Venice Meeting Highlights: Key lessons

Conclusions
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CML therapy in the imatinib era

- CML prognosis has improved dramatically
- Cellular and molecular biology studies help improve prognosis and treatment
- However, Sokal / Hasford risk definition is still required to plan CML therapy:
  - age
  - spleen size
  - blood counts
  - blood differential
  prior to any treatments
Imatinib in early chronic phase CML

• IRIS study (n=1106) 54 month update: imatinib continues to show good tolerability and efficacy as first line therapy for CML

• Does CCyR to imatinib have an effect on long-term outcome?
  – Patients with a CCyR have greatest protection from progression
  – Time to achievement of CCyR within the first 12 months has no effect on EFS
  – Patients who are > 95% Ph+ at 6 mos or > 35% Ph+ (i.e. less than PCyR) at 12 mos are unlikely to achieve a CCyR
Molecular biology

- RT-Q-PCR method of choice for monitoring residual disease / measuring BCR-ABL transcripts
- Need to know absolute concentration of BCR-ABL transcripts
- Abl probably best control gene (BCR, GUS also acceptable)
- Need to assess absolute, not relative reduction in BCR-ABL

Labs differ in efficiency of RNA detection; comparability:
- compare with reference samples (centrally prepared and distributed) corresponding to 100%, 1%, 0.1%, 0.01% BCR-ABL/control gene (=international scale)
- identify BCR-ABL/control gene values corresponding to International Scale reference values
- calculate conversion factor to identify absolute log reduction
Diagnostic and Pre-treatment Work-up

Panel recommendations:

1. Spleen assessment, blood counts and differential before any treatment

2. Sokal/Hasford prognostic groups
Response-related prognostic factors: the cytogenetic response

• In early chronic phase CML
  
  – CyR at 6 mos = first relevant cytogenetic prognosticator
  
  – CCyR at 12 mos accurately predicts freedom from progression to AP/BC in >95% of patients CCyR seems to override pretherapeutic Sokal risk
Response-related prognostic factors: the cytogenetic response

• In advanced CML
  – The more advanced the disease the less protection is afforded by CCyR
  • In AP and BC, even CCyR should not be used as the basis to delay allogeneic transplant if this is an option
  • In late CP more rapid achievement of CCyR may be associated with superior PFS
Response-related prognostic factors: the molecular response

- Although small, a risk of losing MMolR exists
- The probability to achieve MMolR correlates to Sokal risk
- High or intermediate risk patients achieving MMolR have a risk of subsequent progression as small as low risk patients
- Shorter time to MMolR may improve prognosis
- Most patients stopping imatinib therapy relapse, even when PCR negative
- BCR-ABL transcript levels to trigger search for mutation:
  - 2-fold rise? (Branford et al., Blood 2004)
  - consecutive rises? (Wang et al., Haematologica 2006)
Bcr-Abl Kinase Domain Mutations

- Frequency of imatinib resistance depends on stage of CML
- Major causes of resistance: BCR-ABL mutations and clonal evolution
- Prospective evaluation needed
- Some BCR-ABL mutations impair prognosis more than others, in particular on continuous imatinib therapy
- Early identification of imminent resistance might contribute to individualized therapy based on molecular data
Response Definition, Evaluation and Monitoring

- **Failure**: continuing imatinib treatment at the current dose is no longer appropriate for the patient, who would likely benefit more from other treatments.

- **Suboptimal response**: the patient may still have a substantial benefit from continuing imatinib at the current dose, but long-term outcome of the treatment would not likely be favorable. The patient is eligible for other treatments.

- **Warnings**: standard dose imatinib may not be the best choice. The case requires more careful monitoring. The patient may become eligible for other treatments.
### Failure and suboptimal response: operational definition (ECP CML on IM 400 mg/d)

<table>
<thead>
<tr>
<th>Time</th>
<th>Failure</th>
<th>Subopt Resp</th>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dx</td>
<td>-</td>
<td>-</td>
<td>High risk Del9q+ ACA in Ph+ cells</td>
</tr>
<tr>
<td>3 mos</td>
<td>No HR</td>
<td>&lt; CHR</td>
<td>&lt; MMolR</td>
</tr>
<tr>
<td>6 mos</td>
<td>&lt; CHR, No CR</td>
<td>&lt; PCR</td>
<td></td>
</tr>
<tr>
<td>12 mos</td>
<td>&lt; PCR</td>
<td>&lt; CCR</td>
<td></td>
</tr>
<tr>
<td>18 mos</td>
<td>&lt; CCR</td>
<td>&lt; MMolR</td>
<td></td>
</tr>
<tr>
<td>Anytime</td>
<td>Loss of CHR, Loss of CCR, Mutation (IM-insensit.)</td>
<td>ACA in Ph+ cells, Loss of MMolR Mutation (IM-insensit.)</td>
<td>Any # transcr level OCA in Ph- cells</td>
</tr>
</tbody>
</table>

**Subopt Resp**:
- Any time: ACA in Ph+ cells, Loss of MMolR, Mutation (IM-insensit.)
- 18 mos: < PCR
- 12 mos: < CCR
- 6 mos: < CHR
- Dx: -

**Warnings**: High risk Del9q+ ACA in Ph+ cells, Any # transcr level OCA in Ph- cells
## Monitoring response

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>(x)</td>
<td>x</td>
<td>x</td>
<td>q 6-12 mo (marrow)</td>
</tr>
<tr>
<td>RT-Q-PCR</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

*FISH should be done before treatment (del9 q+) and can be used during treatment if conventional cytogenetics fail or cannot be obtained

Mutational analysis only in case of failure, suboptimal response, or sustained – confirmed increase of bcr-abl transcripts level
Treatment Policy

- Early chronic phase: initial therapy
  - Standard dose imatinib, 400 mg/d
- Alternatives
  - IFN + HU and/or low-dose Ara-C (standard risk only)
  - High dose imatinib (experimental)
  - Allografting
  - 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
## Treatment Policy: Alternative therapies and indications

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

- **Intolerance**: Consider alternative therapies and shared decision-making.
- **Failure**: Consider SCT or IM 600 or 800 mg/d and rule out highly resistant mutations.
- **Suboptimal response**: Continue IM 400 mg/d.
- **Toxicity**: IM 600 or 800 mg/d with consideration for SCT if low SCT risk and high disease risk.
- **'Warnings'**: Observe and check compliance.

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**Note**: The table outlines the treatment options and considerations for different outcomes, emphasizing the importance of shared decision-making and monitoring for compliance and potential resistance.
Evolving Concepts in the Management of Chronic Myeloid Leukemia

Recommendations from an Expert Panel on Behalf of the European LeukemiaNet