Imatinib as a paradigm of targeted cancer therapies

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Historical perspective on CML

1845

First description of CML

1985

BCR-ABL

Specific therapy for CML

2001

Clinical description of CML
Chronic myeloid leukemia (CML)

- 15 - 20% of all leukemias
- 1 - 2 cases per 100,000 per year

Average age of onset - 50 - 60 yrs of age

CML

- Tri-phasic illness
  - Chronic or stable phase
  - Accelerated phase
  - Blast crisis

95% at presentation

Advanced disease
Stable phase of CML

- Median duration 4 - 6 years
- Massive expansion of myeloid cells
- Maturation of myeloid cells is normal

Advanced stages of CML

- A malignant clone loses the capacity for terminal differentiation resulting in disease progression to an acute leukemia
- Highly refractory to therapy

Molecular pathogenesis of CML

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Molecular pathogenesis of CML

- Fusion gene/protein generated from t(9;22)
- Detected in 95% of patients with CML
- Causative molecular abnormality of CML
- Constitutively activated intracellular tyrosine kinase
  - Kinase activity is required for function
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BCR-ABL as a therapeutic target

Imatinib
Gleevec™, Glivec®
STI571 (CGP 57148B)

Summary of preclinical data

- Imatinib is a potent and selective inhibitor of the ABL, PDGFR and KIT tyrosine kinases
- Imatinib selectively kills BCR-ABL-expressing cells in vitro and in vivo
- Highly bioavailable as an oral formulation

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Phase I clinical trials of Imatinib

- 300 mg per day and above
- Significant therapeutic benefits
- Minimal side effects
- Chronic phase - interferon failures
  - CHR - 98%, 96% durable
- Blast crisis
  - 59% response rate, 18% durable


500 mg Imatinib

Phase II studies

- Chronic phase patients
- Failed interferon therapy
- Accelerated phase
- Blast crisis

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Summary of phase II data

Relapse rate (4 years)

- Chronic (IFN failure) 26%
- Accelerated 73%
- Blast 95%

Phase III randomized study of Interferon + Ara-C vs. Imatinib in newly diagnosed patients with CML

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Enrollment
- 177 centers in 16 countries
- 1106 patients enrolled
  - June 2000 to January 2001
- 553 patients randomized to each treatment:
  - Imatinib 400 mg per day
  - Interferon plus Ara-C

Summary of 18 month data

Progression-free survival
- 95% CI
  - 91-96
- 81-88
- Progression events:
  - 1% AP/BC
  - 4.5% loss of MCyR
  - 2.4% loss of CHR
  - 1.4% CML-unrelated deaths

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Summary of CML clinical trials

- Imatinib yields high response rates with minimal toxicity in all phases of CML
- Durable responses are achieved in chronic phase patients
- Resistance in advanced phase patients is common

Why do some patients relapse?

Is BCR-ABL kinase inhibited?

- No
  - Drug efflux
  - BCR-ABL amplification
  - Kinase mutations
  - Drug metabolism
  - Others

- Yes
  - Additional mutations

BCR-ABL substrates

Tyrosine phosphorylated proteins in CML patient samples

- BCR-ABL
- CRKL
- p62DOK
- STAT5
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CRKL

- Most heavily tyrosine phosphorylated protein in CML cells
- Direct substrate of BCR-ABL
- Required for BCR-ABL transformation

Reactivation of BCR-ABL kinase at relapse

Why do some patients relapse?

Is BCR-ABL kinase inhibited?

No

- BCR-ABL amplification
- Kinase mutations
- Drug efflux
- Drug metabolism
- Others
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ABL kinase domain mutations

Inhibition of cell proliferation by Imatinib

Contact sites of ABL and Imatinib

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P-loop mutants

Structure of the ABL kinase domain

Imatinib vs. AMN107

Weisberg, E. et al. (2005) Cancer Cell 7, 129-141

Nagar et al. Cancer Research, 2002

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Inhibition of cell proliferation by AMN107

SRC/ABL inhibitors for Imatinib-resistance

- SRC inhibitors were shown to inhibit ABL
  - (JF Dorsey et al., Cancer Res, 60:3127, 2000)
- Bind to the active form of ABL
- 10-100 fold more potent than Imatinib against ABL
- Inhibit more kinases than imatinib

Inhibition of cell proliferation by a SRC/ABL inhibitor
Clinical trials of novel ABL inhibitors

- AMN107 and BMS-354825 (dasatinib, dual SRC/ABL inhibitor)
- Significant activity in Imatinib-resistant patients
- Activity observed against all Imatinib-resistant mutants except T315I
- Relapses common in advanced phase
  - T315I
  - Other causes

