History of CML Treatment
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No conflict of interest

Lisbon, 20th March 2018
What is CML?
The mystery of chronic myeloid leukaemia
Chronic myeloid leukaemia

- Often diagnosed by chance e.g. routine blood test
- Symptoms typically are fatigue, lethargy, abdominal swelling/bloating, night sweats
- Characterised by high white cell count, sometimes anaemia, increased or decreased platelets, enlarged spleen
- Examination of blood shows primitive cells, range of white cells, e.g. neutrophils, eosinophils, basophils
Blood film from CML in CP
Chronic myeloid leukaemia

- Incidence 10-15:1,000,000 population
- 700 new cases per annum in UK
- Median age of onset 50-60 years
- Bi or triphasic disease, chronic phase, acceleration and blast crisis
Clinical course: phases of CML Before TKIs

<table>
<thead>
<tr>
<th>Chronic phase</th>
<th>Advanced phases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Accelerated phase</td>
</tr>
<tr>
<td>Median duration 5–6 years</td>
<td>Median duration 6–12 months</td>
</tr>
</tbody>
</table>

- **Chronic phase**: Median duration 5–6 years
- **Accelerated phase**: Median duration 6–12 months
- **Blast crisis**: Median survival 3–6 months
Clinical course: phases of CML After TKIs

<table>
<thead>
<tr>
<th>Chronic phase</th>
<th>Advanced phases</th>
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</thead>
<tbody>
<tr>
<td>GLIVEC</td>
<td>Accelerated phase</td>
</tr>
<tr>
<td>Stable and durable chronic phase?</td>
<td>Median duration 6-24 months</td>
</tr>
</tbody>
</table>
Estimated Prevalence of CML in Europe until 2050

Assumptions: Population 500 million, mortality 2% per year, incidence constant.
Courtesy to Hasford and Pfirrmann.

250,000 patients x 35,000 € per year = 8.75 Billion € per year
Biology of CML
A normal set of chromosomes
The Philadelphia chromosome

Normal

CML
The t(9;22) translocation produces the Philadelphia (Ph) chromosome. 22q- (Ph) bcr-abl expresses a fusion oncprotein with tyrosine kinase activity.
Classical t(9;22)(q34.1;q11.2) Dual Fusion (D-FISH) Signal Pattern
What’s a cytogenetic response and why does it matter?

<table>
<thead>
<tr>
<th>Type of response</th>
<th>% of Philadelphia-positive cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor/minimal</td>
<td>More than 35%</td>
</tr>
<tr>
<td>Partial</td>
<td>Less than 35%</td>
</tr>
<tr>
<td>Complete</td>
<td>0%</td>
</tr>
</tbody>
</table>

- Test performed on a sample of bone marrow every 6 months or so
- WITH INTERFERON...
- If you have a ‘major’ response you probably live longer
- If you have a ‘complete’ response you probably live even longer
- If you sustain a complete response for several years - ???cure.
Survival Without AP/BC by Level of CyR at 18 Months on First-line Imatinib

Response at 18 months

- CCyR: n= 358, 99% with p<0.001
- PCyR: n= 66, 90% with p<0.001
- No MCyR: n= 56, 83%

Estimated rate at 60 months:
- CCyR: 99%
- PCyR: 90%
- No MCyR: 83%
Molecular Abnormality

Chromosome 22

Chromosome 9

BCR-ABL gene

mRNA

210 KD protein
Proliferation  Adherence  Apoptosis

Bcr  SH1  Abl

p145 Abl

p210 Bcr-Abl
Real time quantitative RT-PCR

I. Hydrolysis Probes
Release from quenching by hydrolysis

II. Hybridization Probes
Increased resonance energy transfer by hybridization

TaqMan™

LightCycler™
What’s a molecular response and why does it matter?

- Test performed on a sample of peripheral blood every 3 months or so
- WITH TKIs...
- If you have a ‘major’ response you probably live longer
- If you have a ‘complete’ response you have a 40% chance of stopping Imatinib
- If you sustain a complete response for several years - ???cure.

