Guidelines and real World: Management of CML in chronic and advanced phases

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Some Issues in CML 2017

- First Line treatment: Imatinib vs 2nd generation TKI
- Value of early molecular response 3 and 6 months
- TKI new toxicities, non-adherence, financial burden
  - Special issues: Original drug availability: No published data on efficacy of non-branded copies.

✓ No progression to advanced phases
✓ Optimal tolerance without serious adverse events
✓ Deep response (MR 4.5): possibility of discontinuation

Patient monitoring by quantitative methods, International Scale RQ-PCR (IS) BCR-ABL
Do we follow guidelines in the Real World and outside clinical trials?

Treatment Success
3 basic points to consider

Availability of effective treatment

Treatment Adherence

40%-64% CML no adherence to 1st line, 25% discontinue adherence 3 months previous to study: young pts <50 years less adherence (p:0.004)

Optimal response monitoring

<50% patients outside clinical trials are monitored according to published guidelines. Patients with low frequency of monitoring: worse evolution.

Monitoring in the Real World

N: 1205 pts CML chronic phase. Retrospective data in US

During first 12 months of diagnosis:
-41% no molecular studies RQ PCR,
-32% only 1 or 2 studies,
-27% followed guidelines

N: 1837 CML pts. World CML Registry
3 m: CG 10%, PCR 15%
6 m: CG/PCR 39%
12 m: From 931 patients: 38% CG, 50% PCR

N: 1200 patients CML SIMPLICITY, observational study
Patients followed for 12 months: 49% (at least) 1 CG study, 83% PCR
Only 37%, 3-4 annual PCR
CG 1st year: 58% (Academic Centers) vs 39% (Community practice)
PCR: 87% vs 79%

Goldberg S. ASCO 2014
As newer, more potent, TKIs have been developed and approved over the past 15 years, the decision about which drug to use as first line therapy, and when to switch treatment in particular patients has become more complicated.

The National Comprehensive Cancer Network (NCCN) and the European LeukemiaNet (ELN) have developed treatment and monitoring guidelines to aide in the management of these patients.

The guidelines were developed by two groups of CML experts and recommendations are based on available data and expert opinion.

With adherence to the recommendations proposed by the NCCN and ELN, we can expect to continue to see excellent outcomes for our patients with CML.
Efficacy and Safety Analyses: IRIS Trial

- 48.3% continued in Imatinib frontline
- 83.3% Estimated 10 year overall survival rate (high risk Sokal 68.9% vs low 89.9%)
- 6.9% progressed to accelerated phase or blast crisis
- 92.1% Rate freedom of progression to accelerated/blast phase at 10 years

No cumulative or late toxicity
Durable efficacy at 10 years of follow up

Deep response “MR4.5” with different TKI

ENESTnd

BCR-ABL level at 3 months is a predictor of progression

DASISION 4-year follow-Up

Dasatinib 100 mg QD
84% had ≤10% BCR-ABL

Imatinib 400 mg QD
64% had ≤10% BCR-ABL

4-year PFS
≤10% = 91.8%
>10% = 67.1%  \( P=0.0004 \)

4-year PFS
≤10% = 95.2%
>10% = 70.3%  \( P<0.0001 \)

BCR-ABL at 3 months
- ≤1%
- >1-10%
- >10%

% Not Progressed
0 20 40 60 80 100
0 6 12 18 24 30 36 42 48 54 60

Months

Calculated from total number of evaluable patients with PCR assessments at 3 months.

Cortes et al. ASH 2013 Abst 653.
Fewer patients progress to advanced phases on Nilotinib vs Imatinib: ENESTnd 5 year update

Progression to Advanced phases: Accelerated and blast phase according to Sokal Risk

- All 3 progressions to AP/BC on study reported since the 4-year analysis occurred in patients with high Sokal risk scores at baseline; all 3 patients also had BCR-ABL1S > 10% at 3 months
- All progressions in patients with low/intermediate Sokal risk scores occurred during the first 2 years on study

Hochhaus et al. Leukemia. 2016 May;30(5):1044-54; Larson et al ASCO 2014 Abstract #7073; Cortes et al. ASH 2014; Abstract #154
DASISION and ENESTnd Study: Overall survival

- Superior rates of cytogenetic and molecular responses in newly diagnosed patients treated with 2\textsuperscript{nd} generation TKI.

