Leucemia Mieloide Cronica: 
la terapia con imatinib

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Imatinib standard dose:
IRIS 7-year update
IRIS Protocol: Study Design

**Randomize**

- Imatinib
  - $n = 553$

- IFN-a + Ara-C
  - $n = 553$

**Crossover**

Crossover for:
- Lack of response
- Loss of response
- Intolerance of treatment
- Reluctance to continue IFN

O’BRIEN et al, NEJM, 2003
IRIS: 7-year update

All randomized to imatinib (n= 553; 100%)

- Discontinued study imatinib* (n = 221; 40%)
- Still receiving study imatinib (n = 332; 60%)

In CCR (n = 317; 97%)
No CCR (n = 15; 3%)

Safety (5%)
Efficacy (15%)
Other (22%)

Cumulative CCgR rate: 456/553 (82%)

164 alive patients (30%) formally off protocol

*Patients may have continued imatinib off study.

Hochhaus A et al, Leukemia 2009
IRIS- Molecular Response

BCR-ABL% (International Scale)

- ≤0.1% (MMoIR)
- ≤0.01%

% of available samples

Months from imatinib start

0 3 6 9 12 15 18 21 24 30 36 42 48 54 60 66 72 78 84

Overall Survival (ITT Principle)

Overall Survival

% alive

Months Since Randomization

Survival: deaths associated with CML
Overall Survival


94%
86%
Imatinib standard dose: Independent analyses
### Imatinib for Newly Diagnosed Patients With Chronic Myeloid Leukemia: Incidence of Sustained Responses in an Intention-to-Treat Analysis

**Patients number**: 204

<table>
<thead>
<tr>
<th>Sokal Level</th>
<th>Patients Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>59 (29%)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>86 (42%)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>59 (29%)</td>
<td></td>
</tr>
</tbody>
</table>

**Median follow-up, mos**: 38 (12-85)

**no of patients (%)**

<table>
<thead>
<tr>
<th>Response</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHR</td>
<td>201</td>
<td>98%</td>
</tr>
<tr>
<td>CCgR</td>
<td>159</td>
<td>78%</td>
</tr>
<tr>
<td>MMoIR</td>
<td>80</td>
<td>39%</td>
</tr>
</tbody>
</table>

**Event**: death, progression to AP/BC, loss of CHR/CCgR, IM discontinuation for AE/ failure to achieve a PCgR

**Results**

- **OS**: 83%
- **PFS**: 82%
- **EFS**: 63%

*De Lavallade et al, JCO 2008; 26: 3358-3363*
GIMEMA CML WP: analysis of 553 Early Chronic Phase patients accrued between 2004 and 2007 in 3 multicentric studies

Complete cytogenetic response rate

- 6 mos: 68%
- 12 mos: 79%
- 18 mos: 79%

OS: 93%
PFS: 92%
FFS: 82%
EFS: 74%

Failures: no CHR at 6 mos, no CgR at 6 mos, no PCgR at 12 mos, no CCgR at 18 mos, loss CHR or CCgR, progression to accelerated/blastic phase and death.

Events: failures, off-treatment for toxicity, refusal and lost to follow-up.
Beyond imatinib standard dose: room for improvements with higher doses?
Imatinib dose optimization

The issue is complex and probably it cannot be applied, or pursued, in all patients irrespective of
1) Response
2) Tolerance
3) Blood level testing data

Rational for higher doses of IM
1) Responses to 800mg after failure to 400mg
2) Chronic phase: Response correlates with actual dose intensity
3) Accelerated phase 600 mg (vs 400 mg): improved response rate, survival and EFS
4) Some mechanisms of resistance may be overcome by higher dose
Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) study

Random 2:1
N=476

N=319 pts
Imatinib 800 mg

N=157 pts
Imatinib 400 mg

MMR at 12 months
PFS, OS

Total 5 years

Accrual: June 2005 – December 2006
Follow-up: 12 months

Cortes et al., JCO 2009, in press
“TOPS” study: IM 400 mg vs 800 mg

By 12 months, CCgR and MMR rates were comparable between 400 and 800 mg/day arms.
Comparison of imatinib 400 mg and 800 mg daily in the front-line treatment of high-risk, Philadelphia-positive chronic myeloid leukemia: a European LeukemiaNet Study

FAILURES
- Lack of CHR at 6 months
- Less than minor CyR at 6 months
- Less than Partial CyR at 12 months
- Loss of CHR
- Loss of CCyR