<table>
<thead>
<tr>
<th>Type of response</th>
<th>% of bcr-abl compared to (normal) abl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suboptimal</td>
<td>More than 0.1%</td>
</tr>
<tr>
<td>Major</td>
<td>Less than 0.1%</td>
</tr>
<tr>
<td>Complete</td>
<td>Less than 0.003%</td>
</tr>
</tbody>
</table>
What’s a molecular response and why does it matter?

Log reduction at 12 months versus time to progression - Imatinib

- No CCyR within 12 months (n=128)
- <3 log reduction (n=103)
- ≥3 log reduction (n=137)

= Censored observations
Tyrosine Kinase Inhibitors in CML
ATP-binding competitors

BCR-ABL

ATP Substrate

TKI

Activated
What a difference a point-mutation made...

Wild type

T315I

(Gorre et al., Science, June 2001)
Treatment challenges in CML
Current Aim of TKI Therapy in CML

- Molecular response
- Lifelong maintenance

CP-CML at Diagnosis
- Leukemic burden
  - M3 <10%
  - M6 <1%
  - CCyR
  - M12
  - MMR
  - M18
  - MMR

PFS
EFS
Near-normal life expectancy
Stable or improving

Treatment change upon lack or loss of an optimal response, progression or unacceptable side effects

Time on TKI therapy

- Baccarani et al. JCO 2009; 27: 6041-6051
- Björkholm et al. JCO 2011; 2514-2420
- Gambacorti-Passerini et al. JNCI 2011; 103: 553-561
0106/IRIS study: design

Randomize

Imatinib
N=553

IFN-α + Ara-C
N=553

Crossover

Crossover for:
• Lack of response
• Loss of response
• Intolerance of treatment

1106 patients total
Complete Cytogenetic Responses

- **Imatinib**
  - 1% at 0 months
  - 3% at 3 months
  - 9% at 6 months
  - 12% at 9 months
  - 14% at 12 months
  - 69% at 15 months
  - 76% at 18 months
  - p < 0.001

- **IFN + Ara-C**
  - 1% at 0 months
  - 3% at 3 months
  - 9% at 6 months
  - 12% at 9 months
  - 14% at 12 months
  - 63% at 15 months
  - 69% at 18 months

Graph showing percentage responding over time since randomization.
**Estimated Response to First-line Imatinib**

- CHR: 97%
- MCyR: 90%
- CCyR: 82%

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**Estimated rate at 30 months**

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<th>Response</th>
<th>Rate</th>
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<tr>
<td>CHR</td>
<td>97%</td>
</tr>
<tr>
<td>MCyR</td>
<td>90%</td>
</tr>
<tr>
<td>CCyR</td>
<td>82%</td>
</tr>
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CML-Study IV
Cumulative incidence of molecular response to imatinib

Hehlmann et al, JCO 2014
ENESTnd: Cumulative Incidence of MMR

MMR, major molecular response (BCR-ABL\textsuperscript{IS} ≤ 0.1%).

By 1 Year\textsuperscript{a} 55%, \( P < .0001 \)

By 4 Years\textsuperscript{a} 76%, \( P < .0001 \)

Δ 17% to 20%

By 5 Years\textsuperscript{a} 77%, \( P < .0001 \)

Δ 17%

\textsuperscript{a} Cumulative response rates reported consider each year to consist of twelve 28-day cycles.

Nilotinib 300 mg BID (n = 282)
Nilotinib 400 mg BID (n = 281)
Imatinib 400 mg QD (n = 283)

Molecular Responses at 5 Years

- **Dasatinib**: n=259
- **Imatinib**: n=260

Achieved response
- **MMR**: 52% (Dasatinib), 49% (Imatinib)
- **MR 4**: 28% (Dasatinib), 25% (Imatinib)
- **MR 4.5**: 18% (Dasatinib), 18% (Imatinib)

Did not achieve response
- **Not evaluated for molecular response at 5 years**

- off treatment: dasatinib n=95 (37%), imatinib n=94 (36%)
- not evaluated: dasatinib and imatinib n=11 each (4%)

* 5 years ± 3 months.

b Patients on treatment with no sample analyzed at 5 years ± 3 months.

MR, BCR-ABL (IS) ≤0.01%.
MR^{4.5} by 5 Years^{a} According to Sokal Risk Score

\[ P = .0004 \]
\[ P = .0148 \]
\[ P = .0082 \]
\[ P < .0001 \]
\[ P = .0082 \]
\[ P = .0105 \]

(n = 283) (n = 282) (n = 281)

By cycle 60 (28 days per cycle).

