Monitoring residual tumor burden

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FHCRC
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Treating cancer
the problem of disease detection

Cell #

relapse
remission

"Cure"

time

10^{12}

10^9
Cytogenetic Abnormality of CML
The Philadelphia Chromosome
The Ph Chromosome and *Bcr-Abl*.

**t(9;22) translocation**

*bcr-abl* gene structure
Natural history of CML

**Chronic phase**
- Ph+
- Median duration: 3-5 years

**Accelerated phase**
- Cytogenetic changes
- Increasing blasts
- Median duration: 6–9 months

**Blast crisis**
- Median survival: 3–6 months
Survival by Phase of CML

<table>
<thead>
<tr>
<th>CML Phase</th>
<th>Total</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic</td>
<td>2449</td>
<td>1043</td>
</tr>
<tr>
<td>Accelerated</td>
<td>479</td>
<td>276</td>
</tr>
<tr>
<td>Blastic</td>
<td>285</td>
<td>219</td>
</tr>
</tbody>
</table>

5 mo 28 mo 71 mo

Survival graph showing cumulative proportion surviving over years from referral.
CML all matched related transplants, 9/95 to 7/01

The influence of phase at transplant on SURVIVAL
"Nested" RT-PCR for *bcr-abl*

1st step BCR-ABL

2nd step BCR-ABL

---

1 2 3 4 5 B K5 BM

b3a2-
b2a2-

BCR ABL

b1 b2 b3 a2 a3

BCR-ABL
Prevalence and significance of \textit{bcr-abl} + post-BMT (N=346)

• \approx 25\% of pts. \textit{bcr-abl} +

• \textit{bcr-abl} + 6-12 m post-BMT associated with a high risk of relapse (RR = 20-30)

• \textit{bcr-abl} + > 12 m post-BMT may have less risk of relapse

Blood 85:2632, 1995
“Real time” quantitative RT-PCR

I. Hydrolysis Probes
Release from quenching by hydrolysis

II. Hybridization Probes
Increased resonance energy transfer by hybridization

TaqMan™

LightCycler™
Median *bcr-abl* in relapsed patients = 40,000 copies/ug RNA
Median in *bcr-abl* + patients without relapse = < 100 copies/ug RNA
Risk of relapse associated with achieving a specific quantitative PCR level

Hazard ratio associated with attaining a maximum PCR value within a specific interval

<table>
<thead>
<tr>
<th>Copy number</th>
<th>3-6 mo.</th>
<th>6-12 mo.</th>
<th>12-18 mo.</th>
<th>&gt;18 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>1.0</td>
<td>2.5</td>
<td>----</td>
<td>3.2</td>
</tr>
<tr>
<td>&gt;1 to 100</td>
<td>0.7</td>
<td>3.6</td>
<td>1.9</td>
<td>3.4</td>
</tr>
<tr>
<td>&gt;100</td>
<td>1.9</td>
<td>5.1</td>
<td>3.2</td>
<td>3.9</td>
</tr>
</tbody>
</table>

* Indicates statistical significance

Hazard ratio associated with attaining a maximum PCR value within a specific interval:

- Negative: 1.0, 1.0, 1.0, 1.0
- 1: 1.0, 2.5, ----, 3.2
- >1 to 100: 0.7, 3.6, 1.9, 3.4
- >100: 1.9, 5.1, 3.2, 3.9

* Indicates statistical significance

Graph showing the probability of clinical relapse over days after max PCR 6-12 months.
Mechanism of Action of Imatinib Mesylate
(a.k.a., SI571, Gleevec, Glivec)

