European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013

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Advances in chronic myeloid leukemia treatment, particularly regarding tyrosine kinase inhibitors, mandate regular updating of concepts and management. A European LeukemiaNet expert panel reviewed prior and new studies to update recommendations made in 2009. We recommend as initial treatment imatinib, nilotinib, or dasatinib. Response is assessed with standardized real quantitative polymerase chain reaction and/or cytogenetics at 3, 6, and 12 months. BCR-ABL1 transcript levels ≤10% at 3 months, <1% at 6 months, and ≤0.1% from 12 months onward define optimal response, whereas >10% at 6 months and >1% from 12 months onward define failure, mandating a change in treatment. Similarly, partial cytogenetic response (PCyR) at 3 months and complete cytogenetic response (CCyR) from 6 months onward define optimal response, whereas no CyR (Philadelphia chromosome–positive [Ph+] >95%) at 3 months, less than PCyR at 6 months, and less than CCyR from 12 months onward define failure. Between optimal and failure, there is an intermediate warning zone requiring more frequent monitoring. Similar definitions are provided for response to second-line therapy. Specific recommendations are made for patients in the accelerated and blastic phases, and for allogeneic stem cell transplantation. Optimal responders should continue therapy indefinitely, with careful surveillance, or they can be enrolled in controlled studies of treatment discontinuation once a deeper molecular response is achieved. (BLOOD. 2013;122(6):872-884)

Introduction

The management of Ph+, BCR-ABL1+ chronic myeloid leukemia (CML) has undergone a profound evolution over a relatively short period of time, starting with allogeneic stem cell transplantation (alloSCT) and recombinant interferon-alfa (rIFNα), and more recently and most significantly, with the tyrosine kinase inhibitors (TKIs).1-3 To ensure the best possible duration and quality of life for a given patient, and to avoid unnecessary complications and potentially achieve a cure, physicians and patients also must understand the proper use of available drugs, the significance of disease end points, the critical importance of monitoring, and, in some cases, the use of alloSCT as appropriate therapy. European LeukemiaNet (ELN) had proposed recommendations for the management of CML in 2006 and 2009.4,5 These were the third version of these recommendations based on data gained from new studies as well as from the update of the most relevant previous studies. We discuss and make recommendations about which TKI should be used as first-line and as second-line therapy, the important end points of treatment, the best approach of evaluating and


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monitoring response, the reporting and interpretation of molecular and cytogenetic tests, the information provided by mutational analysis, the importance of side effects, and the role of allosCT.

Methods

The composition of the ELN panel for recommendations in CML was increased to include 32 experts from Europe, America, and the Asian-Pacific areas. The panel met 4 times, at international meetings of the American Society of Hematology (ASH) in 2011 (San Diego, CA), the European Haematology Association (EHA) in 2012 (Amsterdam, The Netherlands), the European School of Haematology/International CML Foundation in 2012 (Baltimore, MD), and ASH 2012 (Atlanta, GA). Before each meeting, a set of questions was submitted to panel members, and the agenda of the meetings was based on a summary and analysis of the answers from all panel members. After 4 meetings, discordant opinions were harmonized and consensus was reached for all recommendations. The costs for the meetings and for the preparation of the interim and final reports were borne entirely by ELN, a research network of excellence funded by the European Union. There was no financial support from industry for any activity. At the EHA 2012 meeting, representatives of 2 companies (Novartis Pharma and Bristol-Myers Squibb) were invited to present to the panel an unpublished update of their respective studies, ENESTnd and DASSISION, but were not invited to discuss the data. Treatment recommendations are limited to the TKIs that have been approved at least once in CML, either by the US Food and Drug Administration (FDA) and/or by the European Medicine Agency (EMA). These drugs will be listed in order of FDA approval. We acknowledge that all of these drugs may be available worldwide, and that differences in price could make the use of some of these drugs problematic in some countries. The relevant papers that appeared between the publication of the second version of the recommendations in 20095 and February 2013 were identified through the PubMed database and were comprehensively and critically reviewed. With few exceptions, only papers published after 2008 were referenced. The panel also reviewed and used as appropriate the abstracts presented at the latest meetings of the EHA (June 2012) and of the ASH (December 2012).