- No Overall survival benefit has been demonstrated

<table>
<thead>
<tr>
<th></th>
<th>Overall Survival</th>
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<tbody>
<tr>
<td>DASISION 5year OS</td>
<td>91% DASATINIB 90% IMATINIB</td>
</tr>
<tr>
<td>ENESTnd 4year OS</td>
<td>94.3% NILOTINIB 600 93.3% IMATINIB</td>
</tr>
</tbody>
</table>

Off target effects and dosing

**Imatinib**
- GI Toxicity
- Edema (pleural effusions rare)
- Rash
- Myalgia
- Diarrhea
- Once/day.
  - Take with food.

**Nilotinib**
- QTc prolongation
- Lipase elevation
- **Peripheral artery occlusion**
- Take on an empty stomach q 12 hrs

**Dasatinib**
- Bleeding
- Pleural effusions
- **Pulmonary artery hypertension**
- Once/day.
  - Take with or without food.
<table>
<thead>
<tr>
<th>Time (mo)</th>
<th>Failure</th>
<th>Warning</th>
<th>Optimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>No CHR, And/or Ph+ &gt;95%</td>
<td>BCR-ABL &gt;10%, and/or Ph+ 36-95%</td>
<td>BCR-ABL ≤10%, and/or Ph+ &lt;35%</td>
</tr>
<tr>
<td>6</td>
<td>BCR-ABL &gt;10% and/or Ph+ &gt;35%</td>
<td>BCR-ABL 1-10%, and/or Ph+ 1-35%</td>
<td>BCR-ABL &lt;1%, and/or Ph+ ≤35%</td>
</tr>
<tr>
<td>12</td>
<td>BCR-ABL &gt;1% and/or Ph+ &gt;0%</td>
<td>BCR-ABL &gt;0.1-1%</td>
<td>BCR-ABL &lt;0.1%</td>
</tr>
<tr>
<td>Any</td>
<td>Loss of CHR Loss of CCyR Confirmed loss of MMR Mutations CCA/Ph+</td>
<td>CCA/Ph- (-7, or 7q-)</td>
<td>BCR-ABL &lt;0.1%</td>
</tr>
</tbody>
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Baccarani et al. Blood 2013; 122: 872-84
Intolerance/Resistance Occurs in Some Patients treated with Imatinib

Disposition of Patients After 10.9 Yrs of median Follow-up (IRIS Trial)

- 48% Discontinued frontline imatinib
- 52% Continued frontline imatinib

ELN: Mutation test Recommendations

- Chronic Phase: Mandatory in treatment “failure” Recommended in “Warning”

Advanced Phases: Previous and during treatment

## Resistance to Imatinib: Response to 2\textsuperscript{nd} line

<table>
<thead>
<tr>
<th>Response</th>
<th>Percentage</th>
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<tbody>
<tr>
<td></td>
<td>Dasatinib(^\d)</td>
</tr>
<tr>
<td>Follow Up (months)</td>
<td>&gt;24</td>
</tr>
<tr>
<td>Complete Hemat. Response</td>
<td>89</td>
</tr>
<tr>
<td>Major Cytogenetic Response</td>
<td>59</td>
</tr>
<tr>
<td>Complete cytogenetic response (0%)</td>
<td>44</td>
</tr>
<tr>
<td>24 mo PFS(^*)</td>
<td>80%</td>
</tr>
<tr>
<td>24 mo OS(^*)</td>
<td>91%</td>
</tr>
</tbody>
</table>

Survival with Ponatinib and transplant in Chronic Phase-CML with Mutation T315I

<table>
<thead>
<tr>
<th>Chronic Phase resistant 2-3 lines treated with Ponatinib</th>
<th>Major Cy Response</th>
<th>Complete Cy response</th>
<th>Major Molecular response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56%</td>
<td>46%</td>
<td>34%</td>
</tr>
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</table>

Nicolini et al, Cancer 2017 [In press]
## Treatment Strategy recommendations for Advanced Phases (ELN - NCCN)

<table>
<thead>
<tr>
<th>Accelerated Phase and Blast Phase</th>
<th>newly diagnosed: TKI naive patients</th>
</tr>
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<tbody>
<tr>
<td>Imatinib 400 mg twice daily or</td>
<td>Stem cell donor search</td>
</tr>
<tr>
<td>dasatinib 70 mg twice daily or 140 mg once daily</td>
<td>Then, allo stem cell transplant is recommended for all Blast phase and for Accelerated phase patients who do not achieve an optimal response</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy may be required before alloSCT to control the disease</td>
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</tbody>
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<table>
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<tr>
<th>Accelerated Phase and Blast Phase as progression from chronic phase in TKI pretreated patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anyone of the TKIs that were not used before progression (Ponatinib in T315I) then allo stem cell transplant in all patients</td>
</tr>
<tr>
<td>Chemotherapy is frequently required to make patients elegible for alloSCT</td>
</tr>
</tbody>
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Summary

- Multiple 1\textsuperscript{st} and 2\textsuperscript{nd} line options
- Treatment choice does not depend only of efficacy
- 10\% BCR-ABL transcript levels at early timepoints are prognostically significant
- Comorbid conditions and mutation analysis can help guide treatment choice
- Adherence to therapy is critical for optimal response
- Treatment-related adverse effects must be well managed by the clinician
- Following guidelines helps to reach better outcomes
Thank you !!

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