Achievement of <10% BCR-ABL Transcripts at 3 Months: Evaluable Patients

Evaluable: patients with an assessment at 3 months or later.

Data as of 1 April 2014
Achievement of <10% BCR-ABL Transcript Levels at 3 Months by Sokal Risk Score: Evaluable Patients

Data as of 1 April 2014

- Low risk (n=45): Ponatinib 98, Imatinib 76 (P=0.002)
- Intermediate risk (n=44): Ponatinib 96, Imatinib 69 (P=0.002)
- High risk (n=20): Ponatinib 85, Imatinib 42 (P=0.008)
OS: BCR-ABL (IS) at 3 months ≤1% vs. 1-10% vs. >10%

Hanfstein et al, 2012; Leukemia, 26: 2096-2101)
All 3 progressions to AP/BC on study reported since the 4-year analysis occurred in patients with high Sokal risk scores at baseline; all 3 patients also had BCR-ABL<sub>IS</sub> > 10% at 3 months.

All progressions in patients with low/intermediate Sokal risk scores occurred during the first 2 years on study.

Progression to AP/BC or death due to advanced CML on core treatment or during follow-up after discontinuation of core treatment.

Hughes T, EHA 2014
Survival After Progression to AP/BC

Median survival ~10.5 months

First line therapy in CML in CP

The main advantage of 2nd generation TKI as first line is the increase in the proportion of patients candidates for discontinuation.
Molecular Relapse free survival

200 interim patients - overtime, loss MMR=89

Relapses within 6 months , n=77

At 6 months : 63 %  (95% CI : 55% - 69%)
At 12 months: 56 %  (95% CI : 49 % - 63 %)
At 18 months : 55 %  (95% CI : 47 % - 61 %)

63% remained without relapse the first 6 mo
250,000 patients x 40% discontinuation = 100,000 patients = 3.5 Billion € per year
Possible role of SCT in CML

- **Soon after diagnosis**
  - Good risk for transplant
  - Low chance of responding to TKI
  - Patient's preference

- **After failing TKIs**
  - Imatinib failure, suboptimal response, intolerance
  - Failure to 2nd generation TKIs
  - Resistance to TKIs associated with the T315I mutation

- **In accelerated phase or blast crisis**
Path to SCT in CML: First Line Imatinib

1. Imatinib first line
2. 60% Durable response
3. 40% eligible for trial of treatment withdrawal
   - Up to 15% achieve operational cure
4. 40% Require 2GTKI
5. 50% Require 3GTKI
6. 50% Require alternative treatment
   - Around 10-15% of initial group may benefit from HSCT
7. 50% Durable response
Allo-SCT for CML in Europe

SCT for CML: the EBMT score

Prognostic factors for survival (defined before SCT):

- Age
- Disease phase
- Disease duration
- Histocompatibility
- Patient/Donor gender
Outcome after allo-SCT for CML in advanced phase

Overall Survival of CML patients in AP/BC transplanted between 1995-2005

Courtesy of CLWP-EBMT
Survival after SCT for early CML-CP

Survival of patients in early first chronic phase according to the revised chronic phase risk score (N=2049)

<table>
<thead>
<tr>
<th>Risk score (0–2 points per category)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years:</td>
</tr>
<tr>
<td>&lt;30 (0); 30–40 (1); &gt;40 (2)</td>
</tr>
<tr>
<td>Donor:</td>
</tr>
<tr>
<td>sibling (0); unrelated (2)</td>
</tr>
<tr>
<td>Interval diagnosis-SCT:</td>
</tr>
<tr>
<td>&lt;1 year (0); &gt;1 year (1)</td>
</tr>
<tr>
<td>Sex match:</td>
</tr>
<tr>
<td>female–male (1); all other (0)</td>
</tr>
</tbody>
</table>
Progress in allo-SCT for CML

Overall survival among good risk patients (score=0–1)

1980–1990
1991–1999
2000–2003


Overall survival for allo SCT in German CML-IV study

Elective, n = 19, 3-yr survival: 88%
Imatinib failure in 1 CP, n = 37, 3-yr survival: 94%
Advanced phase, n = 28, 3-yr survival: 59%