Primary Endpoint:
CCgR at 1 year
ELN “CML022” study

CCgR

- 400 mg: 52% (6 mos), 64% (12 mos)
- 800 mg: 50% (6 mos), 58% (12 mos)

p NS

HIGH DOSE ARM
CCgR according to average daily dose

- 700-800 mg: 91%
- 699-400 mg: 73%
- <400 mg: 20%

MMoIR

- 400 mg: 42% (6 mos), 49% (12 mos)
- 800 mg: 32%, 41%

p NS

CCyR rates appeared to be related to the actual dose
Beyond imatinib alone: room for improvements with combination therapies?
GIMEMA CML 011- IM+PegIFN-α in 76 ECP-CML

Cytogenetic response rate (5 yrs)

- **87%** Complete
- **10%** Partial

- **95%** progression-free survival
- **96%** overall survival
GIMEMA CML 011 – Compliance to PegIFN-α
French “SPIRIT” trial
636 ECP patients

Randomization
1:1:1:1:1
Study initiation:
Sept 2003

Imatinib 400 mg
Imatinib 600 mg
Imatinib 400 mg + Ara-C
Imatinib 400 mg + PegIFN

Courtesy of dr. F. Guilhot
SPIRIT: Major Molecular Response at 18 months (ITT)

- IM + IFN: 62%
- IM 600: 52%
- IM + AraC: 53%
- IM 400: 41%

P = 0.0001

46% of the patients discontinued IFN during the first year.

Courtesy of dr. F. Guilhot

German CML Study IV

Imatinib n=336

Imatinib + IFNa n=362

Imatinib + AraC n=158

Imatinib after IFNa n=131

Imatinib 800 mg n=350

Failure

No significant differences between treatment arms for CCgR, MMolR and PFS

alloSCT n=84

Median follow-up: 45 months

Hehlmann R. Haematologica 2009; 94:193

Courtesy of dr. R. Helhmann
Beyond imatinib: room for therapy discontinuation?
The STTop IMatinib ("STIM") study

Molecular relapse in 36 pts

15/34 (44%) LCP
21/36 (58%) ECP

STOP IMATINIB AND MOLECULAR RELAPSES

Follow-up

Number of patients

Median follow-up: 4 mos (1-20)

Courtesy dr. P Rousselot
1. IM 400 mg daily in early chronic phase CML:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>CHR</td>
<td>≥ 95%</td>
</tr>
<tr>
<td>CCgR</td>
<td>75-90%</td>
</tr>
<tr>
<td>MMoIR</td>
<td>50-70%</td>
</tr>
<tr>
<td>7-yrs PFS</td>
<td>85-90%</td>
</tr>
<tr>
<td>7-yrs OS</td>
<td>90-95%</td>
</tr>
</tbody>
</table>

2. IM 800 mg: cytogenetic and molecular responses more rapid, but no differences at 1 year. Limited compliance.

3. IM in combination/rotation with other agents is investigational. The feasibility of the combination with IFN-alpha seems to be limited.
1. Imatinib is not always a “magic bullet”
   D/C IMATINIB FOR FAILURE 15 - 20%
   D/C IMATINIB FOR TOXICITY 8 - 10%
   MMoIR RATE 40 - 90%

2. Imatinib and “Quality of Life”

3. Imatinib and safe procreation

4. Imatinib and “CURE”
Thank you!

GIMEMA CML WP

Scientific Committee
Michele Baccarani (Bologna)
Giuliana Alimena (Roma)
Renato Fanin (Udine)
Francesco Frassoni (Genova)
Giovanni Martinelli (Bologna)
Gianantonio Rosti (Bologna)
Domenico Russo (Brescia)
Giuseppe Saglio (Torino)
Giorgina Specchia (Bari)

Department of Hematology “L. and A. Seràgnoli”
Bologna University Hospital
BACK-UP
IRIS: 7-year update

Annual Event Rates

**All patients**

- % With Event
  - Year 1: 3.3%
  - Year 2: 1.5%
  - Year 3: 1.6%
  - Year 4: 1.7%
  - Year 5: 0.9%
  - Year 6: 0.5%
  - Year 7: 0.4%

**Event**
- Loss of CHR
- Loss of MCR
- AP/BC
- Death

**CCgR patients**

- Number Progressing After CCR
  - 1st year: 7
  - 2nd year: 3
  - 3rd year: 1
  - 4th year: 1

- Time to CCR:
  - <12 months (n = 373)
  - >12-<24 months (n = 50)
  - >24 months (n = 33)

