Introduction into CML: science and data

Gianantonio.rosti@unibo.it
Case of disease of the spleen in which death took place from suppuration of the blood. Edinburgh Medical and Surgical Journal, 1845;64:400-412

Virchow R
Weiβes Blut (Leukamie)
Archiv fur Path Anat 1847;1:563

Bennet JH
Leucocythaemia or white cell blood in relation to the physiology and the pathology of the lymphatic and glandular system. 1852 Sutherland & Knox, Edinburgh
CHRONIC MYELOGENOUS LEUKEMIA

AGE INCIDENCE, DURATION, AND BENEFIT DERIVED FROM IRRADIATION *

GEORGE R. MINOT, M.D.
THOMAS E. BUCKMAN, M.D.
AND
RAFAEL ISAACS, M.D.
BOSTON
A HISTORICAL OVERVIEW OF CML

1845  FIRST DESCRIPTION
1879  Ehrlich’s Staining Method
1924  EVOLUTION and OUTCOME
       (Minot)
1960  Ph1 CHROMOSOME (Nowell)
1973  t(9;22) (Rowley)
1984  BCR-ABL (Groffen, Konopka, Stivelman)
1990  BCR-ABL LEUKEMOGENIC IN MICE (Daley)
1996  IMATINIB (Druker)

1865  ARSENIC TRIOXIDE
1895  X-RADIATION
1955  BUSULFAN
1972  HYDROXYUREA
1979  STEM CELL Transplant
1983  INTERFERON alfa
2001  GLIVEC
Chronic Myeloid Leukemia: Epidemiology

New Cancer Cases, 2008

- Leukemias: 97%
- CML: 3%
- Other leukemias: 3%

Age-Adjusted Incidence Rate 2004-2008

- Leukemias: 87%
- CML: 13%
- Other leukemias: 4%

CML, chronic myeloid leukemia.

Etiology of CML

- CML is most probably an acquired disease, very few familial cases only
- High dose ionising radiation (e.g. Hiroshima)
- Chemical exposures to benzene, organic solvents, alkylating agents and topoisomerase II inhibitors are rarely associated with the development of CML. CML is not a “secondary leukemia”
- Very little is known about the etiology of CML
CHRONIC MYELOID LEUKEMIA, AGE AND GENDER DISTRIBUTION, AND INCIDENCE

<table>
<thead>
<tr>
<th></th>
<th>MALES</th>
<th>FEMALES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FREQUENCY</strong></td>
<td>56%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>AGE (Median, years)</strong></td>
<td>56</td>
<td>57</td>
</tr>
<tr>
<td><strong>RAW INCIDENCE (/100,000/year)</strong></td>
<td>1.12</td>
<td>0.82</td>
</tr>
</tbody>
</table>

**RAW INCIDENCE BY AGE**

- Children and adolescents: < 0.2/100,000/year
- Young adults (20-40 years old): ~ 0.4/100,000/year
- Adults (41-64 years old): ~1.4/100,000/year
- Elderly (≥ 65 years old): >2.0/100,000/year
CML, ER+SICILY, 2008-2012, M+F, n = 337
RAW INCIDENCE (x10^5/ year) BY AGE

RAW INCIDENCE / 10^5 / YEAR

<table>
<thead>
<tr>
<th>AGE (Y)</th>
<th>Raw Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-29</td>
<td>0.35</td>
</tr>
<tr>
<td>30-39</td>
<td>0.77</td>
</tr>
<tr>
<td>40-49</td>
<td>1.41</td>
</tr>
<tr>
<td>50-59</td>
<td>1.62</td>
</tr>
<tr>
<td>60-69</td>
<td>2.20</td>
</tr>
<tr>
<td>70-79</td>
<td>2.31</td>
</tr>
<tr>
<td>≥ 80</td>
<td>1.61</td>
</tr>
</tbody>
</table>
EUTOS Population-based Patients
Sex distribution by age groups

%   Male  Female

Age-groups
Identification of the Philadelphia Chromosome


ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; t(9;22), translocation of chromosomes 9 and 22.
Cromosoma Philadelphia
Rappresentazione schematica
ACTIVITY STRICTLY MONITORED

ABL

ACTIVITY STRICTLY MONITORED
bcr-abl

Gene Constitutively Activated
GCT9310

CML progression is mainly due to genetic instability

Additional genetic defects

blast crisis
CML: Natural Progression

Chronic phase
- 1%-14% BM blasts (PB or BM)
- No symptoms, or few mild symptoms
- Lasts months to years

Accelerated phase
- 15%-29% blasts (PB or BM)
- Multiple cytogenetic abnormalities
- Lasts months

Blast crisis
- ≥ 30% blasts (PB or BM)
- Blastic tumors outside of BM
- Rapidly fatal

Majority of patients diagnosed in CML-CP

BM, bone marrow; CP, chronic phase; PB, peripheral blood.