Definitions

The definitions of chronic phase (CP), accelerated phase (AP), and blastic phase (BP) (Table 1) were unchanged from prior published versions.4,5 For treatment-naive CP patients, 3 risk scores were analyzed (Table 2): Sokal, Euro, and EUTOS.1-9 The definitions of complete hematologic response (CHR) and of CyR were maintained from prior versions.4,5 We agreed that only chromosome banding analysis (CBA) of marrow cell metaphases can be used to assess the degree of CyR, with at least 20 metaphases analyzed, and that fluorescence in situ hybridization (FISH) of blood interphase cell nuclei could substitute for CBA of marrow cell metaphases only for the assessment of CCyR, which is then defined by <1% BCR-ABL1-positive nuclei of at least 200 nuclei.5,10 Molecular response is best assessed according to the International Scale (IS) as the ratio of BCR-ABL1 transcripts to ABL1 transcripts, or other internationally recognized control transcripts, and it is expressed and reported as BCR-ABL1% on a log scale, where 10%, 1%, 0.1%, 0.01%, 0.0032%, and 0.001% correspond to a decrease of 1, 2, 3, 4, 4.5, and 5 logs, respectively, below the standard baseline that was used in the IRIS study.5,11-14 A BCR-ABL1 expression of $0.1% corresponds to major molecular response (MMR). We further confirm that the following criteria should be used to define deep molecular response (MR).14 MR 0.5% is either (i) detectable disease with <0.01% BCR-ABL1 IS (or (ii) undetectable disease in cDNA with >10,000 ABL1 transcripts; MR 0.5% is either (i) detectable disease with <0.0032% BCR-ABL1 IS or (ii) undetectable disease in cDNA with >32,000 ABL1 transcripts in the same volume of cDNA used to test for BCR-ABL1. Assay sensitivity should be defined in a standardized manner when BCR-ABL1 mRNA is undetectable. The term complete molecular response should be avoided and substituted with the term molecularly undetectable leukemia, with specification of the number of the control gene transcript copies. These working definitions depend critically on the ability of testing laboratories to measure absolute numbers of control gene transcripts in a comparable manner, as well as their ability to achieve the polymerase chain reaction (PCR) sensitivity required for BCR-ABL1 detection.

Data review

Imatinib. Several studies of imatinib as first-line therapy have been updated or newly reported.16,39 The proportion of patients who achieved CCyR and MMR after 1 year of 400 mg imatinib daily ranged from 49% to 77%, and from 18% to 58%, respectively13,24,26,35-37 (supplemental Table 1, available on the Blood website). With a 600 mg or 800 mg daily, the CCyR rate ranged from 63% to 88% and the MMR rate from 43% to 47% (supplemental Table 1). A superiority of 800 mg daily was reported in 1 large randomized study.18 In high-risk patients,15,16,24,26,55-58 the CCyR and the MMR rates at 1 year ranged from 48% to 64%, and from 16% to 40%, respectively (supplemental Table 2). The outcome data, with a median follow-up ranging between 3.2 years and >6 years, are reported in Table 3. At >5 years, progression-free survival (PFS) ranged between 83% and 94%, and overall survival (OS) ranged between 83% and 97%. The number of patients still receiving initial imatinib treatment was reported at 63% to 79% after 3 to 5 years, and at ~50% after 8 years.11,13,25-31,34 To date, there have been no other reports of more, or of new, clinically relevant late side effects or complications.

Imatinib combinations. Imatinib has been tested in combination with low-dose arabinosyl cytosine, without showing superiorly,5,31 and with IFNα.28,31,40-41 in newly diagnosed CP patients. In the French SPIRIT trial, using pegylated rIFNα2a (90, then 45 µg weekly) compared with patients treated with imatinib alone: 30% vs 14% (P = .001) at 1 year, and 38% vs 21% (P = .001) at 2 years.28 In the Nordic and MD Anderson Cancer Center (MDACC) trials, patients were assigned to a combination of imatinib 400 mg daily or 400 mg twice daily,41 and pegylated rIFN-α2b, 50 µg40 or 0.5 µg/
kg weekly. In the Nordic study, the MMR rate at 1 year was higher in the combination arm. In the MDACC study, the MMR and CCyR rates were the same in both arms. In the German CML Study IV, imatinib 400 mg once daily with the nonpegylated form of rIFNα2a or rIFNα2b, 1.5 to 3.0 MIU 3 times weekly, was tested vs imatinib alone; at 1 and 2 years, the cumulative incidence of MMR rate was similar to that achieved with imatinib 400 mg and inferior to that with imatinib 800 mg. None of these combination studies has reported a superior PFS or OS.

