Management of Advanced Phase Chronic Myelogenous Leukemia

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Seattle Cancer Care Alliance
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

Med. Survival 71 m 28 months 5 months

Survival by phase of CML

20 years B.I. (Before imatinib)

CML Phase | Total | Dead
---|---|---
Chronic | 2449 | 1043
Accelerated | 479 | 276
Blastic | 285 | 219

Cumulative proportion surviving

Years from referral

5 mo 28 mo 71 mo
Survival in Early CP-CML

The University of Texas MD Anderson Cancer Center Database.

1.0
0.8
0.6
0.4
0.2
0
0 3 6 9 12 15 18 21 24 27
Proportion Alive

Year Total Dead
Imatinib 302 15
(302 censored non-CML deaths)
Imatinib 302 31
1990-2000 963 425
1982-1989 364 273
1975-1981 132 129
1965-1974 123 123

Start of the TKI era
Interferon
Busulfan, Hydroxyurea

The University of Texas MD Anderson Cancer Center Database.

Therapy of CML in 2016

• Frontline
  – Imatinib 400 mg daily
  – Nilotinib 300 mg twice daily
  – Dasatinib 100 mg daily

• Second/third line
  – Nilotinib, dasatinib, bosutinib, ponatinib
  – Omacetaxine
  – Allogeneic SCT

• Other
  – Decitabine, interferon
  – Hydroxyurea, cytarabine, combos of TKIs
  – Investigational agents, clinical trials
**Definition of AP and BC**

- **AP\(^1\)**
  - 15 – 29% blasts in blood or marrow (WHO 10 – 19%)
  - More than 20% basophils in blood
  - Persistent thrombocytopenia unrelated to therapy
  - Unresponsiveness to therapy

- **BC\(^2\)**
  - More than 30% blasts in blood or marrow (WHO 20%)
  - Extramedullary blastic infiltrates
  - Varying degrees of fever, anemia, splenomegaly, leukocytosis

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**Additional cytogenetic aberrations (ACA) in advanced phase (AP and BC) CML**

- **“Major route” aberrations**
  - +8 (30%)
  - +\text{der}(22)t(9;22) (30%)
  - +19 (10%)
  - i(17)(q10) (20%)

- **“Minor route” aberrations**
  - Gains of chromosomes 17 and 21
  - Losses of chromosomes Y, 7, 17
  - t(3;21)(q26;q22)
Impact of major route aberrations at diagnosis on progression and survival

- Progression to blast crisis is still a phenomenon that is only incompletely understood.
- In up to 80% of BC patients, additional chromosomal aberrations are reported.
- In up to 77% mutations are detected.
- In gene expression profiles blast crisis appears as a disease distinct from CML.
- Treatment continues to be mostly unsuccessful unless allo SCT is offered.
WHO vs. traditional classification: Does blast count at diagnosis make a difference in outcome?

Criteria set #1 (True blast phase):
- >30% blasts + promyelocytes in PB

Criteria set #2:
- Fever, increased splenomegaly, anemia, and WBC ≤30% blasts + promyelocytes


A simple model of CML progression/resistance

Some mutations die → Many possible mutations affect a small number of critical pathways

If treatment starts too late, cells with critical changes already present

If treatment starts early, potential "cure" without TKI?

Resistance and/or progression
Prevention of blast crisis
Cumulative Incidences 1983 – 2013

German CML Study group, unpublished

Progression on IRIS trial declines over time

Incidence of blast crisis under TKI (CML study IV)

German CML Study Group, unpublished

Lead time bias and progression

Already passed “the point of no return”
Progression during Rx!

Disease starts

Natural history

Blast crisis

Rx starts

Time
Survival Based on 3 Months of Molecular Response

Survival After Imatinib Therapy by Molecular Response Achieved at 3 Months

- BCR-ABL/ABL <9.8% OS = 93.3%
- BCR-ABL/ABL >9.8% OS = 57%

Survival Based on 3 Months of Molecular Response

Cumulative Incidence of MMR According to BCR-ABL level at 3 Months

- Dasatinib 100 mg QD
- Imatinib 400 mg QD

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EMR according to Sokal score


Molecular response in patients who progressed on imatinib arm of ENEStnd

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EMR Failure: What is at stake?

