Chronic Myeloid Leukemia (CML)

- 1-2 cases per 100,000
- Accounts for 15-20% of all leukemias
- Median age of onset >50 years
- Median survival 3-5 years

Chronic Myeloid Leukemia (CML)

The disease has two major phases:

- **Chronic phase < 10% blasts**
  
  These is an intervening phase called the "accelerated phase"

- **Blast crisis > 30% blasts**
  
  occurs within 4-6 years
  inevitably fatal

These develop in the bone marrow
Chronic Myeloid Leukemia (CML)

Standard treatment-
- Classic chemotherapy and IFNα treatment
- Some but not all patients respond
- Almost all eventually relapse
- Only cure is stem cell transplant

CURE RATE < 20%

Chronic Myeloid Leukemia (CML)

1960s -
Nowell and Hungerford observed a consistent chromosomal abnormality in CML patients PHILADELPHIA CHROMOSOME

Shown to be a reciprocal translocation between the long arms of chromosomes 9 and 22, t(9;22)(q34;q11).
Chronic Myeloid Leukemia (CML)

Philadelphia chromosome expresses a fusion protein p210<sup>bcr-abl</sup>
This has N-terminal sequences of c-bcr and C-terminal end of c-abl

95% of CML patients express p210<sup>bcr-abl</sup>

The BCR protein domain locks c-abl into the active conformation
Is \( p210^{bcr-abl} \) responsible for CML? Express \( p210^{bcr-abl} \) in transgenic mouse

Find that the mice develop clinical features of CML by 10-58 days after birth
Identification of Kinase Inhibitors
Novartis

Large library of chemical compounds

Screen for kinase inhibitory activity

Lead compound (a 2-aminopyrimidine) with low potency and poor specificity

Create panel of related compounds

Relate activity to structure

Optimize compounds to inhibit specific targets

Identification of Kinase Inhibitors
Novartis

Isolate STI-571

Optimized against PDGF-R

Shown to have strong inhibitor activity against p210^bcr-abl

STI-571 inhibit proliferation of cells transformed with p210^bcr-abl

Tissue culture cell line

Control retroviral

p210^bcr-abl

Transformant

Grow each of these cell lines in the absence or presence of STI-571
STI-571 does not affect proliferation of control cells

\[ \text{Cell # (log)} \]

\[ \text{Time} \]

- STI-571
- STI-571

STI-571 inhibit proliferation of cells transmformed with p210\(^{bcr-abl}\)

\[ \text{Cell # (log)} \]

\[ \text{Time} \]

- STI-571
- STI-571

STI-571 inhibits proliferation of leukemic cells derived from CML patient

CML patient
Harvest bone marrow
Grow Hematopoietic cells in culture
High levels of Ph\(^+\) myeloid cells
Low levels of Ph\(^+\) myeloid cells

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Test STI-571 in mouse models of CML

- Has activity against p210^{bcr-abl} expressing cells (requires continuous dosing)
- Drug is relatively stable (half life 13-16hrs)
- Toxicity is acceptable

STI-571, Phase I clinical trial

CML stages-
- Chronic or stable
- "Accelerated phase"
- Blast crisis

Treated patients in chronic phase who had failed standard therapies

53/54 patients responded within 3 weeks of treatment
ST1-571, Phase I clinical trial

Saw a major reduction in level of proliferating Ph+ cells

Response is sustained

EXPAND ST1-571 treatment to all stages of CML

- Chronic (CP)
- Accelerated (AP)
- Blast crisis (BC)

Good response - especially in early stages

Childhood leukemia

75-80% ALL
20% AML
2% CML

1962 - Only 5% of children were long term survivors
Now - Very successful treatment for ALL
(3-drug chemotherapy)
Cure rate is 75%
5% of childhood ALL patients are Ph⁺. These respond poorly to classic therapies. 15-30% of adult ALL are Ph⁺. These respond poorly to classic therapies.

The breakpoint in ALL differs slightly from CML. The fusion protein - p185BCR-ABL. Find that ALL patients also have a good initial response to STI-571.