Second-generation TKIs as first-line therapy. Two prospective, randomized, company-sponsored studies showed an initial superiority of nilotinib and dasatinib over imatinib, when they were used up front in newly diagnosed patients, particularly in the speed and the depth of patient response. The ENESTnd study, testing nilotinib 300 mg twice daily vs imatinib 400 mg once daily, reported a significantly higher rate of CCyR after 1 and 2 years (80% vs 65%, and 87% vs 77%), a significantly higher rate of MMR after 1 year (50% vs 27%) and 3 years (73% vs 53%), and a significantly higher rate of MR1 after 3 years (32% vs 15%). The DASISION study, testing dasatinib 100 mg once daily vs imatinib 400 mg once daily, reported a significantly higher rate of CCyR after 1 year (83% vs 72%) but not after 2 years (85% vs 82%), a significantly higher rate of MMR after 1 year (46% vs 23%) and 3 years (68% vs 55%), and a significantly higher rate of MR1 after 3 years (22% vs 12%).

A US and Canadian Intergroup trial of dasatinib vs imatinib reported similar results. The BELA study, testing bosutinib 500 mg once daily vs imatinib 400 mg once daily, reported a significantly higher rate of CCyR after 1 year (83% vs 72%) but not after 2 years (85% vs 82%), a significantly higher rate of MMR after 1 year (46% vs 23%) and 3 years (68% vs 55%), and a significantly higher rate of MR1 after 3 years (22% vs 12%). A US and Canadian Intergroup trial of dasatinib vs imatinib reported similar results. The BELA study, testing bosutinib 500 mg once daily vs imatinib 400 mg once daily, reported a significantly higher rate of CCyR after 1 year (83% vs 72%) but not after 2 years (85% vs 82%), a significantly higher rate of MMR after 1 year (46% vs 23%) and 3 years (68% vs 55%), and a significantly higher rate of MR1 after 3 years (22% vs 12%).

Second-generation TKIs as second- and third-line therapies. For several years, dasatinib and nilotinib have been approved for second-line treatment of CML patients intolerant of or in whom imatinib treatment failed, based on reported CCyR rates of 40% to 60%. Two major company-sponsored, phase 2, single-arm studies have been updated, reporting an MMR rate of 28% after 2 years (nilotinib) and 42% after 5 years (dasatinib), stability of the CCyR, once achieved; and PFS of 57% at 4 years with nilotinib and of 56% at 5 years with dasatinib. However, in both studies the proportion of patients who were still taking core treatment at 4 to 5 years was only 30% and 31%, respectively.

Bosutinib was approved more recently for second- or subsequent line treatment of CML patients intolerant of or in whom imatinib treatment failed, based on a phase 2, single-arm, company-sponsored study reporting an MCyR rate of 58% and a CCyR rate of 48% in imatinib-resistant patients. Ponatinib, a pan-TKI also inhibiting the T315I mutation, has been recently approved for the treatment of the patients in whom previous TKI therapy failed, based on a company-sponsored, phase 2, single-arm study, reporting that in CP patients resistant to 2, and often 3, TKIs, ponatinib was able to induce MCyR, CCyR, and MMR in 56%, 46%, and 34% of patients, respectively, with higher rates in patients with a shorter history of disease and treatment and/or with the T315I mutation. At 1 year, 63% of CP patients were still receiving core treatment and 91% of responders were maintaining the cytogenetic response.

Allogeneic stem cell transplantation. alloSCT remains the only currently available treatment that can render patients durably molecularly negative, but the associated procedural-related morbidity and mortality remain a major deterrent. Since our last publication, there have been few new studies in alloSCT, and the interpretation of these is hindered by the lack of information regarding the reason for transplant and the pre- and posttransplant use of TKI. A prospective study was conducted by the German CML Study Group who reported on 84 patients (median age, 37 years) receiving myeloablative alloSCT between 2003 and 2008, as either first-line therapy (n = 19) or after imatinib failure (n = 37 in CP, n = 28 in AP) and with related (36%) or unrelated (64%) donors. OS at 3 years was 88%, 94%, and 59% in patients transplanted as first-line therapy, after imatinib failure but still in CP, and AP, respectively. Transplant-related mortality was 8% and chronic graft-versus-host disease occurred in 46% of patients. The Center for International Blood

