European LeukemiaNet
Developing stratified diagnostic and treatment approaches

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Content

Short introduction on ELN

Overview on Guidelines

Impact on Health Care
194 centers in 39 countries
- 114 national leukemia study groups
- 109 interdisciplinary partner groups
- 1000 physicians and scientists
- Caring for ten thousands of patients
European LeukemiaNet

concerns: all leukemias with all interdisciplinary partner groups

Interdisciplinary Integration

WP 10-12

basic scientists

exchange & integration at all research activities & scientific meetings

WP 4-9

clinicians

WP 14, 15

pharmaceutical industry biotech companies small & medium enterprises

WP 13

Management Recommendations in CML

- One of the 50 most cited papers of JCO
- 20,000 pocket cards distributed
Improvement of survival of CML by therapy
1983 – 2011

German CML Study Group

Year after diagnosis

Survival propbability

n = 3615

Imatinib, 2002 – 2011 (CML IV)
5-year survival 90%
8-year survival 88%

IFN or SCT, 1997 – 2003
(CML IIIA) 5-year survival 71%

IFN or SCT, 1995 – 2001 (CML III)
5-year survival 63%

IFN, 1986 – 1994
5-year survival 53%

Hydroxyurea, 1983 – 1994, 5 yr surv. 44%

Busulfan, 1983 – 1994 5-year survival 38%
BCR-ABL kinase domain mutation analysis in CML patients treated with TKI: recommendations from an expert panel of ELN

Multicentre validation of a reproducible flow cytometric score for the diagnosis of low-risk MDS

This score may help establish MDS diagnosis especially when morphology and cytogenetics are indeterminate

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**Table 3.** Calculation of the flow cytometric score (FCM-score) for the diagnosis of low-risk MDS.

<table>
<thead>
<tr>
<th>Cytometric Parameter</th>
<th>Cut-off values</th>
<th>Regression coefficient</th>
<th>Variable weighted score #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloblast-related cluster size (%)*</td>
<td>≥2</td>
<td>2.59</td>
<td>1</td>
</tr>
<tr>
<td>B-progenitor-related cluster size (%)**</td>
<td>≤5</td>
<td>1.87</td>
<td>1</td>
</tr>
<tr>
<td>Lympocytes to myeloblasts CD45 ratio</td>
<td>≤4 or ≥7.5</td>
<td>1.76</td>
<td>1</td>
</tr>
<tr>
<td>Granulocytes to lymphocytes SSC ratio</td>
<td>≤6</td>
<td>2.31</td>
<td>1</td>
</tr>
</tbody>
</table>

* in all nucleated cells; ** in all CD34+ cells; # a diagnosis of MDS is formulated in presence of a FCM-score value ≥2.
### Recommended minimal requirements to assess dysplasia in MDS by FC

<table>
<thead>
<tr>
<th>Bone marrow subset</th>
<th>Recommended analyses</th>
<th>Aberrancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immature myeloid and monocytic progenitors</td>
<td>Percentage of cells in nucleated cell fraction&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Increased percentage</td>
</tr>
<tr>
<td></td>
<td>Expression of CD45</td>
<td>Lack of/decreased/increased</td>
</tr>
<tr>
<td></td>
<td>Expression of CD34</td>
<td>Lack of/decreased/increased</td>
</tr>
<tr>
<td></td>
<td>Expression of CD117</td>
<td>Homogenous under/overexpression</td>
</tr>
<tr>
<td></td>
<td>Expression of HLA-DR</td>
<td>Lack of/increased expression</td>
</tr>
<tr>
<td></td>
<td>Expression of CD13 and CD33</td>
<td>Lack of/decreased/increased</td>
</tr>
<tr>
<td></td>
<td>Asynchronous expression of CD11b, CD15</td>
<td>Presence of mature markers</td>
</tr>
<tr>
<td></td>
<td>Expression of CD5, CD7, CD19, CD56&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Presence of lineage infidelity markers</td>
</tr>
<tr>
<td>Maturing neutrophils</td>
<td>Percentage of cells as ratio to lymphocytes</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>SSC as ratio vs SSC of lymphocytes</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>Relationship of CD13 and CD11b</td>
<td>Altered pattern&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Relationship of CD13 and CD16</td>
<td>Altered pattern&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Relationship of CD15 and CD10</td>
<td>Altered pattern&lt;sup&gt;f&lt;/sup&gt;; for example, lack of CD10 on mature neutrophils</td>
</tr>
<tr>
<td>Monocytes</td>
<td>Percentage of cells</td>
<td>Decreased/increased</td>
</tr>
<tr>
<td></td>
<td>Distribution of maturation stages</td>
<td>Shift towards immature</td>
</tr>
<tr>
<td></td>
<td>Relationship of HLA-DR and CD11b</td>
<td>Altered pattern&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Relationship of CD36 and CD14</td>
<td>Altered pattern&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Expression of CD13 and CD33</td>
<td>(Homogenous) under/overexpression</td>
</tr>
<tr>
<td></td>
<td>Expression of CD56&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Presence of lineage infidelity marker</td>
</tr>
<tr>
<td>Progenitor B cells</td>
<td>Enumeration as fraction of total CD34+ based on CD45/CD34/SSC in combination with CD10 or CD19</td>
<td>Decreased or absent</td>
</tr>
<tr>
<td>Erythroid compartment&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Percentage of nucleated erythroid cells</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td>Relationship CD71 and CD235a</td>
<td>Altered pattern&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Expression of CD71</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>Expression of CD36</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>Percentage of CD117-positive precursors</td>
<td>Increased</td>
</tr>
</tbody>
</table>

<sup>a</sup> Percentage of cells in nucleated cell fraction is measured using flow cytometry.

