AUBH 2012 Debate:
Optimal therapy for first line treatment of CML
Cure vs. Control ?

In favor of control

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TKI changed the treatment of CML

- Cure by Allo-SCT, 1970-2000s
- CCyR by Interferon, 1980-2000s
- MMR by 1st TKI--Imatinib, 2001-2010
- CMR by 2nd TKI- Dasatinib, Nilotinib, 2011-
Overall Survival (ITT Principle): Imatinib Arm

Estimated overall survival at 8 years is 85% (93% considering only CML-related deaths)

Survival: deaths associated with CML

Overall Survival

Deininger et al. ASH 2009, Abstract 1126
Probability of Survival after HLA-identical Sibling Donor Transplants for CML, 1998-2009
- By Disease Status and Transplant Year -

3-year probability of OS: 70%
TKIs >20% OS advantage than allo-SCT

→ Mostly come from the risk of early TRM

85%@8yrs IRIS
Late mortality after allo-HSCT for CML
Fred Hutchinson CRC data, 1995-2010

*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. Reprinted with permission.
Allo-SCT for CML Decreased Dramatically

CIBMTR 1998-2008, online data

* Data incomplete
CML: Treatment goal

1. International guidelines (ELN, NCCN, etc)
   - 12M: CCyR
   - 18M: MMR

2. Prevent emergence of resistance

3. Prevent progression to AP/BC

4. Quality life
Case Study 1

Male 54 y/o

2006 CML, CP, t(9;22), started IM 400 mg/day

Interpretation:

CML in durable MMR since IM 18M, in durable CMR since IM 4 yrs
Case Study 2

Male 23 y/o
2007-12 CML, CP, t(9;22), started IM 400 mg/d ⇒ intolarence
RQ-PCR no molecular response, switch to Sprycel
2009-08 t(9;22) 100% ⇒ alloHSCT
2011-01 relapsed ⇒ Teasing 800 mg/d

Interpretation:
CML intolerance to IM, resistance to Spiracle and BMT, excellent response to Teasing, in MMR
Upfront HSCT for CML: possible situation

1. CML-CP with poor Sokal risk and low HSCT risk score
2. Pediatric CML
3. De novo onset of AP/BC
4. Economic issues
Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV

Blood. 2010;115:1880-1885
Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics of 106 matched imatinib-treated patients and 53 patients who underwent transplantation in first CP (matched pair analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplantation</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>Sex, % male</td>
</tr>
<tr>
<td>Median age, y</td>
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<tr>
<td>EURO risk score, %</td>
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<tr>
<td>Low</td>
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<tr>
<td>Intermediate</td>
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<td>High</td>
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No survival difference between SCT and IM for CML-CP

After SCT
3y OS 91%
TRM 8%
88% achieved CMR

Author conclusion:
Allo SCT could become the preferred second-line option after imatinib failure for suitable patients with a donor.
How I treat childhood CML

Jeffrey R. Andolina, ¹ Steven M. Neudorf, ² and Seth J. Corey ³

CML diagnosis confirmed

CML-CP
Chronic Phase

· Begin imatinib OR dasatinib
· Consider

· Monitor disease for response (see Table 2)

CML-AP
Accelerated Phase

· Begin dasatinib and hydroxyurea

CML-BC
Blast Crisis

· Begin dasatinib
· Begin anti-leukemia chemotherapy

· Screen for best stem cell donor and proceed to transplantation once in remission

If patient has suboptimal response or fails therapy, screen for best stem cell donor AND

If started on imatinib, switch to dasatinib

If patient has suboptimal response or fails therapy, proceed to transplantation

If patient meets optimal response criteria, continue imatinib indefinitely

If started on dasatinib, proceed to transplantation

Blood. 2012;119:1821-1830
If money becomes the key issue
One concern: Late events in a real world
Hammersmith H, 2000-2006, N=204, ITT analysis

de Lavallade H et al. JCO 2008;26:3358-3363
ENESTnd: Nilotinib vs Imatinib in Ph+ CML-CP