**EFS at 7 years:** 81%

**PFS at 7 years:** 93%
559 Early Chronic Phase patients accrued between Jan 2004 and Apr 2007 in 3 multicentric studies:

- **CML/021, phase II** 82 pts
  imatinib 800 mg in intermediate Sokal risk

- **CML/022, phase III, randomized** 112 pts
  imatinib 400 vs 800 mg in high Sokal risk

- **CML/023, observational** 365 pts
  imatinib 400 mg, all risks
ELN “CML022” study: IM 400 mg vs 800 mg in high risk pts

<table>
<thead>
<tr>
<th>Treatment discontinuation in the first year</th>
<th>400 (n. 108)</th>
<th>800 (n. 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawals</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Adverse events</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Failures</td>
<td>17%</td>
<td>15%</td>
</tr>
<tr>
<td>Total</td>
<td>27%</td>
<td>31%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Average daily dose</th>
<th>800 mg</th>
<th>400mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>800 mg</td>
<td>NA</td>
<td>53%</td>
</tr>
<tr>
<td>600-799</td>
<td>NA</td>
<td>53%</td>
</tr>
<tr>
<td>400-599</td>
<td>25%</td>
<td>57%</td>
</tr>
<tr>
<td>350-399</td>
<td>6%</td>
<td>31%</td>
</tr>
<tr>
<td>&lt;350</td>
<td>6%</td>
<td>12%</td>
</tr>
</tbody>
</table>
Evaluating Response in CML

Number of leukemic cells

- **CHR** Hematologic response
- **MCR** Cytogenetic response
  - **CCR (CG)**
  - **CCR (FISH)**
- **3 log reduction**
- **4 log reduction**
- **Limits of detection**

Molecular response (Q-PCR)
Late chronic phase

Accelerated/blast phase
GIMEMA CML 002: Imatinib in Late Chronic Phase CML

OS / PFS

Months from IM start

Patients in CCgR

Months from IM start

Palandri et al, GIMEMA CML WP, JCO 2008
# GIMEMA CML 003: Imatinib 600 mg in Accelerated/blast Phase

<table>
<thead>
<tr>
<th></th>
<th>Blast crisis</th>
<th>Accelerated phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>92</td>
<td>111</td>
</tr>
<tr>
<td>Male/female</td>
<td>59/33</td>
<td>70/41</td>
</tr>
<tr>
<td>Median age at IM start</td>
<td>55 (18-88)</td>
<td>58 (26-82)</td>
</tr>
<tr>
<td>ACA at IM start</td>
<td>20 (22%)</td>
<td>21 (22%)</td>
</tr>
<tr>
<td>PS at IM start =2</td>
<td>36 (39%)</td>
<td>18 (16%)</td>
</tr>
<tr>
<td>Chemotherapy prior to IM</td>
<td>27 (29%)</td>
<td>29 (26%)</td>
</tr>
</tbody>
</table>
GIMEMA 003 - Overall survival

**BC patients**

- **Overall survival** months from IM start
- **HR**
- **no HR**

**AP patients**

- **Overall survival** months from IM start
- **MCgR**
- **no MCgR**
DOSE ISSUE
Imatinib high dose: rationale

1. Dose-response in preclinical models
2. Phase I: No MTD, dose-response correlation
3. Responses to 800mg after failure to 400mg
4. Accelerated phase 600 mg (vs 400 mg): improved response rate, survival and EFS
5. Chronic phase: Response correlates with actual dose intensity, plasma levels
6. Improved long-term outcome with early responses
7. Some mechanisms of resistance may be overcome by higher dose
Impact of early dose intensity on cytogenetic and molecular responses in chronic-phase CML patients receiving 600 mg/day of imatinib as initial therapy

Therapeutic Intensification in DE-novo Leukaemia (TIDEL STUDY) Australasian Leukaemia and Lymphoma Group

Dose escalation to 800 mg

IM 600 mg → No CHR → No PCgR → No CCgR → No MMolR

3 months → 6 months → 9 months → 12 months

Accrual: October 2002 - August 2003
No. of patients: 103
“Patients able to dose escalate and those remaining on 600 mg achieved superior responses to patients receiving 600 mg.