Imatinib and Gastrointestinal Stromal Tumor (GIST)

Gastrointestinal Stromal Tumor

- GIST: intestinal sarcoma (formerly intestinal leiomyosarcoma) – KIT positive
- US annual incidence: ~5,000 cases
- Response rates to chemotherapy <5%
- Activating KIT mutations are present in the majority of patients
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Imatinib response data - GIST

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>n=147</td>
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<tr>
<td>Partial response</td>
<td>54%</td>
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<tr>
<td>Stable disease</td>
<td>28%</td>
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<tr>
<td>Progression</td>
<td>14%</td>
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PET scan - GIST

![PET scan images](image)

Pre - 12/7/00
1/9/01

G. Demetri, et al

Extending the Imatinib paradigm

Target expression versus response

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Expression versus response

<table>
<thead>
<tr>
<th>Target Frequency</th>
<th>Target Response Rate</th>
<th>Observed Response Rate</th>
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<tbody>
<tr>
<td>100 patients</td>
<td>100%</td>
<td>60%</td>
</tr>
<tr>
<td>100 patients</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>100 patients</td>
<td>25%</td>
<td>60%</td>
</tr>
<tr>
<td>100 patients</td>
<td>10%</td>
<td>60%</td>
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Imatinib responses in advanced malignancies

<table>
<thead>
<tr>
<th>Disease</th>
<th>Target Expression</th>
<th>Partial Response Rate</th>
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<tbody>
<tr>
<td>CML blast crisis</td>
<td>BCR-ABL+ 100%</td>
<td>50-60%</td>
</tr>
<tr>
<td>GIST</td>
<td>KIT + &gt;90%</td>
<td>50-60%</td>
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Expression of a molecular target correlates with response to an agent directed against that target.
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Is expression sufficient to predict response?

<table>
<thead>
<tr>
<th>Target Expression</th>
<th>Target Activation</th>
<th>Target Response Rate</th>
<th>Observed Response Rate</th>
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<td>90%</td>
<td>80%</td>
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<td>100 patients</td>
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<td>10%</td>
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</tbody>
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Response to Imatinib in GIST patients

M. Heinrich, J. Fletcher, et al

P<0.0001
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Gefitinib and Erlotinib

- Target EGF receptor
- Broadly expressed in cancer
- 10-20% response rate in advanced non-small lung cancer
  - No correlation with EGFR expression
  - Female, non-smokers, bronchoalveolar histology
- Responding patients have EGFR mutations
  - More sensitive to inhibitors than wild-type receptor

Expression of a molecular target does not guarantee a response to an agent that modulates the target

What does it mean if the response rate to a molecularly targeted agent is low?

- Is the target expressed?
- Is the target modulated by the agent?
- Is the target critical to the growth or survival of the tumor?
- Is there a subset of patients who respond well?
Response to Imatinib in GIST patients

M. Heinrich, J. Fletcher, et al

PDGFR activating mutations in GIST

- 6/16 (37.5%) wild-type KIT patients had PDGFRα activating mutations in two different exons
- One set of mutations was imatinib sensitive
  - 2/3 patients had PRs
- Careful study of subsets of patients may reveal important insights


Lessons learned from clinical trials with Imatinib

IT’S THE TARGET!

Good Target + Good Drug

= Good Results
What makes BCR-ABL such an ideal target?

- Causative molecular abnormality of CML
- Sole oncogenic event early in the disease
- Ease of selection of patients for clinical studies based on the presence of the target
  - Ph chromosome – BCR-ABL

Why is KIT an ideal target in GIST?

- KIT mutations are seen in early, incidental tumors
- KIT mutations are acquired before cytogenetic abnormalities
- Familial syndromes of GIST have germline KIT mutations

Lessons learned from clinical trials with Imatinib

Old News

Treatment earlier in the course of a disease yields better responses
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Responses by phase of disease

- Chronic phase (new dx'd)
- Chronic phase (IFN failure)
- Accelerated Phase
- Blast crisis

Translating the success of Imatinib to other malignancies

- Identify the appropriate therapeutic targets
  - Early molecular pathogenetic events
- Treat early in the course of the disease
  - Develop reliable techniques for early detection
- Match the right patient with the right drug

The 21st century

- Identification of the molecular pathogenetic events in all cancers
- Development of improved diagnostic/imaging techniques
- Improved methods of drug discovery
- Understanding of an individual’s cancer risk based on genetic analyses
Acknowledgements

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