Table 3. Outcomes of patients treated first with imatinib

<table>
<thead>
<tr>
<th>Study/Source</th>
<th>Imatinib dose, mg</th>
<th>No. of patients</th>
<th>High-risk patients (Sokal/Euro)</th>
<th>OS</th>
<th>PFS</th>
<th>EFS</th>
<th>AT</th>
<th>Follow-up, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRIS18,19</td>
<td>400</td>
<td>553</td>
<td>18% (S)</td>
<td>85%</td>
<td>92%</td>
<td>NR</td>
<td>8 y</td>
<td>(minimum)</td>
</tr>
<tr>
<td>Hammersmith31,32</td>
<td>400</td>
<td>204</td>
<td>29% (S)</td>
<td>83%</td>
<td>83%</td>
<td>63%</td>
<td>5 y</td>
<td>3.2 (median)</td>
</tr>
<tr>
<td>Houston25</td>
<td>400</td>
<td>258</td>
<td>8% (S)</td>
<td>97%</td>
<td>92%</td>
<td>NR</td>
<td>4.4 (median)</td>
<td></td>
</tr>
<tr>
<td>PETHAMS27</td>
<td>400</td>
<td>210</td>
<td>16% (S)</td>
<td>97%</td>
<td>94%</td>
<td>71%</td>
<td>5 y</td>
<td>4.2 (median)</td>
</tr>
<tr>
<td>Czech registry70</td>
<td>400</td>
<td>343</td>
<td>22% (S)</td>
<td>88%</td>
<td>90%</td>
<td>NR</td>
<td>3.8 (median)</td>
<td></td>
</tr>
<tr>
<td>French SPIRIT28</td>
<td>400</td>
<td>319</td>
<td>24% (S)</td>
<td>NR</td>
<td>92%</td>
<td>NR</td>
<td>5 y</td>
<td>NR</td>
</tr>
<tr>
<td>GIMEMA23</td>
<td>400 (70%) / 800 (24%)</td>
<td>659</td>
<td>22% (S)</td>
<td>90%</td>
<td>87%</td>
<td>65%</td>
<td>5 y</td>
<td>5.0 (median)</td>
</tr>
<tr>
<td>German CML STUDY41</td>
<td>*</td>
<td>1551</td>
<td>12% (E)</td>
<td>88%</td>
<td>86%</td>
<td>NR</td>
<td>5.6 (median)</td>
<td></td>
</tr>
<tr>
<td>Seoul, St. Mary Hospital32</td>
<td>400 (83%)</td>
<td>363</td>
<td>22% (S)</td>
<td>94%</td>
<td>88%</td>
<td>NR</td>
<td>7 y</td>
<td>5.3 (median)</td>
</tr>
<tr>
<td>IRIS18,19</td>
<td>6-800 (17%)</td>
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<td></td>
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<td></td>
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<td></td>
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</tbody>
</table>

EFS, event-free survival, where events are death, progression to AP or BP, failure, and treatment discontinuation for any reason, whichever comes first; med, median; min, minimum; NR, not reported; OS, overall survival; PFS, survival free from progression to AP or BP.

*Imatinib 400 + IFNα (28%), imatinib 800 (27%), imatinib 400 (26%), imatinib 400 + low-dose arabinosyl cytosine (10%), imatinib 400 after IFNα (8%).
and Marrow Transplant (CIBMTR) reported retrospectively on 306 patients greater than 40 years of age who received reduced-intensity conditioning or nonmyeloablative procedures between 2001 and 2007. Approximately half of the patients were in CP at the time of transplant and 74% had received imatinib before their graft. In the 3 age groups selected in patients who developed dasatinib or nilotinib resistance were associated with higher IC50 values had lower hematologic and cytogenetic response rates than those harboring mutations with lower IC50 values; mutations selected in patients who developed dasatinib or nilotinib resistance were those with the highest IC50 values. As yet, there is no evidence.