Progression to AP/BC on Treatment

- No new progressions on treatment were observed since the 2-year analysis.
- Nilotinib has a significantly lower risk of progression than imatinib.
Cumulative Incidence of MMR*

- Nilotinib 300 mg BID: 282 patients, 73%, P < .0001
- Nilotinib 400 mg BID: 281 patients, 70%, P < .0001
- Imatinib 400 mg QD: 283 patients, 53%

By 3 Years:
- Nilotinib 300 mg BID: 73%, P < .0001
- Nilotinib 400 mg BID: 70%, P < .0001
- Imatinib 400 mg QD: 53%

Δ 17%-20%

By 1 Year:
- Nilotinib 300 mg BID: 55%, P < .0001
- Nilotinib 400 mg BID: 51%, P < .0001
- Imatinib 400 mg QD: 27%

Δ 24%-28%

* Equivalent to BCR-ABL transcript levels of ≤ 0.1% (International Scale, IS).

Depth of Molecular Response in Patients With MMR by 3 Years

- 68% of patients who achieved MMR by 3 years on nilotinib 300 mg BID achieved an MR$^4$ or greater vs 49% on imatinib.
Cumulative Incidence of MR$^4.5$*

* Equivalent to BCR-ABL transcript levels of ≤ 0.0032% (IS).


CMR Means…

CMR

- Deepest response at present
- Fire lane from disease progression

Better RFS

- May offer “drug-free” period, and even chance of cure
- Away from fear of cancer and better QoL
- Save money if off TKIs
Proof of Concept

Stop Imatinib after Durable CMR

STIM Trial

Molecular relapse free survival

Retreat imatinib:
- All sensitive
- 56/61 (92%) re-gain CMR

~41%@2yrs
~39%@3yrs

F. Mahon et al. (STIM) Poster 603 @ ASH 2011
Cost Isn’t Everything. Value is.

<table>
<thead>
<tr>
<th>Imatinib</th>
<th>Nilotinib</th>
<th>Dasatinib</th>
<th>Allo-SCT</th>
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<tbody>
<tr>
<td>20 USD</td>
<td>21 USD</td>
<td>42 USD</td>
<td></td>
</tr>
<tr>
<td>100mg/tab</td>
<td>150mg/cap</td>
<td>50mg/tab</td>
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<tr>
<td>400mg/day</td>
<td>600mg/day</td>
<td>100mg/day</td>
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<tr>
<td>29,200/year</td>
<td>$30,660/year</td>
<td>$30,660/year</td>
<td>150K-200K (USA)</td>
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<td>35K-100K (TWN)</td>
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<td></td>
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<td></td>
<td>(First year)</td>
</tr>
<tr>
<td>233K (8 years)</td>
<td>245K (8 years)</td>
<td>245K (8 years)</td>
<td>200K-400K (USA)</td>
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<td></td>
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<td>60K-100K (TWN)</td>
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<td></td>
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<td>(8 years)</td>
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We Need A Safer Parachute

TKI

SCT
Feel Like Normal, and Better QoL

Working, dating, married

Pregnancy, having children

Possible drug-free
CML Treatment Paradigm: 2012

**CP CML**
- Complete diagnostic workup
- Tumor burden by Q-RT-PCR
- Imatinib 400 mg/day
- Nilotinib 300 mg BID
- Dasatinib 100 mg/day

**Advanced-phase CML**
- CHEMO + TKI vs TKI alone
- Imatinib 400 mg BID
- Dasatinib 70 mg BID
- Nilotinib 400 mg BID

**Goals**
- Heme CR in 1-2 mos
- Cyto response in 3-6 mos
- CCyR in 12-15 mos
- MMR in ~ 12 mos

**Non-Response**
- Dasatinib
- Nilotinib

**Allo-HSCT @ progression**

**Allo-HSCT: second or third salvage?**
Thanks for your attention!