Superior responses achieved in patients able to tolerate imatinib at 600 mg suggests that early dose intensity may be critical to optimise response in CP-CML”
### Study 021 - Sokal Intermediate Risk
**IM 800 mg (72 pts)**

<table>
<thead>
<tr>
<th></th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Observed</td>
<td>72</td>
<td>65</td>
<td>43</td>
</tr>
<tr>
<td>CHR</td>
<td>81%</td>
<td>98%</td>
<td><strong>98%</strong></td>
</tr>
<tr>
<td>PHR</td>
<td>19%</td>
<td>2%</td>
<td>//</td>
</tr>
<tr>
<td>ABP</td>
<td>//</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Minimal/absent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCgR</td>
<td>4%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>CCgR</td>
<td>87%</td>
<td>90%</td>
<td></td>
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</tbody>
</table>
## Comparison

<table>
<thead>
<tr>
<th></th>
<th>IRIS 400 mg</th>
<th>Houston 400 mg</th>
<th>Houston 800 mg</th>
<th>GIMEMA 800 mg (021)</th>
<th>TIDEL 600 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCyR Overall</strong></td>
<td>82%</td>
<td>80%</td>
<td>95%</td>
<td>91%</td>
<td>NA</td>
</tr>
<tr>
<td>6 months</td>
<td>52%</td>
<td>55%</td>
<td>82%</td>
<td>87%</td>
<td>80%</td>
</tr>
<tr>
<td>12 months</td>
<td>68%</td>
<td>75%</td>
<td>95%</td>
<td>90%</td>
<td>NA</td>
</tr>
<tr>
<td><strong>MMR 6 months</strong></td>
<td>21%</td>
<td>5%</td>
<td>39%</td>
<td>46%</td>
<td>31%</td>
</tr>
<tr>
<td>12 months</td>
<td>39%</td>
<td>25%</td>
<td>60%</td>
<td>48%</td>
<td>43% m9</td>
</tr>
<tr>
<td>24 months</td>
<td>55%</td>
<td>60%</td>
<td>72%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>PCR undetectable</strong></td>
<td>4%</td>
<td>7%</td>
<td>28%</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
COMBINATION THERAPIES
Front-line treatment of Philadelphia positive (Ph pos), BCR-ABL positive, chronic myeloid leukemia (CML) with two tyrosine kinase inhibitors (TKI) (Nilotinib and Imatinib). A phase II exploratory multicentric study.

NILO 400 mg BID  IM 400 mg OAD  NILO 400 mg BID  IM 400 mg OAD

24 months “CORE” > 36 months “EXTENSION”

3-days wash out
GIMEMA CML 011 - IM + PegIFN-α in de-novo CP-CML

<table>
<thead>
<tr>
<th></th>
<th>All patients (76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, no. (%)</td>
<td>44 (58%)</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>32 (42%)</td>
</tr>
<tr>
<td>Median age at diagnosis, yrs, (range)</td>
<td>47 (18-68)</td>
</tr>
<tr>
<td>Median time on pegIFNα, mos (range)</td>
<td>10 (0.5-49)</td>
</tr>
<tr>
<td>Median follow-up of living patients, mos, (range)</td>
<td>60 (40-68)</td>
</tr>
</tbody>
</table>

1st cohort (27 patients)
- 50 µg/week

2nd cohort (18 patients)
- 100 µg/week

3rd cohort (31 patients)
- 150 µg/week
VACCINOTERAPIA

vaccino antitumorale “IDEALE”

induce una risposta immune sistemica “ATTIVA”

distrugge specificatamente cellule tumorali disseminate

da origine ad una memoria immunologica persistente

OSTACOLI

P 210 TARGET “TUMORE-SPECIFICO”

P 210 IMMUNOGENICO GRAZIE A SEQUENZA AMINOACIDICA “UNICA”
**CMLVAX100: STUDIO DI FASE II**

**CRITERI DI INCLUSIONE**

- diagnosi di LMC b3a2
- almeno 1 di HLA A3, A11, B8, DR11, DR1 o DR4
- Risposta citogenetica maggiore o completa STABILE da almeno 6 mesi durante trattamento convenzionale (IFN-α o IMATINIB)

**DOSE VACCINO**

5 PEPTIDI: 100µg/peptide (500µg/iniezione)
QS-21: 100µg
GM-CSF: 50µg/m²

**PIANO DI TRATTAMENTO**

6 vaccinazioni ogni 2 settimane (IMMUNIZAZIONE)

+ “richiami” ogni 4-6 mesi dal termine (MANTENIMENTO)
CMLVAX100 peptide vaccine: summary clinical results

23 patients with various degrees of cytogenetically and/or molecularly defined MRD persisting after a median time of 2 years of imatinib treatment entered the vaccination protocol.

15/23 (65%) pts measurably reduced their levels of residual disease after immunization (6 vaccinations).