CHRONIC PHASE

BLASTIC PHASE
Proliferation and Cell cycle control

P21

BCR/ABL

P210

Grb2
Sos
Shc

RA
SHS-2

IFN

Integrin

Vinculin
Paxillin
Talin

FA

Adhesive abnormality

STATs

Crkl
Cbl
Shc

p110 P13-K

Cyclin D

E2F1

Myc

Proliferation
**Median survival**

- IFN: 76 months (69-86)
- CHT: 52 months (43-66)

**10-year survival**

- IFN: 29% (23-36)
- CHT: 17% (9-25)

\(p=0.002\)
EFFICACY AND SAFETY OF A SPECIFIC INHIBITOR OF THE BCR-ABL TYROSINE KINASE IN CHRONIC MYELOID LEUKEMIA

BRIAN J. DRUKER, M.D., MOSHE TALPAZ, M.D., DEBRA J. RESTA, R.N., BIN PENG, PH.D., ELISABETH BUCHDUNGER, PH.D.,
JOHN M. FORD, M.D., NICHOLAS B. LYDON, PH.D., HAGOP KANTARIAN, M.D., RENAUD CAPDEVILLE, M.D.,
SAYURI OHNO-JONES, B.S., AND CHARLES L. SAWYERS, M.D.
Inhibition of BCR-ABL Kinase Activity by Imatinib

IRIS STUDY, Design

Randomize

Imatinib

IFN-α + Ara-C

Crossover

- Crossover for
  - lack of response
  - loss of response
  - intolerance of treatment
Complete Cytogenetic Responses

% responding

Months since randomization

Imatinib
IFN + Ara-C

p<0.001
IRIS – OS (ITT) on Imatinib Arm

Estimated OS at 8 years was 85% (93%, considering only CML-related deaths)

BUT ONLY 55% OF PATIENTS ARE STILL ON IMATINIB

Survival of CML by therapy

N = 2784

5-year survival
TKIs: 90%
IFN: 61%
CHT: 39%

Date of diagnosis: 1970 - 2010

GIMEMA CML Working Party (formerly ICSG on CML)
Survival - CML related deaths

CML-related deaths only: death after transformation to accelerated or blastic phase or death in unknown phase, at any time

All deaths: death for any reason, at any time

<table>
<thead>
<tr>
<th>Deaths</th>
<th>N</th>
<th>Age at death, median (range)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CML-related (AP/BP)</td>
<td>32</td>
<td>60 (22-86)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Other causes (in remission)</td>
<td>33</td>
<td>69 (53-85)</td>
<td></td>
</tr>
</tbody>
</table>
CML-related survival by age groups in the TKIs cohort

P = 0.079

Overall survival by age in the TKI cohort

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Events</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–29</td>
<td>3</td>
<td>56</td>
</tr>
<tr>
<td>30–59</td>
<td>26</td>
<td>457</td>
</tr>
<tr>
<td>≥60</td>
<td>47</td>
<td>261</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>774</td>
</tr>
</tbody>
</table>

P<0.001
BCR/ABL Inhibitors

- Imatinib, *Gleevec, STI-571*
- Nilotinib, *Tasigna, AMN107*
- Dasatinib, *Sprycel, BMS-354825*
- Bosutinib, *SK-606*
PONATINIB
A PAN-BCR-ABL INHIBITOR

- Rationally designed inhibitor of BCR-ABL
- Active against T315I mutant
  - Unique approach to accommodating gatekeeper residue
- Potent activity against an array of BCR-ABL variants
- Also targets other therapeutically relevant kinases
  - Inhibits FLT3, FGFR, VEGFR and PDGFR, and c-KIT
- Once-daily oral activity in murine models

FLT3 = FMS-like tyrosine kinase receptor-3; FGFR = fibroblast growth factor receptor; VEGFR = vascular endothelial growth factor receptor
**ABL001**

*Potent allosteric inhibitor with good pharmacologic properties*

<table>
<thead>
<tr>
<th>Assay</th>
<th>ABL001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical IC$<em>{50}$, ABL$</em>{WT}$</td>
<td>1.2 nM</td>
</tr>
<tr>
<td>Cellular IC$<em>{50}$ BCR-ABL$</em>{WT}$</td>
<td>1 nM</td>
</tr>
<tr>
<td>Cellular IC$<em>{50}$ BCR-ABL$</em>{T315I}$</td>
<td>25 nM</td>
</tr>
<tr>
<td>Cellular IC$_{50}$ WT BaF/3</td>
<td>&gt;10 µM</td>
</tr>
<tr>
<td>hERG</td>
<td>&gt;30 µM</td>
</tr>
<tr>
<td>Qpatch Clamp</td>
<td>26 µM</td>
</tr>
<tr>
<td>PAMPA class, F %</td>
<td>36</td>
</tr>
<tr>
<td>CYP3A4,2D6,2C9</td>
<td>&gt;20 µM</td>
</tr>
</tbody>
</table>
CML in 2019: NEWS and CHANGES

GOAL: from survival to cure (treatment-free remission)

HIGH RISK and CCA/Ph+: from “warning” to risk-adapted treatment

MONITORING: from cytogenetics to standardized qPCR

MOLECULAR RESPONSE: from late to early, from MMR to deep MR (MR 4.0 or better)

MUTATIONS: from Sanger Sequencing to Ultra Deep or Next Generation Sequencing

T315I: from stem cell transplantation to ponatinib

FREEDOM and LIFE QUALITY: from one drug to many

COST: from GLIVEC to GENERICS