}; \]
\[ d_1 = \text{death rate of CLL cells in tissue}; \]
\[ m = \text{rate of redistribution of tissue cells to blood}; \]
\[ \alpha = \text{overall nodal decline rate, i.e. rate at which cells disappear from the tissue due to redistribution + death, i.e. } \alpha = m + d_1; \]
\[ x_0 = \text{total body number of CLL cells in tissue}; \]
\[ y_0 = \text{total body number of CLL cells in blood}; \]
\[ \% \text{ restr} = \% \text{ of pre-treatment tissue tumor burden that is redistributed}. \]

<table>
<thead>
<tr>
<th>patient</th>
<th>(d_2) (d(^{-1}))</th>
<th>(d_1) (d(^{-1}))</th>
<th>(m) (d(^{-1}))</th>
<th>(\alpha) (d(^{-1}))</th>
<th>(x_0) (x10(^{9}))</th>
<th>(y_0) (x10(^{9}))</th>
<th>(%) restr.</th>
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<td>1</td>
<td>0.002</td>
<td>0.027</td>
<td>0.0096</td>
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<td>153</td>
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<td>0.032</td>
<td>0.0023</td>
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<tr>
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<td>0.035</td>
<td>0.0034</td>
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<td>average</td>
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<td>0.027</td>
<td>0.008</td>
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<td>8019</td>
<td>221</td>
<td>23.3</td>
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<tr>
<td>st. dev.</td>
<td>0.011</td>
<td>0.010</td>
<td>0.005</td>
<td>0.006</td>
<td>8799</td>
<td>226</td>
<td>17.0</td>
</tr>
</tbody>
</table>
Death rates

In tissue: \( d_1 = 0.027 \pm 0.01 \text{ days}^{-1} \)

2.7\% \pm 0.99\% of the cells die per day in tissue

In blood: \( d_2 = 0.017 \pm 0.012 \text{ days}^{-1} \)

1.7\% \pm 1.1\% of the cells die per day in the blood
Death rates

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In blood: $d_2 = 0.017 \pm 0.012 \text{ days}^{-1}$

$1.7\% \pm 1.1\%$ of the cells die per day in the blood

Previous estimate in the absence of treatment:

$0.5\%$ of cells died per day

treatment increases death rate 5-fold

treatment increases death rate 3-fold
Death rates vs redistribution rate

In tissue: \( d_1 = 0.027 \pm 0.01 \text{ days}^{-1} \)

2.7\% \pm 0.99\% of the cells die per day in tissue

In blood: \( d_2 = 0.017 \pm 0.012 \text{ days}^{-1} \)

1.7\% \pm 1.1\% of the cells die per day in the blood

Redistribution rate: \( m = 0.008 \pm 0.005 \text{ days}^{-1} \)
Death rates vs redistribution rate

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**1.7\%** \( \pm 1.1\% \) of the cells die per day in the blood

Redistribution rate: \( m = 0.008 \pm 0.005 \text{ days}^{-1} \)

The percentage of the tissue CLL cell population that was re-distributed into the blood was **23.3 \( \pm 17\% \)**.
Nodal decline driven by cell death rather than redistribution

(a) There is a significant correlation between the rate of nodal decline and the death rate of cells in tissue (p=0.0005).

(b) There is no significant correlation between the rate of nodal decline and the redistribution rate of CLL cells.
Treatment Kinetics -summary

• Ibrutinib causes a substantial amount of cell death in tissue

• Lymphocytsis only represents a relatively small fraction of total tissue tumor burden

• Treatment can be considered effective

=> Parameters can be measured in individual patients

=> towards personalized prediction of treatment outcomes.
Evolutionary Dynamics of Drug Resistance

Evolution of ibrutinib resistance in chronic lymphocytic leukemia (CLL)

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\textsuperscript{a}Department of Mathematics and \textsuperscript{b}Department of Ecology and Evolutionary Biology, University of California, Irvine, CA 92697; and \textsuperscript{c}Department of Leukemia, MD Anderson Cancer Center, Houston, TX 77230
Resistance mechanisms

Figure 1. B Cell Receptor Signaling in Malignant B Cells
Chronic active BCR signaling is shown. Ibrutinib is shown to inhibit BTK. Red asterisks denote signaling effectors that are the target of ibrutinib resistance mutations in CLL patients.
Question

• Can we plug in the measured parameters in order to predict the time until resistant mutants contribute to disease relapse?

• I.e. can we predict how long ibrutinib monotherapy can maintain control of the disease?
Mathematical model – stochastic birth death process

cancer cell
Mathematical model
Mathematical model

Probability $L$

Probability $D$

death
Mathematical model

Probability $D$

Probability $L$

Probability $u$

resistant cell

death
Mathematical model – growth phase

L > D,

i.e. division rate > death rate

-> Clonal Expansion
Mathematical model – treatment phase

\[ L < D, \]

i.e. division rate < death rate

\[ \rightarrow \text{Exponential Decline} \]
Principles of model

(ii) with resistance

pre-treatment
treatment

$N$

time
Virtual patients

Parameter estimates have been obtained from only a limited number of patients

A population of 1000 artificial “patients” is simulated with parameters randomly drawn from the experimentally available bounds
First result: Resistant mutants are almost certainly present before the start of therapy.

Number of CLL cells in tissue is $10^{12}$-$10^{13}$

Mutation rate is $10^{-9}$-$10^{-8}$

Drug resistant cells are almost certain to exist before detection.
Heterogeneity of patient populations

• Although resistance is predicted to be present with certainty, its dynamics are very different for different patients

• The only variables are CLL growth rates and population size at detection
## Predictions

**Standard Ibrutinib therapy**

<table>
<thead>
<tr>
<th>Timing</th>
<th>% patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance before 2 years</td>
<td>6%</td>
</tr>
<tr>
<td>Resistance before 5 years</td>
<td>46%</td>
</tr>
<tr>
<td>Resistance before 10 years</td>
<td>75%</td>
</tr>
<tr>
<td>No resistance after 30 years</td>
<td>5%</td>
</tr>
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</table>
Personalized prediction

measure kinetic parameters in individual patient

predict how long ibrutinib monotherapy can maintain control

Long time, e.g. > 10 years
=> therapy ok

Short time, e.g. 1 year
=> ibrutinib monotherapy is insufficient
=> other approaches needed.
Predictions

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“Debulking” by a factor of 1/100

- 24% less than 5 yrs
- 55% less than 10 yrs
- 14% more than 30 yrs
Conclusions

• CLL is a disease where all kinetic parameters can be measures in individual patients

• Plugging those into evolutionary models allows us to make personalized predictions about treatment outcomes

• We need to test this predictive ability of the model => work under way in larger patient cohorts and in mice.
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Jan Burger

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Danelle James