**Additional clonal cytogenetic abnormalities emerging on therapy.** Metaphase karyotyping may reveal additional clonal chromosomal abnormalities in Ph+ cells (CCA/Ph+), a situation referred to as clonal cytogenetic evolution. CCA/Ph+ defines TKI failure. CCA/Ph+ is associated with shorter OS on second-line imatinib (after rIFN failure) but not second-line dasatinib or nilotinib. Clonal cytogenetic abnormalities in Ph+ cells (CCA/Ph+) occur in 5% to 10% of patients and, in the absence of dysplasia, do not seem to adversely affect outcome. The exception are abnormalities of chromosome 7 (monosomy 7 and del(7q)), where some case reports indicate a risk of myelodysplasia and acute leukemia and justify long-term follow-up bone marrow biopsy. Other patients with CCA/Ph+ require marrow examination only in case of cytopenias or dysplastic peripheral blood morphology.

**Baseline prognostic factors.** Several factors have been reported to influence the response to TKI and the outcome. Three prognostic systems—Sokal, Euro, and EUTOS (Table 2)—based on simple clinical and hematologic data, have been shown to still be of value. As yet, there is no evidence.

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### Table 4. In vitro sensitivity of unmutated BCR-ABL1 and of some more frequent BCR-ABL1 kinase domain mutants to imatinib, nilotinib, dasatinib, bosutinib, and ponatinib

<table>
<thead>
<tr>
<th>BCR-ABL1</th>
<th>Imatinib IC50 range (nM)</th>
<th>Nilotinib IC50 range (nM)</th>
<th>Dasatinib IC50 range (nM)</th>
<th>Bosutinib IC50 (nM)</th>
<th>Ponatinib IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmutated</td>
<td>260-678</td>
<td>&lt;10-25</td>
<td>0.8-1.8</td>
<td>41.6</td>
<td>0.5</td>
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<tr>
<td>M244V*</td>
<td>1600-3100</td>
<td>38-39</td>
<td>1.3</td>
<td>147.4</td>
<td>2.2</td>
</tr>
<tr>
<td>L248V</td>
<td>1866-10000</td>
<td>49.5-919</td>
<td>9.4</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Q250E*</td>
<td>1350 to &gt;20000</td>
<td>48-219</td>
<td>1.8-8.1</td>
<td>179.2</td>
<td>4.1</td>
</tr>
<tr>
<td>Q252H</td>
<td>734-3120</td>
<td>16-70</td>
<td>3.4-5.6</td>
<td>33.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Y253F</td>
<td>&gt;6400-8953</td>
<td>182-725</td>
<td>6.3-11</td>
<td>40</td>
<td>2.8</td>
</tr>
<tr>
<td>Y253H*</td>
<td>&gt;6400-17 700</td>
<td>450-1300</td>
<td>1.3-10</td>
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<td>6.2</td>
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<tr>
<td>E255K*</td>
<td>3174-12 100</td>
<td>118-566</td>
<td>5.6-13</td>
<td>394</td>
<td>14</td>
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<td>E255V</td>
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<td>430-725</td>
<td>6.3-11</td>
<td>230.1</td>
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<tr>
<td>D276G</td>
<td>1147</td>
<td>35.3</td>
<td>2.6</td>
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<tr>
<td>E279K</td>
<td>1872</td>
<td>36.5-75</td>
<td>3</td>
<td>39.7</td>
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<tr>
<td>V299L</td>
<td>540-814</td>
<td>23.7</td>
<td>15.8-18</td>
<td>1066</td>
<td>NA</td>
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<tr>
<td>F311L</td>
<td>480-1300</td>
<td>23</td>
<td>1.3</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>T315I*</td>
<td>&gt;6400 to &gt;20 000</td>
<td>697 to &gt;10 000</td>
<td>137 to &gt;1000</td>
<td>1890</td>
<td>11</td>
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<tr>
<td>T315A</td>
<td>125</td>
<td>N.A.</td>
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<tr>
<td>F317L*</td>
<td>810-1500</td>
<td>39.2-91</td>
<td>7.4-18</td>
<td>100.7</td>
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<td>350</td>
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<td>NA</td>
<td>10</td>
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<td>M351T*</td>
<td>880-4900</td>
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<td>1.1-1.6</td>
<td>29.1</td>
<td>1.5</td>
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<tr>
<td>F359V*</td>
<td>1400-1825</td>
<td>91-175</td>
<td>2.2-2.7</td>
<td>38.6</td>
<td>10</td>
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<tr>
<td>V379I</td>
<td>1000-1630</td>
<td>51</td>
<td>0.8</td>
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<tr>
<td>L384M*</td>
<td>674-2800</td>
<td>39-41.2</td>
<td>4</td>
<td>19.5</td>
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<tr>
<td>L387M</td>
<td>1000-1100</td>
<td>49</td>
<td>2</td>
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<td>H396R*</td>
<td>1750-5400</td>
<td>41-55</td>
<td>1.3-3</td>
<td>33.7</td>
<td>NA</td>
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<td>H396P</td>
<td>850-4300</td>
<td>41-43</td>
<td>0.6-2</td>
<td>18.1</td>
<td>NA</td>
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<tr>
<td>F359V</td>
<td>2278-9100</td>
<td>32.8-87</td>
<td>5.6</td>
<td>96.1</td>
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**Plasma drug concentration**

