CML: Prädiktion und Behandlung der fortgeschrittenen Erkrankungsphasen
Conflicts of Interest

- Advisory Board: Novartis, BMS, Pfizer, Ariad
- Honoraria: Novartis, BMS, Pfizer, Ariad
- Unrestricted Research Grant: Novartis
Life Expectancy of CML Patients in Comparison to the General Population over Time

Population-based study included 3,684 CML patients diagnosed in Sweden between 1973 and 2013; Swedish Cancer Registry

Bower H et al, JCO 2016;34:2851-58
Transformation to Accelerated Phase (AP) and Blast Crisis (BC) in CML: Facts

- Risk of transformation decreased markedly with use of TKIs
  - TKI-Era: 1 – 1.5% per Year¹
  - Pre-Imatinib Era: >20%²

- A significant minority will transform to AP or develop BC

- Only few patients present in AP (4%) or BC (2%) at diagnosis³

- Prognosis and survival in BC remained poor (7-11 months)!

- Very few long term survivors after BC (recipients of allo-transplants in 2nd CP)

# Definitions of AP and BC

## Accelerated phase

<table>
<thead>
<tr>
<th>WHO criteria</th>
<th>ELN criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Blasts in blood or marrow 10-19%</td>
<td>- Blasts in blood or marrow 15-29%, or blasts plus promyelocytes in blood or marrow &gt; 30%, with blasts &lt; 30%</td>
</tr>
<tr>
<td>- Basophils in blood ≥ 20%</td>
<td>- Basophils in blood ≥ 20%</td>
</tr>
<tr>
<td>- Persistent thrombocytopenia (&lt;100 x 10^9/L) unrelated to therapy</td>
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</tr>
<tr>
<td>- CCA/Ph+ on treatment</td>
<td>- Clonal chromosome abnormalities in Ph+ cells (CCA/Ph+), major route, on treatment</td>
</tr>
<tr>
<td>- Thrombocytosis (&gt;1000 x 10^9/L) unresponsive to therapy</td>
<td></td>
</tr>
<tr>
<td>- Increasing spleen size an increasing white blood cell count unresponsive to therapy</td>
<td></td>
</tr>
</tbody>
</table>

## Blast crisis

<table>
<thead>
<tr>
<th>WHO criteria</th>
<th>ELN criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Blasts in blood or marrow ≥ 20%</td>
<td>- Blasts in blood or marrow ≥ 30%</td>
</tr>
<tr>
<td>- Extramedullary blast proliferation, apart from spleen</td>
<td>- Extramedullary blast proliferation, apart from spleen</td>
</tr>
<tr>
<td>- Large foci or clusters of blasts in the bone marrow biopsy</td>
<td></td>
</tr>
</tbody>
</table>
Progressions are rare with TKI Therapy, less with 2ndG TKI

<table>
<thead>
<tr>
<th></th>
<th>Dasatinib 100 mg QD (n = 259)</th>
<th>Imatinib 400 mg QD (n = 260)</th>
<th>Nilotinib 300 mg BID (n = 282)</th>
<th>Nilotinib 400 mg BID (n = 281)</th>
<th>Imatinib 400 mg QD (n = 283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative MMR at 3 yr</td>
<td>68%</td>
<td>55%</td>
<td>73%</td>
<td>70%</td>
<td>53%</td>
</tr>
<tr>
<td>MR4 by 3 yr</td>
<td>35%</td>
<td>22%</td>
<td>50%</td>
<td>44%</td>
<td>26%</td>
</tr>
<tr>
<td>MR4.5 by 3 yr</td>
<td>22%</td>
<td>12%</td>
<td>32%</td>
<td>28%</td>
<td>15%</td>
</tr>
<tr>
<td>Progression to AP/BP (on study)</td>
<td>8 (3.1%)</td>
<td>13 (5%)</td>
<td>2 (0.7%)</td>
<td>3 (1.1%)</td>
<td>12 (4.2%)</td>
</tr>
<tr>
<td>36-month OS</td>
<td>93.7%</td>
<td>93.2%</td>
<td>95.1%</td>
<td>97.0%</td>
<td>94.0%</td>
</tr>
<tr>
<td>36-month PFS</td>
<td>91%</td>
<td>90.9%</td>
<td>96.9%</td>
<td>98.3%</td>
<td>94.7%</td>
</tr>
</tbody>
</table>

