Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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incidence

The incidence of chronic myeloid leukaemia (CML) is reported as between 1 and 2 cases/100 000/year, without major geographical differences. Median age at diagnosis is close to 60–65 years.

diagnosis

In most cases, 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 (CP), 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. fluorescent in situ hybridization (FISH), or reverse transcriptase–polymerase chain reaction (RT–PCR).

staging and risk assessment

More than 90% of patients are diagnosed in CP. The typical clinical course is triphasic: CP, accelerated phase (AP) and blastic phase (BP) or blast crisis (BC). AP is defined by 15%–29% blasts in blood or bone marrow, >20% basophils in blood, thrombocytosis, thrombocytopenia unrelated to therapy or clonal chromosome abnormalities in the Ph+ clone (CCA/Ph+). 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 from large patient population in the pre-imatinib era, but still allow the discrimination of risk groups with a different prognosis, i.e. with a different response rate, a different progression-free survival and a different overall survival, also for patients treated with imatinib.

The degree and timing of haematologic, cytogenetic and molecular responses provide very important prognostic information as time-dependent variables. In particular, the prognostic importance of complete cytogenetic response (CCgR) has been confirmed.

treatment

Drug treatment is superior to allogeneic stem cell transplantation (SCT) in first-line therapy of CML, because of transplant-related mortality. Thus, initial allogeneic SCT cannot be recommended anymore.

On the basis of a randomized trial of imatinib, which is a selective ABL tyrosine kinase inhibitor (TKI), versus interferon-α (IFNα) and low-dose cytarabine (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 has confirmed and extended the earlier results, reporting a progression-free survival of 84% and an overall survival of 88% after 6 years.

The initial standard dose of imatinib is 400 mg daily. Outside a clinical trial, there is no indication to use a higher dose e.g. of 600 or 800 mg, as two prospective randomized studies have failed to show a superiority of 800 mg over 400 mg. IFNα monotherapy can no longer be recommended, but combination of IFN with imatinib is currently being tested in phase III prospective studies.
Hydroxyurea can no longer be recommended, unless for short periods of time or therapeutic palliation. In particular, the practice of prescribing hydroxyurea in the elderly has no basis, since imatinib is effective irrespective of age.

**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. The patients who achieve a complete molecular 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 IFNα or vaccines, to eliminate minimal residual disease.

In case of ‘failure’, second-line treatment is based on second-generation TKI dependent on the identified BCR-ABL mutation, namely dasatinib (also known as BMS 354825; Sprycel, Bristol-Myers Squibb) and nilotinib (also known as AMN107; Tasigna, Novartis Pharma). About 50% of CP patients resistant or intolerant to imatinib achieve a CCgR with either agent, but both agents are ineffective in the 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 into three categories, namely optimal, suboptimal and failure (Table 1).

In the case of ‘suboptimal response’ to imatinib, which frequently represents a transitory state, the best treatment option is still a matter of investigation. The patients can be continued on imatinib, same dose or higher dose, but are also eligible for a trial with a second-generation TKI. In any case, these patients should be referred to a centre with high expertise in the treatment of CML patients.

**Table 1. Definition of response to imatinib**

<table>
<thead>
<tr>
<th></th>
<th>Optimal</th>
<th>Suboptimal</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>CHR</td>
<td>&lt;CHR</td>
<td>No HR</td>
</tr>
<tr>
<td>6 months</td>
<td>2PCgR</td>
<td>&lt;PCgR</td>
<td>No CGR</td>
</tr>
<tr>
<td>12 months</td>
<td>CCgR</td>
<td>&lt;CCgR</td>
<td>&lt;PCgR</td>
</tr>
<tr>
<td>18 months</td>
<td>2MMoIR</td>
<td>&lt;MMoIR</td>
<td>&lt;CCgR</td>
</tr>
<tr>
<td>Any time</td>
<td>No response loss</td>
<td>Loss of MMoIR</td>
<td>Loss of CHR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mutations*</td>
<td>Loss of CGR</td>
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<tr>
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Modified from ref. 1.

CHR, complete haematological response (WBC <10×10⁹/l, differential with no immature granulocytes and <5% basophils, platelet <450×10⁹/l, spleen non palpable); PCgR, partial cytogenetic response (Ph+ metaphases 1%–35%); CCgR, complete cytogenetic response (Ph+ metaphases absent); MMoIR, major molecular response (BCR-ABL-ABL <0.1% by International Scale, on RT-Q-PCR).

*BCR-ABL KD mutations still sensitive to imatinib.

Once a patient has progressed to AP or BP/BC, further treatment depends on prior treatment, and may include other TKIs, different from those used in CP, other experimental targeted agents, homocetaxine or cytotoxic chemotherapy, always with the purpose of performing an allogeneic SCT, whenever it may be possible.

**follow-up (monitoring)**

Monitoring is essential for treatment optimization and for a cost-effective outcome. At the beginning, and during the first 3 months, clinical, biochemical and haematological monitoring is recommended every 2 weeks, to ensure the compliance of the patient. From the third month on, cytogenetics (chromosome banding analysis of marrow cell metaphases) is recommended at least every 6 months until a CCgR has been achieved and confirmed, and RT-Q-PCR (BCR-ABL/ABL %, on blood cells) is recommended every 3 months until a MMoIR has been achieved and confirmed. Once a CCgR and a MMoIR have been achieved and confirmed, cytogenetics can be performed every 12 months and RT-Q-PCR every 6 months, but 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 the case of failure or suboptimal response. Measuring imatinib concentration in the peripheral blood is recommended only in the case of suboptimal response, failure, dose-limiting toxicity or adverse events.

**literature**


