Treatment Policy

Rüdiger Hehlmann
Historic Development of CML Therapy

- **Palliative Therapy**
  - Arsenic
  - Spleen irradiation

- **Curative Therapy**
  - Busulfan
  - Hydroxyurea
  - Stem cell transplantation
  - Combination chemotherapy
  - Interferon alpha
  - Imatinib
  - Nilotinib, Dasatinib

Timeline:
- 1865
- 1903
- 1953 1964
- 1975
- 1983
- 1999
- 2005

No Therapy
Rationale for CML "guidelines"

- TKIs: paradigm shift in CML
- 1998 ASH guideline on CML Tx does not cover TKIs
- 2006
  - too early for evidence-based analysis of IM effects
  - Not too early to review available data
ELN review of CML therapy

- Review panel: 19 expert members of ELN

Scope
- Review of literature after 1998
- Panel meetings
- Discussion limited to early chronic phase (ECP)
  - More advanced phases more difficult to generalize
  - Importance of 1st line Tx strategy

Requirements
- Definition of phase, remission
- Definition of risk of progression / death
Summary of ELN expert panel "guidelines"

- Confirm value in CML Tx of
  - IM 400 mg/d
  - Allogeneic SCT

- Recommend
  - initial Tx decision to be based on established risk factors
  - For patients initially on IM
    - with Tx failure: increase dose or change Tx
    - with suboptimal response: consider increase in dose or change of Tx
  - Regular monitoring at expert centers
Review findings
Summary and update of recombinant IFNα

- rIFNa superior to conventional CT
- rIFNa + ara-C vs. rIFNa: higher CR, equal OS
- Low dose (3 MIU 3x/wk) as effective as high dose (5 MIU/m2/d) but better tolerated
- 9-10-year OS for rIFNα: 27%-53%
- 10-year OS for complete cytogenetic responders (n=317)
  - 90% (low Sokal risk)
  - 40% (high Sokal risk)
Summary and update of allogeneic SCT (1/2)

- **allo SCT in first CP**
  - 10-yr OS 60%, 10-yr EFS 50%
  - 10-yr OS 47%, 15-yr EFS 52%
  - 10-yr OS 63%, 15-yr EFS 65% (meta-analysis, n=316)

- **CIBMTR (n=4513)**
  - 18-yr OS 50% (first CP), 37% (others)
  - 18-yr cum. incidence of relapse 25% (CP), 37% (others)

- **EBMT (n=2628)**
  - 20-yr OS 34%
    - 41% for first CP, HLA-identical sibling
    - 49% for EBMT risk score 0-1
Survival Probability of Transplantation

Gratwohl et al., Haematologica 2006, 513
Summary and update of allogeneic SCT (2/2)

● EBMT (n=3142, any phase, any donor):
  – OS 72%-11% depending on risk (70%-25% for ECP)

● Improved results today due to better
  – allele matching
  – management of infections and supportive care
  – Immunosuppression

● PB stem cells not better than BM stem cells

● RIC-alloHSCT under evaluation; may permit SCT also in older patients
Summary and update of autologous SCT

- Treatment intensification with autoHSCT to achieve more remissions and prolong OS
- Meta-analysis of 6 randomized studies did not show advantage for autoHSCT
Summary and update of Imatinib (ECP)

- IM superior to rIFNa and LDAC (IRIS)
- 2 independent retrospective analyses confirmed superiority to other non-transplant Tx
- Current survival outcome in ECP better than for any other reported Tx
  - Annual rate of progression to AP/BC during 1st 4 years of Tx fairly constant (1.5%, 2.8%, 1.6%, 0.9%)
Summary Treatment Criteria

- Phase of disease
- Risk profile at diagnosis
- Transplantation risk
- Time to remission, remission quality
- Mode of resistance (Clonal evolution, IC$_{50}$ of mutants, NB: P-loop-mutants [aa 248-256] and T315I)
- Additional chromosomal abnormalities?
Principle of CML-Management

Weigh

- disease risk (phase, risk profile)
- against therapy risk (adverse effects, transplantation risk)
- Consider response
The Importance of Response Monitoring

- Hematologic (q 2 weeks until CHR)
- Cytogenetic (q 6 months until CCR)
- Molecular (q 3 months after CCR)
Reduction in BCR-ABL transcripts on IM therapy

