Diagnostic and Pre-treatment Work-up

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Chronic Myelogenous Leukemia

Diagnosis and pre-treatment work-up

Guidelines

Expert recommendations
3 parts

• Diagnosis

• Pre therapeutic assessment

• Staging and prognosis
DIAGNOSIS

- Spleen
- Blood smear
- Bcr-Abl rearrangement

Quantitative reverse transcriptase polymerase chain reaction (RT-PCR)

FISH
Cytogenetics - FISH

• Bone marrow aspiration for cytogenetics

• FISH on peripheral blood
  – Dual probes for BCR and ABL genes
  – Detection of cytogenetically « silent » BCR-ABL rearrangements
  – Deletion in the derivative 9q+ (prognostic)
Cytogenetics

Clonal evolution
  - second Ph chromosome
  - trisomy 8
  - isochromosome 17
  - trisomy 19

- Y, +21, +17, -7

Major route
Relationship between chromosome abnormalities and outcome

- Lower cytogenetic response rate
- Higher hematologic relapse rate (50% versus 9%)
- Shorter overall survival (90% versus 75% at 2 years)
Figure 1. Survival of patients in chronic phase, with cytogenetic clonal evolution only, and in accelerated phase with or without cytogenetic clonal evolution.
BONE MARROW BIOPSY

fibrosis

CELLS

DNA

RNA

For subsequent analysis
Fibrosis and response to Imatinib

110 patients post-IFN failure, chronic phase
67 (61%) severe reticulin (grade 3-4) fibrosis

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<thead>
<tr>
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<th>Yes</th>
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<tbody>
<tr>
<td>Complete cytogenetic response</td>
<td>67 %</td>
<td>58 %</td>
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<tr>
<td>4 year survival rates</td>
<td>80 %</td>
<td>88 %</td>
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<tr>
<td>Failure free survival rates</td>
<td>69 %</td>
<td>77 %</td>
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(Leukemia Lymphoma, 2005)
Myelofibrosis in early chronic phase

198 patients
75 patients (38 %) severe reticulin (grade 3-4) fibrosis

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<th>Yes</th>
<th>No</th>
<th>p-value</th>
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<tr>
<td>Complete cytogenetic</td>
<td>76 %</td>
<td>89 %</td>
<td>0.07</td>
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<td>response</td>
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<td>3 year survival rates</td>
<td>87 %</td>
<td>97 %</td>
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15 % of patients with grade 4 = worse outcome

(Cancer, 2005)
Before starting the treatment with Imatinib

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<td>Bcr-Abl transcript level</td>
<td></td>
<td>* point mutation</td>
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<tr>
<td>% of BM Ph + cells</td>
<td></td>
<td>* Crkl phosphorylation</td>
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<td></td>
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<td>* genomic profile</td>
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<tr>
<td></td>
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<td>* Wilms tumor gene expression</td>
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<tr>
<td>9q+</td>
<td></td>
<td>* phosphotyrosine levels in CD34+ cells</td>
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<td>Bone marrow biopsy</td>
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Warning situation

- High risk patients
- Additional chromosomal abnormalities
- 9q+

Warnings imply that the patient should be monitored very carefully and may become eligible for other treatments.
Pre therapeutic assessment

- Performance status
- Relevant past medical history (psychiatric disorder)
- Biochemistry (renal and liver functions)
- Platelet dysfunction
- Concomitant medications
3 phases

Chronic phase

Accelerated phase

Blastic phase

⇒ Physical exam
⇒ Peripheral blood count ; differential
⇒ Bone marrow aspiration
⇒ Cytogenetic analysis
⇒ Scan. = spleen size
Conclusion: panel recommendations

1. Spleen assessment, complete blood test before any treatment

2. Sokal/Hasford prognostic subcategories

3. Bone marrow aspiration with cytogenetic analysis

4. Cases with warning features
Evolving Concepts in the Management of Chronic Myeloid Leukemia

Recommendations from an Expert Panel on Behalf of the European LeukemiaNet