- Risk of transformation >10%
- Risk of death >10%
- Risk of failing to achieve MR4.5 >90%

Pathways to progression

Skorski et al. Leuk Lymphoma. 2011 Feb;52 Suppl 1:23-29
Molecular findings in progression

- Mutations / deletions,
  - p53 in ~24% of myeloid BC
  - p16 in ~50% of lymphoid BC
  - RUNX-1, IKZF1 (Ikaros), ASXL1, WT1, TET1, IDH1, NRAS, KRAS, CBL, in ~77% of all BC

- Alteration of gene expression (progression genes)


Cytologic, cytogenetic and molecular findings in blast crisis (n = 39)

Mutations in 77% by deep-sequencing

Grossmann et al., Leukemia 2011; 25: 557 – 560
Two lessons from gene expression arrays

1. AP is similar to BC
   *Thus, progression more like a two-step process*

2. BC is pretty similar to normal CD34+ cells
Conceptual models of CML progression

```
Instability ↑
Proliferation Bcr-Abl
Point mutations
Chromosomal Δs
↓Differentiation
↑Cell cycle
↓Apoptosis
```

"Targetable" pathways in CML progression

<table>
<thead>
<tr>
<th>Keyword</th>
<th>Number (%)</th>
<th>Examples</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribosome</td>
<td>18 (21)</td>
<td>ROK13A*</td>
<td>9 x 10^{-11}</td>
</tr>
<tr>
<td>Wnt signaling</td>
<td>16 (11)</td>
<td>Cadherin, MD11, Prickle 1, FZD2</td>
<td>2 x 10^{-4}</td>
</tr>
<tr>
<td>Nucleosome</td>
<td>22 (22)</td>
<td>BSZ1A, HIST1H2AE*</td>
<td>3 x 10^{-11}</td>
</tr>
<tr>
<td>Sugar metabolism</td>
<td>45 (26)</td>
<td>RPTA, ALDOC, G6PD</td>
<td>4 x 10^{-9}</td>
</tr>
<tr>
<td>Myeloid differentiation</td>
<td>27 (14)</td>
<td>CEBPA, CEBPE, FOXO3A</td>
<td>3 x 10^{-8}</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>42 (10)</td>
<td>GADD45G, BCL2, FOXO3A</td>
<td>2 x 10^{-7}</td>
</tr>
<tr>
<td>DNA damage response</td>
<td>36 (10)</td>
<td>GADD45G, FANCG, XRNR2</td>
<td>2 x 10^{-7}</td>
</tr>
</tbody>
</table>

New drugs and trials of advanced phase CML

1. Wnt/SHH: B-catenin co-factor inhibitors (CBP, p300), SMO inhibitors
2. Differentiation: PRAME
3. Apoptosis: histone deacetylase inhibitors
4. Proliferation: PP2A inhibitors (SET overexpression)
Accumulation of mutations over time
Imatinib resistance within 3 years

- Primary resistance
- Relapse / progression

Percent

Early chronic phase: 4
Late chronic phase: 7
Accelerated phase (600 mg/d): 20
Blastic phase (600 mg/d): 93


IM resistant cases look like advanced phase

PNAS 2006;103(8):2794–2799.
CML progression and IM resistance are similar

CP AP BC 2899 1238 1587 CP (unRx) v. IMR CP

DIFF IMR

IM R

blast crisis

6 genes predict advanced phase and outcome?

Training Set- 72 samples: average over 100 CV runs
Test Set – 21 samples

At probability score cut-off of 0.3:
(< 0.3) 1/6 died
(> or = 0.3) 7/11 died (OR = 9)

Samples from:
- Early = RIGHT trial
- Late = AMN trial
- 2 early cases misclassified: both relapsed
- 5 late cases misclassified: 3 relapsed, two responded

Oehler, Blood 2009
Super 6 predicts outcome in CP transplants

![Graph showing predicted probability of relapse over years after transplant.](Image)

Oehler, Blood 2009

Mouse model of CML: Induction of BCR-ABL and “Sleeping Beauty” recapitulates human CML BC

![Diagram illustrating the induction of BCR-ABL and the CML BC process.](Image)

Giotopoulos et al, JEM 2015
A murine model that mimics human progression

Gene expression CP->BC

Pathways CP->BC

Giotopoulos et al, JEM 2015

Newly diagnosed AP do *surprisingly* well on TKIs

Roa et al Leukemia, 2012

N= 42 new AP cases

16 heme AP (15-30% blasts)

16 new cyto (AC)

10 both
Newly diagnosed AP CML do well with TKIs


Treatment of BC in the 80s and 90s

- Acute leukemia type induction therapies
- Various combinations of 5-azacytidine, etoposide, mitoxantrone, carboplatin, ara-C, fludarabine, decitabine etc.
- No benefit, ↑ toxicity
- Return to CP ~9%
- No cures in absence of SCT