- High frequency of CCR on IM Tx calls for measurement of MRD
- 3-log reduction from a standard baseline (MMoIR) in 50% of patients in ECP (70% of pts in CCR)
- BCR-ABL transcripts undetectable in 4%-34%
- Rate of further reduction in BCR-ABL decreases over time
- stem cells less sensitive to IM?
- Cure uncertain Tx not to be discontinued
Imatinib: $BCR-ABL$ Transcript Levels After CCR in Chronic Phase

Müller et al., Leukemia 2003, update Hochhaus
Relevance of Molecular Monitoring (RQ-PCR)

- Only method to measure residual disease after CCR
- The degree of transcript reduction has prognostic relevance (Hughes et al., NEJM 2003)
Molecular Response Definition

- Complete Transcripts undetectable
- Major BCR-ABL/ABL ratio ≤0.1

Check every 3 months, search for mutation in case of failure, suboptimal response or rising transcript level.
Relationship of Response to Tumor Load

Number of leukemic cells

- Diagnosis, Pretreatment or Hematologic Relapse
- Complete Hematologic Response
- Complete Cytogenetic Response
- Major Molecular Response
- Undetectable transcript (Complete Molecular Response)

BCR-ABL ratio (according to the International Scale)
- 10^12
- 10^11
- 10^10
- 10^9
- 10^8
- 10^7
- 10^6

BCR-ABL ratio
- 100
- 10
- 1
- 0.1
- 0.01
- 0.001
- 0.0001
Initial Treatment Options CP

- Standard dose imatinib (400 mg)

Alternatives:

- Interferon combined with HU and/or low dose AraC (ECP, standard risk only)
- High dose imatinib (experimental)
- Allografting (on patients’ request)
Criteria for Alternative Treatments

- Imatinib failure
- Suboptimal response
- Clonal evolution to AP/BC
- Resistant mutant
# Imatinib IC$_{50}$ for BCR-ABL Mutants

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Alternative Treatment Options

- Increase of imatinib dose (600-800 mg)
- New tyrosine kinase inhibitors (dasatinib, nilotinib)
- HU, AraC, (IFN)
- Combination chemotherapy
- Allografting
IM dose issues

- 600 mg/d more effective than 400 mg/d in AP/BC
- 800 mg/d can benefit some subgroups of patients
- Unclear whether higher doses will increase overall number of CCR and MMolR
- Prospective studies on high-dose IM in progress
- Lower doses not explored:
  - subtherapeutic doses may lead to resistance
  - 400 mg are well tolerated
Combination Tx

- IM 400 mg/d + pegylated rIFNα2b (50-150µg/wk) (n=77)
  - Limited compliance, high discontinuation rate with IFN
- IM 400 mg/d + LDAC (n=30)
  - CCR 70% at 1 year,
    grade 3-4 hematological toxicity 53%
- Ongoing prospective randomized studies
  - IM alone vs IM + rIFNα / LDAC / HD AC
- Synergies with IM or overcoming of IM resistance seen with several drugs (preliminary results)
IM and SCT

- IM prior to alloHSCT did not increase TRM or morbidity
- IM can control leukemia in patients relapsing after alloHSCT, molecular negativity 15/18 cases
- Synergy of IM with donor lymphocyte infusion suggested
Resistance and mutations

- Multifactorial
  - BCR-ABL mutations of kinase domain (42%-90%)
  - BCR-ABL amplification or overexpression
  - clonal evolution
  - decreased IM bioavailability or cell exposure
- Mutant subclones may not be consistently associated with subsequent relapse
- Ph+ primitive cells can harbour BCR-ABL mutations prior to IM exposure and can develop rapidly under IM pressure
- Some mutations can be overcome by dose increase or are functionally irrelevant. Interpret within clinical context!
Additional chromosome abnormalities (ACA) in Ph+ cells and other chromosome abnormalities in Ph- cells (OCA)

- ACA (clonal evolution) rare in ECP but more frequent with disease progression
- Negative relationship of ACA with IM response
- OCA in app. 5% of pts in IM-induced CCR
- Many of these in LCP, with IFN pretreatment
  - Trisomy 8 ± other abnormalities
  - del7
  - Association with MDS (particularly in del7 and/or other complex abnormalities)
- OCA may be transient; often does not end CCR
## Failure and suboptimal response: operational definition (ECP CML on IM 400 mg/d)

