Chronic myelogenous leukemia: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence
The incidence of chronic myeloid leukemia (CML) is reported between 1 and 2 cases/100 000/year, without major geographic differences. Median age at diagnosis is close to 60 years.

diagnosis
Diagnosis is based on blood counts (leukocytosis and frequently also thrombocytosis) and differential (immature granulocytes, from the metamyelocyte to the myeloblast, and basophilia). Splenomegaly is present in >50% of cases of CML in the initial chronic phase, but ~50% of patients are asymptomatic.

Proof of diagnosis is attained by demonstration of the Philadelphia (Ph) chromosome (22q–) resulting from the balanced translocation t(9; 22) (q34;q11), and/or the BCR–ABL rearrangement in peripheral blood or bone marrow cells. In some cases (~5%) a Ph chromosome cannot be detected and confirmation of diagnosis rests on molecular genetic methods, e.g. fluorescence in situ hybridization or reverse transcription–polymerase chain reaction (RT–PCR). Screening for BCR–ABL KD mutations is especially recommended in acceleration and/or blast crisis (for definition see below).

staging and risk assessment
More than 90% of patients are diagnosed in chronic phase (CP). The typical clinical course is triphasic: CP, accelerated phase (AP) and blastic phase (BP) or blast crisis (BC). The most accepted definition of AP is 15%–29% blasts in blood or bone marrow, >20% basophils in blood, thrombocytosis or thrombocytopenia unrelated to therapy, or clonal cytogenetic evolution. Similarly, the BP/BC of the disease is characterized by ≥30% blasts in blood or bone marrow or extramedullary blastic infiltration.

Prognostic scores based on age, spleen size, blood cell counts and differential have been established in the pre-imatinib era and allow the discrimination of risk groups with a different response rate, progression-free survival and overall survival.

The degree and time points of hematologic, cytogenetic and molecular responses provide very important prognostic information as time-dependent variables (Table 1).

treatment
Imatinib is the current standard approach. On the basis of a randomized trial of imatinib, a selective ABL tyrosine kinase inhibitor (TKI), versus interferon (IFN)–α and low-dose arabinosyl cytosine (IRIS study), imatinib 400 mg daily has been established as standard front-line treatment of all patients with CP CML. The update of the IRIS study reported a progression-free survival of 84% and an overall survival of 88% after 6 years. Other comparisons of imatinib with IFN–α provide clear evidence of the superiority of imatinib also with regard to survival.

Outcome after allogeneic stem cell transplantation (SCT) in the first-line therapy is inferior because of transplant-related mortality. Thus, initial allogeneic SCT cannot be recommended anymore.

IFN–α is currently tested in combination with imatinib in phase III prospective studies. Hydroxyurea is recommended only for initial cytoreduction or therapeutic palliation, since imatinib is also superior in the elderly.

response evaluation
The response to imatinib (standard dose, 400 mg daily) may fall into three categories, namely optimal, suboptimal and failure (Table 1):

- In case of ‘optimal response’, imatinib should be continued indefinitely. The patients who achieve a complete molecular
Table 1. Definition of response to imatinib (modified, from ref. 1)

<table>
<thead>
<tr>
<th>Optimal</th>
<th>Suboptimal</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Months</td>
<td>CHR</td>
<td>&lt; CHR</td>
</tr>
<tr>
<td>6 Months</td>
<td>≥ PCgR</td>
<td>&lt; PCgR</td>
</tr>
<tr>
<td>12 Months</td>
<td>≥ CCgR</td>
<td>&lt; CCgR</td>
</tr>
<tr>
<td>18 Months</td>
<td>≥ MMolR</td>
<td>&lt; MMolR</td>
</tr>
<tr>
<td>Anytime</td>
<td>No response</td>
<td>Loss of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MMolR Mutations*</td>
</tr>
</tbody>
</table>

*BCR–ABL KD mutations still sensitive to imatinib.

1. BCR–ABL KD mutations insensitive to imatinib.

CHR, complete hematologic response (white blood cells <10 × 10^9/l, differential with no immature granulocytes and ≤5% basophils, platelets <450 × 10^9/l, spleen non-palpable); PCgR, partial cytogenetic response (Ph+ metaphases 1%–35%); CCgR, complete cytogenetic response (Ph+ metaphases absent); MMolR, major molecular response (BCR–ABL:ABL <0.1% by International Scale on RT-Q-PCR).

Response [BCR–ABL undetectable by real-time, quantitative PCR (RT-Q-PCR)] can be eligible for prospective trials of treatment discontinuation or of immunotherapy with IFN-α or vaccines, to eliminate minimal residual disease.

In case of ‘suboptimal response’ to imatinib, the best treatment option is still a matter of investigation. The patient can be continued on imatinib at a higher dose, but is also eligible for a second generation TKI.

In case of ‘failure’, second-line treatment is based on second generation TKI, namely dasatinib and nilotinib. About 50% of CP patients resistant or intolerant of imatinib achieve a complete cytogenetic response (CCgR) with either agent, but both agents are ineffective in case of a T315I BCR–ABL kinase domain (KD) mutation. The response to either agent is usually rapid and within 6 months it may be possible to decide to continue with the second generation TKI or to move to allogeneic SCT, if the patient is eligible. Currently, the eligibility criteria for SCT have been expanded by the extended use of reduced conditioning or non-myeloablative procedures and by the availability of alternative stem cell sources, including cord blood.

Once a patient has progressed to AP or BP/BC, treatment depends on prior treatment and may include other TKIs, other experimental targeted agents (e.g. homoharringtonine) or cytotoxic chemotherapy. An allogeneic SCT consolidation should be performed whenever possible.

follow-up (monitoring)

Monitoring is essential for treatment optimization and a cost-effective outcome. During the first 3 months, clinical, biochemical and hematologic monitoring is recommended every 2 weeks. From month 3 on, cytogenetics (chromosome banding analysis of marrow cell metaphases) is recommended at least every 6 months until a CCgR has been achieved and confirmed.

Real-time, quantitative PCR (RT-Q-PCR) (BCR–ABL:ABL %, on blood cells) is recommended every 3 months until a major molecular response (MMolR) has been achieved and confirmed.

Once a CCgR and a MMolR have been achieved and confirmed, cytogenetics can be performed every 12 months and RT-Q-PCR every 6 months. If the patients was high risk by Sokal, or was a suboptimal responder, more frequent monitoring is advisable.

Screening for BCR–ABL KD mutations is recommended only in case of failure or suboptimal response.

Measuring imatinib blood concentration may be important in all patients and is recommended in case of suboptimal response, failure, dose-limiting toxicity or adverse events. Standardization of molecular monitoring and of imatinib blood concentration assays is underway in Europe, based on a project of the European Leukemia Network (The European Treatment and Outcome Study of CML).

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

literature