May 2001: BCR/ABL-tyrosine kinase inhibitor ST571 (Gleevec) approved by FDA.
But - patients who initially respond to Gleevec/imatinib can relapse

Chronic Phase - 16% relapse @ 42 months

The odds are worse for blast crisis and ALL patients

EXPAND STI-571 treatment to all stages of CML

• Chronic (CP)
• Accelerated (AP)
• Blast crisis (BC)

Current treatment strategy for CML and Ph+ ALL patients
What is mechanism of relapse?

Is p210\textsuperscript{bcr- abl} still inhibited?

NO

• Drug efflux
• Drug metabolism
• Protein binding
• Increased expression p210\textsuperscript{bcr- abl}
• Mutations in p210\textsuperscript{bcr- abl}

YES

• Mutations in other genes

60-90% of relapse cases

10-30% of relapse cases

Mutated residues fall in 4 regions

- A-loop (aa 381 to 402) regulates kinase activity
- Imatinib locks it in the inactive conformation

- P-loop (aa 244 to 255) accommodates the ATP.
- Imatinib displaces the P-loop
Pluripotent Stem Cell
Myeloid Progenitor
Lymphoid Progenitor
Megakaryocyte/erythrocyte Progenitor
Granulocyte/macrophage Progenitor
Megakaryocyte
Platelets
Erythrocytes
Erythroblasts
Monocytes
Immature dendritic cell
T cell
Adaptive immunity
Innate immunity

These develop in the bone marrow

Fig. 3. Effect of BMS-354825 in a mouse model of imatinib-resistant BCR-ABL-dependent hematological disease. A) In vivo assay of growth inhibition of imatinib-resistant mutant BCR-ABL-expressing Baf3 cells. E2A-mice were treated with a 50:50 mixture of propranolol (5 mg/kg) and vehicle (1 ml/kg) or BMS-354825, beginning 2 days after engraftment of the Baf3 cells. Images were acquired after sacrifice on day 15. Increase activity and primarily detected in the spleen.
GASTROINTESTINAL STROMAL TUMOR (GIST)

- Highly resistant to classic therapies
- Results from activating mutations in the c-kit tyrosine kinase

STI-571 also inhibits c-kit
- Shows strong preference for mutant forms
- In phase I clinical trials, 60% of GIST patients responded to STI-571

GASTROINTESTINAL STROMAL TUMOR (GIST)

LUNG CANCER

- Leading cause of cancer deaths in the US and worldwide for both men and women
- Non-small cell lung carcinoma (NSCLC) accounts for approximately 85% of lung cancer cases
- Classic chemotherapy is marginally effective for NSCLC
LUNG CANCER

- The EGFR tyrosine kinase inhibitor, gefitinib (Iressa), was developed for the treatment of NSCLC because EGFR is often over-expressed in lung tumors.

- The clinical response of variable -
  - Japan - 27.5%
  - European-derived population - 10.4%,

- In US, partial clinical responses to gefitinib are most frequently seen in women, in nonsmokers, and in patients with adenocarcinomas of the lung

- EGFR expression (detected by immunohistochemistry) is not a good predictor of response to gefitinib.
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EGFR expression (detected by immunohistochemistry) is not a good predictor of response to gefitinib.
Inhibit function
• Cause receptor internalization
• Attract an immunological response
• Active killing of tumor cells (by attaching a poison to the Ab)

POSSIBLE CONSEQUENCES-

SUCCESSFUL EXAMPLES-
1) HERCEPTIN (originally Trastuzumab) - GENENTECH
   FDA APPROVED IN 1998
   • Targets HER2 (human epidermal growth factor 2)
   • Her2 is amplified in 25-30% of women with metastatic breast cancer
   • HER2 status correlates with more aggressive tumors, greater probability of recurrence and poorer prognosis (life expectancy is half than of women with HER2- tumors)
   • Herceptin used in treatment of breast cancer in combination with chemotherapy
   • It blocks her2 signaling

3) AVASTIN (originally bevacizumab) - GENETECH
   FDA APPROVED IN 2004
   • Targets VEGF and prevents it from binding to VEGF-R
   • Approved for treatment of metastatic cancer of colon and rectum in combination with 5-Fluorouracil

Can also antibodies to target secreted antigens-