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<th>Failure</th>
<th>Subopt Resp</th>
<th>Warnings</th>
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<td>Dx</td>
<td>-</td>
<td>-</td>
<td>High risk Del9q+ ACA in Ph+ cells</td>
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<td>3 mos</td>
<td>No HR</td>
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<td>6 mos</td>
<td>&lt; CHR</td>
<td>&lt; PCR</td>
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<td>12 mos</td>
<td>&lt; PCR</td>
<td>&lt; CCR</td>
<td>&lt; MMolR</td>
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<td>18 mos</td>
<td>&lt; CCR</td>
<td>&lt; MMolR</td>
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<td>Loss of CHR</td>
<td>ACA in Ph+ cells</td>
<td>Any # transcr level OCA in Ph- cells</td>
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<td></td>
<td>Loss of CCR</td>
<td>Loss of MMolR Mutation (IM-insensit.)</td>
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<tr>
<td></td>
<td>Mutation (IM-insensit.)</td>
<td>Loss of MMolR Mutation (IM-insensit.)</td>
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## Failure and suboptimal response ('anytime' events)

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| Anytime | Loss of CHR ¹  
Loss of CCR ²  
Mutation ³ | ACA in Ph+ cells ⁴  
Loss of MMolR ⁴  
Mutation ⁵ | Any # transcr level  
OCA in Ph- cells |

1) confirmed on 2 occasions, unless progression to AP/BC  
2) confirmed on 2 occasions, unless CHR loss or progr. to AP/BC  
3) **High level** of insensitivity to IM  
4) confirmed on 2 occasions, unless loss of CHR or CCR  
5) **Low level** of insensitivity to IM
Failure and suboptimal response due to mutation

- Mutant subclones may not be consistently associated with subsequent relapse
- Mutations
  - can be overcome by dose increase
  - can be functionally irrelevant
- Interpret within clinical context!
Treatment policy: recommendations
ECP initial standard Tx

- Standard dose imatinib, 400 mg/d

- Alternatives
  - IFN + HU and/or low-dose Ara-C (standard risk only)
  - High dose imatinib (experimental)
  - Allografting (on patients’ request)
Preferred Tx in high-risk disease, low transplantation risk

- Trial with IM first
- Discuss choice between IM and alloHSCT with patient
- Little reason to deny IM trial, as early response to IM can reinforce or weaken indication for alloHSCT
# Preferred Tx other than IM 400 mg/d

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<th>SCT or IFN ± LD Ara-C vs. New agents</th>
<th>Shared decision-making</th>
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<td>Toxicity</td>
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<td>Failure</td>
<td>SCT or IM 600 or 800 mg/d</td>
<td>Check compliance! Rule out highly resistant mutation</td>
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<tr>
<td>Suboptimal response</td>
<td>IM 600 or 800 mg/d (SCT if low SCT risk and high disease risk)</td>
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<td>Continue IM 400 mg/d</td>
<td>Observe! Check compliance!</td>
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Treatment Choices

In case of intolerance or toxicity:

- Allografting
- IFN± LD AraC
- investigational agents
  (shared decision making)
Treatment Choices

In case of failure/resistance (check compliance!, rule out highly resistant mutation)

• Trial with imatinib 600 or 800 mg (if mildly resistant mutation)
• Trial with dasatinib or nilotinib (if available)
• Allografting
• Hydroxyurea
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Treatment Choices

In case of suboptimal response:

- Imatinib 600 or 800 mg
- Allografting, if low transplantation risk and high disease risk
Treatment Choices

In case of warnings:

- Continue imatinib 400 mg
- Observe

Check compliance!
Other scenarios

- **Patient requires IM dose reduction or frequent interruption**
  - Advise pt to adhere to 400 mg/d as far as possible
  - Provide appropriate supportive care
  - Monitor response frequently
  - Monitor IM blood level in case of failure, co-medication of drugs interfering with Cyt. p450, or drug-related SAE

- **Pt with no other Tx options**
  - Continue IM if CHR maintained; otherwise resort to HU
Summary and update of Imatinib (late CP, AP, BC)

● IM in late CP
  - CCR 41%-64%
  - 5-yr PFS 69%, 4-yr OS 86%-88%
  - Better OS than historical controls even when no CCR

● IM in AP
  - Best results at 600 mg/d: CHR 37%, CCR 19%, 3-yr PFS 40%

● IM in BC
  - CHR ca. 25%, some CCR, short PFS (<10 ms median), 3-yr OS 7%
Tx in initial AP and BC

- Treatment initially with IM

- Trial of other TKI (based on mutational analysis)

- Then proceed to allografting
CML in chronic phase 2006

- **Standard risk**
  - IFN/HU/AraC
  - ECP only
  - Failure

- **High risk low transplantation risk**
  - Imatinib
  - Failure
  - Transplantation
  - Failure
  - High dose imatinib, new drugs