Impact of previous Imatinib on SCT

Adjusted Probability of Survival by IM+ vs IM- for first chronic phase CML

Stratified Cox regression Model with adjustment for covariates
(HLA match, graft type, time from Dx to Tx)

P-value = 0.006

The Effect of Prior Therapy with Nilotinib or Dasatinib on the Outcome after Allo SCT for Patients with CML
EBMT Non-Interventional Prospective Study

The diagram shows the effect of prior therapy with Nilotinib or Dasatinib on the outcome after Allo SCT for patients with CML. The data is categorized by response status (BC, > CP1, CP1) and the type of therapy: Dasatinib, Nilotinib, Sequential Dasa/Nilo. The graph visually represents the proportion of patients at TKI and SCT stages.
The Effect of Prior Therapy with Nilotinib or Dasatinib on the Outcome after Allo SCT for Patients with CML

EBMT Non-Interventional Prospective Study

No differences in outcomes between Nilotinib, Dasatinib and Sequential TKI
The Effect of Prior Therapy with Nilotinib or Dasatinib on the Outcome after Allo SCT for Patients with CML

EBMT Non-Interventional Prospective Study
Response after Allogeneic SCT for CML

- **Haematologic Remission**: q-PCR negative
- **Cytogenetic Remission**: Cytogenetics negative
- **Molecular Remission**: q-PCR positive
- **Leukaemic cells**
Complications after SCT for CML

D Heim (CLWP-EBMT) Unpublished data
Detection of Relapse

- **High Disease Burden**
- **Medium Disease Burden**
- **Low Disease Burden**
- **No Detectable Disease**

- **Haematological Relapse**
- **Cytogenetic Relapse**
- **Molecular Relapse**

- **Cytogenetics positive**
- **Cytogenetics negative**
- **q-PCR positive**
- **q-PCR negative**

Sensitivity of Test

- 10^{-2}
- 10^{-6}
- 10^{-8}

Leukaemic cells
Treatment of relapse

- DLI (n=91)
- 2nd BMT (n=27)
- Other (n=47)

Probability of survival over months post relapse.
## Results of DLI in CML

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>271</td>
<td>188</td>
<td>83</td>
</tr>
<tr>
<td>GvHD</td>
<td>45</td>
<td>47</td>
<td>40</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>19</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Cytogenetic Response</td>
<td>69</td>
<td>80</td>
<td>43</td>
</tr>
<tr>
<td>Survival at 3y</td>
<td>67</td>
<td>80</td>
<td>38</td>
</tr>
<tr>
<td>Failure free survival</td>
<td>53</td>
<td>66</td>
<td>25</td>
</tr>
<tr>
<td>DLI-related mortality</td>
<td>15</td>
<td>12</td>
<td>21</td>
</tr>
</tbody>
</table>
Molecular response to DLI

Months post DLI

Molecular/Cytogenetic relapse

Haematological relapse

Overall

Molecular remission (%)

87%

61%

47%

p = 0.004
Probability of molecular remission

Cytogenetic remission (%)

Months post first DLI

- **BDR (n=28)**: 91%
- **EDR (n=20)**: 67%
Molecular relapse after remission with DLI
Incidence of GHVD after DLI (n=500)

<table>
<thead>
<tr>
<th>Response*</th>
<th>GvHD post DLI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>24%</td>
</tr>
<tr>
<td>Yes</td>
<td>32%</td>
</tr>
</tbody>
</table>

* Molecular and/or cytogenetic remission
Imatinib in relapse: overall survival

- CP (n=51)
- AP (n=31)
- BC (n=46)

Probability of Survival

Months

$p = 0.0001$
Response after Relapse

- Haematologic Remission: q-PCR positive
- Haematologic Remission: q-PCR negative
- Cytogenetic Remission: Cytogenetics positive
- Cytogenetic Remission: Cytogenetics negative
- Molecular Remission: FBC positive
- Molecular Remission: FBC negative
- DLI or TKI
- Sensitivity of PCR: $10^{-8}$, $10^{-6}$, $10^{-4}$, $10^{-2}$

Leukaemic cells
MUITO OBRIGADO!