Hehlmann, CML and IFN, Springer 1988; Saschi et al., Cancer 1999; 86: 2632 – 2641;
Treatment of BC: resistance is apparently not so futile

<table>
<thead>
<tr>
<th>Response</th>
<th>Med. Surv.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>30-50% 6 m.</td>
</tr>
<tr>
<td>AML like</td>
<td></td>
</tr>
<tr>
<td>ALL like</td>
<td></td>
</tr>
<tr>
<td>Others (Flag-IDA, MEA)</td>
<td></td>
</tr>
<tr>
<td>TKI</td>
<td>40-50% 6 m.</td>
</tr>
<tr>
<td>Imatinib</td>
<td></td>
</tr>
<tr>
<td>Second generation (Dasatinib)</td>
<td></td>
</tr>
<tr>
<td>Chemo and TKI</td>
<td>~50% 6 m.</td>
</tr>
<tr>
<td>IM, Ara-c, IDA</td>
<td></td>
</tr>
<tr>
<td>IM, MEA</td>
<td></td>
</tr>
</tbody>
</table>

OS After Progression to AP/BC in the ENESTnd and IRIS Trials

Progression during TKI therapy is not good

Median Survival ~10.5 months

Survival of BC on Imatinib (IRIS)

Estimated % alive at:
- 12 months: 43%
- 24 months: 30%

- At 12 months, 57% of patients who progressed on imatinib died (IRIS data on file).

Imatinib in BC
(5 studies, 484 patients, 50 with Lymphoid BC)

- HR: 50% – 70% (70% with LBC)
- CR: 12% – 17% (all responses)
- Survival at 1 year: 22% – 36%
- Median survival: 6.5 – 10 months

Druker et al., NEJM 2001; Sawyers et al., Blood 2002; Kantarjian et al., Blood 2002; Sureda et al., Haematologica 2003; Palandri et al., Haematologica 2008.
How can you treat AP? **Nilotinib** in AP-CML

<table>
<thead>
<tr>
<th>Response</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic response</td>
<td>38 (59)</td>
</tr>
<tr>
<td>CHR</td>
<td>15 (23)</td>
</tr>
<tr>
<td>NEL</td>
<td>8 (13)</td>
</tr>
<tr>
<td>RTC</td>
<td>15 (23)</td>
</tr>
<tr>
<td>Cytogenetic</td>
<td></td>
</tr>
<tr>
<td>Major CG response</td>
<td>23 (36)</td>
</tr>
<tr>
<td>Complete CG response</td>
<td>14 (22)</td>
</tr>
</tbody>
</table>

CHR = complete hematologic response; NEL = no evidence of leukemia; RTC = return to chronic phase.

Kantarjian H et al. ASH 2006. Abstract 2169.

Survival of myeloid and lymphoid BC with **nilotinib** 400 – 600 mg bid

Giles et al., Leukemia 2012
Dasatinib in Advanced Phase CML/Ph+ ALL

<table>
<thead>
<tr>
<th>Phase of CML</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accelerated Phase CML</strong>¹</td>
<td></td>
</tr>
<tr>
<td>Major Hematologic Response (CHR + NEL)</td>
<td>64%</td>
</tr>
<tr>
<td>Major Cytogenetic Response</td>
<td>45%</td>
</tr>
<tr>
<td>Complete Cytogenetic Response</td>
<td>32%</td>
</tr>
<tr>
<td><strong>Myeloid Blast Phase CML</strong>²</td>
<td></td>
</tr>
<tr>
<td>Major Hematologic Response (CHR + NEL)</td>
<td>33%</td>
</tr>
<tr>
<td>Major Cytogenetic Response</td>
<td>33%</td>
</tr>
<tr>
<td>Complete Cytogenetic Response</td>
<td>26%</td>
</tr>
<tr>
<td><strong>Lymphoid Blast Phase CML</strong>²</td>
<td></td>
</tr>
<tr>
<td>Major Hematologic Response (CHR + NEL)</td>
<td>35%</td>
</tr>
<tr>
<td>Major Cytogenetic Response</td>
<td>52%</td>
</tr>
<tr>
<td>Complete Cytogenetic Response</td>
<td>46%</td>
</tr>
<tr>
<td><strong>Ph+ ALL</strong>²</td>
<td></td>
</tr>
<tr>
<td>Major Hematologic Response (CHR + NEL)</td>
<td>41%</td>
</tr>
<tr>
<td>Major Cytogenetic Response</td>
<td>56%</td>
</tr>
<tr>
<td>Complete Cytogenetic Response</td>
<td>54%</td>
</tr>
</tbody>
</table>