6/23 (26%) pts achieved a CMR after immunization.

Clinical responses were durable and tended to improve further after boosts of vaccine.
IM SAFETY
IRIS SAEs in Years 6 and 7

No unique, previously unreported AEs attributed to imatinib observed over the past 24 months

In years 6 and 7, 13 SAEs with suspected relationship to imatinib were reported:

• Congestive Heart Failure (n=3): all of the patients had pre-existing cardiac disease prior to study entry
• Second malignancy (n=3)*
• Myositis (n=1); elevated CK (n=1); multiple sclerosis (n=1)
• Pancreatitis (n=1); vomiting (n=1)
• Renal failure (n=1)
• Dermatitis (n=1)

*With >400,000 patient years of estimated imatinib exposure, the analysis of clinical safety data from clinical trials and spontaneous reports did not provide evidence for an increased incidence of malignancies for patients treated with imatinib compared to that of the general population
The issue of cardiotoxicity

“...Here we report ten individuals who developed severe congestive heart failure while on imatinib and we show that imatinib-treated mice develop left ventricular contractile dysfunction.”
## IN REPLY TO “CARDIOTOXICITY OF THE CANCER THERAPEUTIC AGENT IMATINIB MESYLATE”

*Nature Medicine 2007; 13: 13-16*

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Pts</th>
<th>Years Pts Exposure</th>
<th>No. CHF</th>
<th>% of Pts</th>
<th>% of Years Pts Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>HATFIELD et al NOVARTIS</td>
<td>2327</td>
<td>5595</td>
<td>12</td>
<td>0.51</td>
<td>0.21</td>
</tr>
<tr>
<td>GAMBACORTI et al MILANO</td>
<td>103</td>
<td>412</td>
<td>0</td>
<td>&lt;0.97</td>
<td>&lt;0.24</td>
</tr>
<tr>
<td>ATALLAH et al M.D. ANDERSON</td>
<td>1276</td>
<td>6380</td>
<td>7*</td>
<td>0.55</td>
<td>0.11</td>
</tr>
<tr>
<td>ROSTI et al GIMEMA CML WP</td>
<td>833</td>
<td>2383</td>
<td>0**</td>
<td>&lt;0.12</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>4539</strong></td>
<td><strong>14770</strong></td>
<td><strong>19</strong></td>
<td><strong>0.42</strong></td>
<td><strong>0.13</strong></td>
</tr>
</tbody>
</table>

*22 RECORDED, 7 CONFIRMED ** 3 CASES OF MYOCARDIAL INFARCTS RCTUS*
Imatinib and pregnancy
Current Recommendations

Data still not conclusive BUT estimated risk of foetal abnormalities 7-10%

It is currently advised to avoid imatinib in pregnancy unless absolutely essential.

Women of child-bearing age receiving imatinib should take adequate contraceptive measures.

In case of accidental pregnancy, a risk-benefit evaluation on an individual basis
Exposure To Imatinib During Pregnancy

- Imatinib is teratogenic, embryotoxic (not genotoxic) and causes increased rates of post implantation loss
- Clinical trials excluded pregnant women
- Most pregnancies are unplanned
- Insufficient data available yet
- “Specific” pharmacovigilance requested
### Outcome known for 128/180 (63%)

<table>
<thead>
<tr>
<th>Pregnancy outcome</th>
<th>Total number</th>
<th>(%) with known outcome n=125</th>
<th>(%) of total n=180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Live Infant</td>
<td>63</td>
<td>50</td>
<td>35</td>
</tr>
<tr>
<td>Elective Termination*</td>
<td>35</td>
<td>28</td>
<td>19.5</td>
</tr>
<tr>
<td>Foetal Abnormality</td>
<td>12</td>
<td>9.6</td>
<td>6.7</td>
</tr>
<tr>
<td>Spontaneous Abortion</td>
<td>18</td>
<td>14.4</td>
<td>10</td>
</tr>
</tbody>
</table>

* Includes 3 terminated following identification of fetal abnormalities
Imatinib and Plasma level testing
DISTRIBUTION OF IMATINIB TROUGH LEVELS (N = 351) (IRIS STUDY)

Quartiles 2 and 3
≥647-1170 ng/mL
N=178

Quartile 1
<647 ng/mL
N=87

Quartile 4
>1170 ng/mL
N=86

Imatinib Trough Level in ng/mL (Day 29)

Imatinib Trough Levels is an independent prognostic factor for CCgR

N=297

N=54

1009±544

812±409

p=0.004 by Wilcoxon test