DASISION: Hochhaus A et al., JCO, 2012;30:418s [abstract 6504]
ENESTnd: Kantarijian HM et al., JCO, 2012;30(15s):418s [abstract 6509]
Larson RA et al., Leukemia, 2012;26:2197-2203
Therapy of CML Blast Crisis

Depends on

- Previous therapy
- Type of Blast Crisis
  - Myeloid
  - Lymphoid
- Individualized Therapy: Transplantation possible: yes vs no

Most important prognostic factor: Response to therapy; goal: Return to 2\textsuperscript{nd} CP
Survival of Patients in CML BC with Imatinib 600mg: 6 Year Follow up

Palandri F et al, Haematologica 2008;93:1792-96
2nd G TKI Dasatinib in AP and BC: PFS

Imatinib resistant or intolerant AP/BC

Accelerated Phase
median PFS: NR, 8 months follow up

Myeloid BC
median PFS: 5.0 months

Lymphoid BC
median PFS: 2.8 months

Treatment of Patients in AP with 3rdG TKI Ponatinib

B Accelerated-Phase CML

- Total (N=83)
- Resistance or side effects (N=65)
- T315I (N=18)

- Total (N=46)
- Resistance or side effects (N=37)
- T315I (N=9)

- Total (N=83)
- Resistance or side effects (N=65)
- T315I (N=18)

Cortes JE et al, NEJM 2013,369:1783-96
Treatment of Patients in BC with 3\textsuperscript{rd}G TKI Ponatinib

C Blast-Phase CML
- Total (N=62)
- Resistance or side effects (N=38)
- T315I (N=24)

Probability of Sustained Major Hematologic Response
- Total (N=19)
- Resistance or side effects (N=12)
- T315I (N=7)

Probability of Overall Survival
- Total (N=62)
- Resistance or side effects (N=38)
- T315I (N=24)

median OS: 7.0 months!

Cortes JE et al, NEJM 2013,369:1783-96
Hyper-CVAD plus Imatinib or Dasatinib in Lymphoid BC CML

n=42

CHR: 90%
CCyR: 58%
DMR: 25%
Median OS: 17 mo

Median OS: 93 vs 9 months

SCT: 18/42 pts
All in 1st CHR

p<0.001

Dasatinib

p=0.007

Strati P et al, Cancer 2014;120:373-80
Chemo (Mitoxantrone/Etoposide and AraC) plus TKI (Imatinib) in Myeloid BC CML

- Total patients: n=16
- Patients transplanted in HR: n=6

- Median OS: 16.2 mo
- Median OS: 4.7 mo
## TKI plus chemotherapy/investigational Agents in CML BC

Saußele S et Silver RT, Ann Hematol 2015; 94:S159-S165

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Patients</th>
<th>Overall survival</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frühauf et al., 2007[^50]</td>
<td>Imatinib 600, Mitox/Etop.</td>
<td>16</td>
<td>OS at 12 months 50 %</td>
<td>OR 81 %, (30 %); 6 SCT, OS without SCT 30 %</td>
</tr>
<tr>
<td>Oki et al., 2007[^51]</td>
<td>Imatinib 600, decitabine</td>
<td>28 (10 BC)</td>
<td>OS at 12 months 50 %</td>
<td>OR 50 %, CR in 33 % (20 %); responders vs non-resp. 86 vs. 16 weeks</td>
</tr>
<tr>
<td>Quintás-Cardama et al., 2007[^52]</td>
<td>Imatinib 600, araC, ida</td>
<td>19</td>
<td>OS at 12 months 48 %</td>
<td>OR 74 %, CR in 47 %</td>
</tr>
<tr>
<td>Cortes et al., 2007[^53]</td>
<td>Imatinib, Ionaafarnib</td>
<td>3</td>
<td></td>
<td>OR 75 %; hematologic improvement in 2 out of 3 pts</td>
</tr>
<tr>
<td>Fang et al., 2010[^54]</td>
<td>Imatinib, homoharringtonin</td>
<td>12</td>
<td></td>
<td>OR 100 %</td>
</tr>
<tr>
<td>Rea et al., 2006[^55]</td>
<td>Imatinib 800 mg, vincristine, dexamethasone</td>
<td>31 (Incl ALL)</td>
<td></td>
<td>HR 90 %</td>
</tr>
<tr>
<td>Deau et al., 2011[^56]</td>
<td>Imatinib 600 mg, araC, daunorubicin</td>
<td>36</td>
<td>Median OS 16 months</td>
<td>CR 55.5 %</td>
</tr>
<tr>
<td>Milojkovic et al., 2012[^57]</td>
<td>Dasatinib, FLAG-IDA</td>
<td>4</td>
<td></td>
<td>All are alive</td>
</tr>
<tr>
<td>Strati et al., 2014[^58]</td>
<td>Imatinib or dasatinib, HCVAD</td>
<td>42 (LBC)</td>
<td>Median OS 17 months</td>
<td>OR 90 %; 25 % (MMR)</td>
</tr>
<tr>
<td>Ghez et al., 2013[^59]</td>
<td>5-Azacytidine, TKI</td>
<td>5</td>
<td></td>
<td>4 Alive, median follow-up 24 months</td>
</tr>
</tbody>
</table>
5-Azacytidine plus 2ndG TKI in myeloid BC