Dasatinib in advanced CML and Ph+ ALL progression-free survival

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Dasatinib in BC
(3 studies, 400 patients, 119 with Lymphoid BC)

- HR 33% – 61%
  (LBC 36% – 80%)
- CR (major) 35% – 56%
- Survival at 1 year 40% – 50%
  at 2 years 20% – 30%
- Median survival 8 – 11 months

Talpaz et al., NEJM 2006; Cortes et al., Leukemia 2008; Gambacorti et al., ASH 2007; Saglio et al., Cancer 2010; 116: 3852 – 3861

Survival of myeloid and lymphoid BC with dasatinib 140 mg qd vs. 70 mg bid

A. Myeloid

B. Lymphoid

Saglio et al., Cancer 2010; 116: 3852 – 3861
### Treatment of BC by BCR-ABL TKI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
<th>Patients</th>
<th>CR MBC / LBC</th>
<th>Survival 12 months</th>
<th>Survival Median, months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Imatinib</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 – 600 mg</td>
<td>Druker et al., 2001</td>
<td>58 (20 LBC)</td>
<td>12%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>400 – 600 mg</td>
<td>Sawyers et al., 2002</td>
<td>229 (MBC only)</td>
<td>16%</td>
<td>30%</td>
<td>6.9</td>
</tr>
<tr>
<td>300 – 1000 mg</td>
<td>Kantarjian et al., 2002</td>
<td>75 (10 LBC)</td>
<td>16%</td>
<td>22%</td>
<td>6.5</td>
</tr>
<tr>
<td>600 mg</td>
<td>Sureda et al., 2003</td>
<td>30</td>
<td>13%</td>
<td>36%</td>
<td>10</td>
</tr>
<tr>
<td>600 mg</td>
<td>Palandri et al., 2008</td>
<td>92 (20 LBC)</td>
<td>17%</td>
<td>29%</td>
<td>7</td>
</tr>
<tr>
<td><strong>Dasatinib</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 – 100 mg bid</td>
<td>Talpaz et al., 2006</td>
<td>33 (10 LBC)</td>
<td>52% / 90%</td>
<td>~22% (^4)</td>
<td>~6</td>
</tr>
<tr>
<td>70 – 100 mg bid</td>
<td>Cortes et al., 2008</td>
<td>157 (48 LBC)</td>
<td>35% / 56%  (^5)</td>
<td>49% / 30%</td>
<td>11.8 (5.3)</td>
</tr>
<tr>
<td>70 bid vs. 140 mg qd</td>
<td>Saglio et al., 2010</td>
<td>210 (61 LBC)</td>
<td>25 – 28% / 40 – 50%</td>
<td>34 – 39% / 39 – 46%</td>
<td>8 (10)</td>
</tr>
<tr>
<td><strong>Nilotinib</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>up to 1200 mg</td>
<td>Kantarjian et al., 2006</td>
<td>33 (9 LBC)</td>
<td>18%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>400 – 600 mg bid</td>
<td>Giles et al., 2012</td>
<td>136 (31 LBC)</td>
<td>40%</td>
<td>42%</td>
<td>10</td>
</tr>
</tbody>
</table>

LBC: lymphoid blast crisis; MBC: myeloid blast crisis; HR: hematologic remission, includes complete HR, return to CP and no evidence of leukemia; CR: cytogenetic response, includes complete, partial, minimal and minor response when available; NA: not available; TKI: tyrosine kinase inhibitors

* at 18 months; \(^4\) only complete and major cytogenetic response listed. Updated from Hehlmann and Saußele., Haematologica. 2008; 93 (12): 1765–1769.

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### Survival after blast crisis 1983 – 2013

**Still bad, but better**

![Graph showing survival probability over years after diagnosis of BC](image)

- **CML IV (n = 78, 60 died, median survival: 8 Mo.)**
  - 18 alive, 13 patients transplanted, Imatinib era
- **CML I – IIA (n = 699, 678 died, median survival: 4 Mo.)**
  - 21 alive, 15 transplanted, Pre-imatinib era

n = 777 patients

German CML Study group, unpublished

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Comparison myeloid vs. lymphoid BC

*German CML IV, n= 78*

Survival probability

- Lymphoid BC [median survival: 1.62 (0.01 – 9.8+)]
- Myeloid BC [median survival: 0.74 (0.02 – 9.6+)]