<sup>b</sup> CD56 expression is assessed by flow cytometry.

<sup>c</sup> Progenitor B cells are studied by analyzing the enumeration of B cells using flow cytometry.

<sup>d</sup> Erythroid compartment data is collected by evaluating the percentage of nucleated erythroid cells.
AML Intergroup study - Overall survival (n = 3106)

Standard treatment arm, 5-year survival probability: 44.3 [37.7; 50.7]

Study A: 5-year survival probability: 41.4 [36.9; 45.8]
Study B: 5-year survival probability: 46.6 [41.1; 51.8]
Study C: 5-year survival probability: 47.5 [40.1; 54.6]
Study D: 5-year survival probability: 43.6 [39.6; 47.6]
Study E: 5-year survival probability: 46.4 [41.0; 51.7]

n = 3106 patients, 1542 events
Model for interconnecting AML registries

Automatized
Core Data Transfer

Population-based
Swedish Registry

Trial-based
AMLSG

Trial-based
AMLCG/SAL

Trial-based
HOVON/SAKK

Permitted
Data Access

Core-data Registry Tool

Population-based
Swedish Registry

Trial-based
AMLSG

Trial-based
AMLCG/SAL

Trial-based
HOVON/SAKK

Trial-based
MRC
Signatures and molecular markers in AML-NK

Marker
- NPM1+, CEBPAwt
- NPM1wt, CEBPA+
- NPM1wt, CEBPAwt

Ellipsoid
- NPM1 wild type
- NPM1 mutated
- CEBPA mutated

Kohlmann et al., Leukemia; 24(6):1216-20, 2010
Signatures and molecular markers in AML-NK

NPM1
- wild type
- mutated

CEBPA
- wild type
- mutated

cases: n=233
genes: n=461

Kohlmann et al., Leukemia; 24(6):1216-20, 2010 [29]
Complete study database uploaded to GEO repository

All CEL files available (n = 3248)

Individual rows of gene expression values:

GSE13204

114,888,960
Myelofibrosis

JAK Inhibition with Ruxolitinib versus Best Available Therapy - Changes in Spleen Volume

Figure 1. Changes in Spleen Volume and Spleen Length, According to Treatment Group. Panel A shows the percentage of patients in the efficacy-analysis population (all patients who underwent randomization and had both a baseline measurement and at least one subsequent assessment) who had a reduction in spleen volume of at least 35% from the baseline volume, as assessed by magnetic resonance imaging (MRI) or computed tomography (CT) at 48 weeks. Panel B shows the best percentage change from baseline in spleen volume, as assessed by MRI or CT, at any time within the first 48 weeks of treatment, among patients with a baseline assessment and at least one subsequent assessment. Data are shown for individual patients. Panel C shows the median length of time that a reduction of at least 35% in spleen volume, as assessed by MRI or CT, was maintained, among patients who were continuously receiving ruxolitinib. Patients were considered to have had a loss of response (event) if the spleen volume was no longer reduced by at least 35% from the baseline volume and was increased by 25% or more from the nadir. Data from patients who did not have an assessment subsequent to the baseline assessment, or who were still having a response at the time of cutoff of the data, were censored. Panel D shows the mean percentage change from baseline in palpable spleen length over time. I bars represent standard errors. BAT denotes best available therapy.
Critical concepts and management recommendations on Philadelphia-negative classical MPNs

Continuous ruxolitinib therapy, as compared with the best available therapy, was associated with marked and durable reductions in splenomegaly and disease-related symptoms, improvements in role functioning and quality of life, and modest toxic effects. An influence on overall survival has not yet been shown.

➢ With the introduction of JAK2 inhibitors study design with relevant endpoints is critical

➢ The WP works on outcome definition and related issues
Development of standardized approaches to reporting of MRD data using a reporting software package

- Differences in data analysis and presentation complicate multicenter clinical trials
- A highly flexible MRD-reporting software program was designed
- Data from various qPCR platforms can be imported, processed, and presented in a uniform manner. The software was tested in a two-step quality control study.
Summary

• The ELN combines 108 national leukemia study groups and 105 partner groups within 38 countries building a network of more than 1000 scientists and physicians

• 184 studies are listed within the ELTR of which 93 are active

• More than 40 guidelines and treatment recommendations have been published with major impact on diagnostics and treatment of leukemia patients

• Multiple projects of this network received additional funding (e.g. EUTOS, ESF support, COST program); in total >40 Mio Euro