# Summary of Phase II results

<table>
<thead>
<tr>
<th>% of Patients (CI&lt;sub&gt;95%&lt;/sub&gt;)</th>
<th>Study 0110 Chronic Phase IFN-α Failure (n=532)</th>
<th>Study 0109 Accelerated Phase (n=235)</th>
<th>Study 0102 Blast Crisis (n=260)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>88% (84.9–90.6)</td>
<td>63% (56.5–69.2)</td>
<td>26% (20.9–31.9)</td>
</tr>
<tr>
<td>No evidence of leukemia</td>
<td>–</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>Return to chronic phase (RTC)</td>
<td>–</td>
<td>24%</td>
<td>19%</td>
</tr>
<tr>
<td><strong>Major cytogenetic response (MCR)</strong></td>
<td>49% (45.1–53.8)</td>
<td>21% (16.2–27.1)</td>
<td>13.5% (9.6–18.2)</td>
</tr>
<tr>
<td>Complete</td>
<td>30%</td>
<td>14%</td>
<td>5%</td>
</tr>
<tr>
<td>Partial</td>
<td>19%</td>
<td>7%</td>
<td>8.5%</td>
</tr>
</tbody>
</table>
International Randomized trial of Interferon/Ara-C versus STI571 (IRIS)

1106 CML-cp patients enrolled from June 2000 to January 2001

Imatinib Mesylate

IF:
- Loss of MCR or CHR
- Increasing WBC count
- Intolerance of treatment
- Failure to achieve MCR at 12 m*
- Failure to achieve CHR at 12 m*
- Request to discontinue IFN-α*

39%
Crossover

IFNα + ara-C

1%

Progression
- Increasing WBC count
- Loss of MCR or CHR
- Accelerated phase or blast crisis
- Death

S = screening.
R = randomization.

*Independent Data Monitoring Board Recommended Protocol Amendments
# Cytogenetic responses
## Imatinib v. IFN/Ara-C

<table>
<thead>
<tr>
<th>Cytogenetic Response</th>
<th>Imatinib Mesylate (n=553)</th>
<th>IFN - + ara-C (n=553)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major (35% Ph+, MCR)</strong>*</td>
<td>457 (83%)</td>
<td>112 (20%)</td>
</tr>
<tr>
<td>Complete (0% Ph+)*</td>
<td>375 (68%)</td>
<td>41 (7%)</td>
</tr>
<tr>
<td>Partial (1%&lt;35% Ph+)</td>
<td>32 (15%)</td>
<td>71 (13%)</td>
</tr>
</tbody>
</table>

*P<0.001.
International Randomized Interferon vs Imatinib Mesylate (IRIS) Study: Time to progression*

*TTP defined as time from start of therapy to accelerated or blastic phase, relapse, or discontinuation of therapy.

Gleevec (imatinib mesylate) PI.

HR [95% CI]: 0.334 [0.24, 0.45]
Progression-free Survival and Survival Without AP/BC on First-line Imatinib

Progression events:
- 6.1% AP/BC
- 4.5% loss of MCyR
- 2.4% loss of CHR
- 1.4% CML-unrelated deaths

PFS
Survival without AP/BC

94% (95% CI: 91-96)
84% (95% CI: 81-88)

94%
84%

% without progression

0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51

Months since randomization

95% CI
(91-96)
(81-88)
Time to Progression on First-line Imatinib by MCyR within 12 months

Estimated rate (95% CI) at 42 months:
- MCyR: n=436, 91% (88-94)
- No MCyR: n=66, 66% (53-78)

p<0.001
Molecular response of Bcr-Abl
IRIS trial for CCyR

Log reduction

Months since CCyR

Imatinib
IFN+Ara-C

CCyR 3 6 9 12 15 18 21 24
IRIS molecular response

Log reduction of BCR-ABL

Standardised Baseline

Major molecular response

Months from the start of Imatinib

Pre 6 12 18 24 30 36 42
IRIS trial: Overall estimated log reduction of BCR-ABL after IM treatment

Months since start of treatment

- 3 months: 75% No CCyR
- 6 months: 50% No CCyR
- 12 months: 32% No CCyR
- 18 months: 26% No CCyR
- 24 months: 24% No CCyR

% of all patients

- 4 log
- 3-<4 log
- 2-<3 log
- <2 log
- No CCyR
Progression-free Survival on First-line Imatinib by Molecular Response at 12 months

Estimated rate (95% CI) at 42 months:

- No CCyR: n=138, 75% (67-84)
- <3 log reduction: n=94, 90% (84-97)
- >=3 log reduction: n=136, 98% (96-100)

p<0.001
‘SPIRIT’
STI571 (Imatinib) Prospective International Randomized Trial

- Imatinib 400 mg/d
- Imatinib 800 mg/d
- Imatinib + IFN
- Imatinib + Ara-C

Survival

CML-cp within 6 m of dx

SWOG: depth of MRD burden (log reduction in bcr-abl at 12 months) as a surrogate outcome variable
Intergroup CML trial