TKI in blast crisis

<table>
<thead>
<tr>
<th>TKI</th>
<th>Studies / Patients</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib¹⁻⁵</td>
<td>5 / 484 pts, 50 with LBC</td>
<td>6.5 – 10 months</td>
</tr>
<tr>
<td>Dasatinib⁶⁻⁸</td>
<td>3 / 400 pts, 119 with LBC</td>
<td>8 – 11 months</td>
</tr>
<tr>
<td>Nilotinib⁹⁻¹⁰</td>
<td>2 / 169 pts, 40 with LBC</td>
<td>10 (LBC 7.9) months</td>
</tr>
</tbody>
</table>

¹ Druker et al., 2001; ² Sawyers et al., 2002; ³ Kantarjian et al., 2002; ⁴ Sureda et al., 2003; ⁵ Palandri et al., 2008;
⁶ Talpaz et al., 2001; ⁷ Cortes et al., 2008; ⁸ Saglio et al., 2010; ⁹ Kantarjian et al., 2006; ¹⁰ Giles et al., 2012.
Investigational approaches

<table>
<thead>
<tr>
<th>Mode of action</th>
<th>Agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP2A activation</td>
<td>Fingolimod (FTY720)</td>
</tr>
<tr>
<td></td>
<td>SET antagonist OP449</td>
</tr>
<tr>
<td></td>
<td>CIP2A inhibitor</td>
</tr>
<tr>
<td>Self renewal of LSC</td>
<td>BCL6 + TK inhibitors</td>
</tr>
<tr>
<td></td>
<td>HIF1α inhibitor</td>
</tr>
<tr>
<td></td>
<td>IL1 RAP antibodies</td>
</tr>
<tr>
<td></td>
<td>Smoothened inhibitors (in combination with TKI)</td>
</tr>
<tr>
<td></td>
<td>Jak2 inhibitor (in combination with TKI)</td>
</tr>
<tr>
<td>Activation of apoptosis</td>
<td>BCL2-inhibitor ABT-737</td>
</tr>
<tr>
<td></td>
<td>Triptolide</td>
</tr>
<tr>
<td></td>
<td>Dual-kinase inhibitor ON044580</td>
</tr>
<tr>
<td></td>
<td>MEK inhibitor PD184352 + farnesyltransferase inhibitor BMS-214662</td>
</tr>
<tr>
<td>Others</td>
<td>Peg-IFN, HDAC inhibitor, Hsp90 inhibitors</td>
</tr>
</tbody>
</table>


The demise of allogeneic HCT in CML

EBMTR

FHCRC, CP and AP/BP

IM phase 1

IM FDA 2001
Allogeneic HCT is getting better

Non-relapse mortality

1. Pharmacologic (Bu,Cy,Flu)
2. Treatment of GVHD (beclo↓pred)
3. Ursodiol
4. Hardwired management of CNI dosing, CMV rx
5. Fungal treatment

CML Survival After Allogeneic HCT (FHCRC)

*Includes both matched related and unrelated donors.

Patients receiving allografts at the Fred Hutchinson Cancer Research Center from 1995 to the present. Figure is courtesy of Dr. Ted Gooley.
Allogeneic HCT for CML in the Imatinib Era

*CML Study IV (n = 84)*


Allogeneic HCT as 2nd line therapy in CML BC

*Hamburg (n = 68)*

Survival after transplantation

Survival probability

Years after SCT

HCT in BC

- Successful in only a minority of patients,
- Mostly after return to CP
- 10 year survival ~16 – 25%, but
- Best chance of a cure in BC
- Most long term BC survivors have received transplant in 2\textsuperscript{nd} CP

Sauvage et al., Blood 2010; 115: 1880 – 1885
What’s in a name? STI571

- Then: “Stop transplantation now!”
- Now: “Some transplants indicated.”

Success of TKI might increase BMT
(assumption: 1 or 10% AP/BC, resistance, intolerance)

Kantarjian, Cancer 2012
NCCN and ELN recommendations for allogeneic HCT in CML

- **Baseline:** Never
- **Second-line:** “Always” in blast phase irrespective of the response to TKIs
  “Always” in accelerated phase, if the response to TKI is less than optimal
- **Third-line:** “Always” if the response to second-line TKI is less than optimal
- The value and the meaning of “Always” depend on transplant risk (age, comorbidities, performance status, donor, etc.).
Summary-progression in the TKI era

- Incidence of BC greatly decreased with TKI!
- Survival in BC not clearly improved with TKI since 1970s
- No recommendation of a specific drug treatment possible
- Transplantation carries the best long term prognosis in BC
- Allogeneic HCT recommended in BC by NCCN and ELN