n=5

All pts achieved a CHR
2 pts achieved a CCyR and MMR
2 pts underwent allo-Tx (1 died from relapse at 34 months)
Other 3 pts still in CHR after 15, 24 and 33 months

Update*: n=16
median follow-up: 23.1 months
CHR rate: 81.3%
Median OS, EFS, RFS: 31.5, 23.3 and 32.2 months
Five patients were bridged to allo-Tx
safe and efficient regimen
Allo-Tx in CML
Best Results in Advanced Phase: Tx after Return to 2^{nd} CP

adopted from Saußele S et al, Blood 2010; 115:1880-85
Post Tx Maintenance Therapy with TKIs

Median follow up: 3.6 years

5-yr OS for adv. CML/Ph+ ALL in CR2: 79%

CML AP/BC: n=9/11

DeFilipp Z et al, Clin Lymphoma, Myeloma & Leukemia 2016;16:466-471
**Treatment Algorithm for CML BC**

**BC at Diagnosis**
- Any TKI
  - 2nd and 3rd G TKI preferred (Mutation!)
  - consider combination with Chemo (Myeloid/Lymphoid AL Induction)

**BC under TKI**
- 2nd or 3rd G TKI (Mutation!)
  - consider combination with Chemo (Myeloid/Lymphoid AL Induction)

**Any Remission**
- Yes
  - Allo-Tx
- No
  - AL Induction

**TKI – Maintenance?**

**BC, allo-Tx not possible**
- Best available Therapy
  - Any TKI
    - 2nd or 3rd G TKI preferred (Mutation!)
    - or ………

**Investigational Agents Study**
Prediction/Prevention of AP/BC CML
Identification of patients at risk for early progression to AP/BC

- Risk scores at diagnosis:
  - Sokal\(^1\): High - intermediate - low risk group
  - Eutos\(^2\): recognizes a small group of high risk patients (Score > 87; ~12%) with a higher progression rate than low risk group when treated with a TKI

- Early Predictors:
  - Major route ACA (trisomy 8, additional Ph-chromosome, isochromosome (17q), trisomy 19)
  - p190\(^{BCR-ABL}\)
  - BMI1, CIP2A (cancerous inhibitor of PP2A) levels at diagnosis\(^3,4\)

- Not reaching defined response landmarks at 3, 6, 12, and 18 months

Influence of „major route ACA“ at Diagnosis on PFS and OS

Acquired ACAs are high risk features by ELN definition and indicate treatment failure!

Fabarius A et al, Blood 2011; 118:6760-68
Progression to AP/BC by molecular Response with Imatinib at 18 Months

Estimated rate without progression to AP/BC: 100%

Prediction of Progression to advanced Phase (AP/BC) on 2nd Line TKI Therapy

- n=113; nilotinib (n=43), dasatinib (n=70)
- Patients achieving a MCyR at 12 months (12MMCyR) have a significant survival advantage
  - Projected 1 Year progression to AP/BC: 3% vs 17%, p=0.003
- Early cytogenetic response is strongly predictive of achievement of 12MMCyR

Projected 1 Year OS:
- 97% (12MMCyR)
- 84% (miCyR or CHR)
- 88% (Hem Failure)

adopted from Tam CS, Blood 2008,112:516-518
Conclusions

- Event of AP/BC has become rare since the introduction of TKIs
- Success of treatment of AP/BC remains poor
- Goal of therapy in AP/BC: Return to 2nd CP followed by allo-Tx
- Intention: Prevention of AP/BC
Ende

Danke für die Aufmerksamkeit!