- Chronic phase CML
- IM 400 v. 800 v. dasatinib
- Endpoint-4 log bcr-abl reduction at 12 m
  - N=~100 each arm
  - First trial to use molecular endpoint
Track Individual Response

Log reduction of BCR-ABL

Base line

Imatinib ceased

Months from the start of Imatinib

Pre 3 6 9 12 15 18
Track Individual Response

Log reduction of BCR-ABL

Base line

Pre 3 6 9 12 15 18

Months from the start of Imatinib

Imatinib ceased

Restarted
Track Individual Response

Standardised baseline

BCR-ABL/BCR%

Log Reduction

Months from the start of Imatinib

E453G

2.1-fold rise

Pre 3 6 9 12 15 18 21 24 27 30 33 36 39

Standardised baseline

.0008

.08

80
Track Individual Response

![Graph showing the track of BCR-ABL/BCR% over time. The graph includes data points at various months from the start of Imatinib treatment. There is a significant log reduction in BCR-ABL/BCR% indicated by a drop in the line from 800mg Imatinib dose. The graph also highlights E453G mutation and shows a standardised baseline.](image-url)
MRD detection in ALL predicts relapse after chemo or BMT

- **Chemotherapy**-MRD after induction or consolidation predicts relapse.
  - RR of relapse ~ 5-15

- **Transplantation**-MRD pre- or post-BMT predicts relapse and outcome.
  - MRD pre-BMT has worse outcome
  - MRD post-BMT -> RR relapse 5-10
MDR in Pediatric ALL

TABLE 3. Relative Risk of Relapse According to the Presence or Absence of Residual Disease at Two Time Points.

<table>
<thead>
<tr>
<th>Residual Disease*</th>
<th>After Induction Therapy, After Consolidation Therapy</th>
<th>After Induction Therapy, After Interval Therapy</th>
<th>After Consolidation Therapy, After Interval Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>No. with Relapses</td>
<td>Relative Risk†</td>
</tr>
<tr>
<td>Absent, absent</td>
<td>73</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>Present, absent</td>
<td>15</td>
<td>3</td>
<td>4.9</td>
</tr>
<tr>
<td>Present, present</td>
<td>32</td>
<td>15</td>
<td>15.0</td>
</tr>
</tbody>
</table>

Graphs showing survival rates with different levels of residual disease.
MRD in t(15;17) AML (APL)

- MRD detection of PML/RARA is strongly associated with relapse (Diverio, Blood, 1998).
- 163 APL patients studied after consolidation.
  - All in molecular remission after consolidation
  - 21 converted to PML/RARA +; 20/21 relapsed
  - 8/142 PML/RARA - patients relapsed
MRD in t(15;17) AML (APL)

~ N=163 patients who were PCR- after consolidation, > 6 months f/u post-consolidation, and > 2 PCR assays

~ 21 pts. became PCR+; 20/21 relapsed
~ 8/142 PCR- pts. relapsed (RR=32)
MRD in t(8;21) AML

• MRD variably associated with relapse.
  – Most (all?) survivors are AML1/ETO +!
    • “Dormancy”
  – AML1/ETO found in erythroid, lymphoid cells
    • Is this a stem cell disease?
  – Quantitative RT-PCR helps in picking patients at highest risk of relapse.
MRD in t(8;21) AML
Targets for monitoring

- Chronic myeloid leukemia
  - BCR/ABL by RT-PCR

- Acute myeloid leukemia
  - PML/RAR
  - AML/ETO
  - MYH11/CBFFB
  - FLT3

- Acute lymphoblastic leukemia
  - BCR/ABL
  - IgH VDJ or TCR rearrangements

- Non-Hodgkins lymphoma
  - IgH-Bcl2
The Natural History of most things

Diagram showing the peaks of excitement followed by disappointment, followed by reality.
Good night and thanks from...

Radich lab (FHCRC)
Rosetta Inpharmatics
Cheryl Willman (SWOG)
Brian Druker (OHSU)
Wendy Stock (U Chicago)
Charles Sawyers (UCLA)