<table>
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<tr>
<th></th>
<th>Cmin</th>
<th>Cmax</th>
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<tr>
<td></td>
<td>2062 ± 1334</td>
<td>1923 ± 1233</td>
</tr>
<tr>
<td></td>
<td>5.5 ± 1.4</td>
<td>268 (30-1533)</td>
</tr>
<tr>
<td></td>
<td>4402 ± 1272</td>
<td>2329 ± 772</td>
</tr>
</tbody>
</table>

The half maximal inhibitory concentration (IC50) shown here is universally regarded as a measure of the degree of sensitivity of a BCR-ABL1 mutant to a given TKI and is experimentally determined by quantifying the TKI concentration required to reduce by 50% viability of a Ba/F3 mouse lymphoblastoid cell line engineered to express that mutant form of BCR-ABL1. The table lists all of the BCR-ABL1 mutants for which the IC50 values of at least 2 TKIs are available. For imatinib, dasatinib, and nilotinib, ranges of IC50 values were provided when differences in IC50 values reported by different studies were observed (reviewed in Baccarani et al16). For bosutinib and ponatinib, IC50 values come from a single study each. Plasma drug concentration is also given in nM. Values of plasma drug concentration are mean ± standard deviation for imatinib (400 mg once daily), nilotinib (300 mg twice daily), dasatinib (100 mg once daily), and ponatinib (45 mg once daily), and median (range) for bosutinib (500 mg once daily). The results for patients transplanted between 2000 and 2010, with a 6-year OS of 89%, 60%, and 30% for patients transplanted with EBMT risk scores of 89%, 60%, and 30%, respectively. Outcome for patients transplanted in blast crisis was very poor, with an OS of <10%.

**BCR-ABL1 mutations.** BCR-ABL1 kinase domain point mutations are detectable in ~50% of patients with treatment failure and progression. To date, the clinical impact of mutations has been assessed using low sensitivity techniques (Sanger sequencing). The presence of mutations at lower levels can be identified with more sensitive techniques, such as mass spectrometry or ultra-deep sequencing, but data are not yet sufficient to interpret the clinical relevance of the mutations detected by these more sensitive techniques. Mutations, which should not be confused with ABL1 polymorphisms, are suggestive of genetic instability and increased risk of progression. More than 80 amino acid substitutions have been reported in association with resistance to imatinib. Dasatinib and nilotinib have much smaller spectra of resistant mutations, but neither inhibit the T315I. Patients relapsing while taking nilotinib were most frequently found to have acquired V299L, F317LV/IC, T315A, or T315I mutations. T315I is also resistant to bosutinib, whereas ponatinib inhibits T315I in vitro and is effective in patients with T315I in vivo. Table 4 reports the in vitro sensitivity of the most common BCR-ABL1 mutants to imatinib, nilotinib, dasatinib, bosutinib, and ponatinib, expressed as half-maximal inhibitory concentration (IC50). In CP patients, there is a correlation between the IC50 value for a specific mutation in vitro and the clinical response in patients harboring the same mutation in vivo, in that patients harboring mutations with higher IC50 values had lower hematologic and cytogenetic response rates than those harboring mutations with lower IC50 values; mutations selected in patients who developed dasatinib or nilotinib resistance were those with the highest IC50 values.
Response to treatment

The response to TKI is the most important prognostic factor. In the previous versions of the ELN recommendations the response to first-line treatment was limited to imatinib. Now that there are more TKIs, we do not recommend which TKI should be used but which response should be achieved, irrespective of the TKI that is used. The responses are defined as “optimal” or “failure” (Table 5). Optimal response is associated with the best long-term outcome—that is, with a duration of life comparable with that of the general population, indicating that there is no indication for a change in that treatment. Failure means that the patient should receive a different treatment to limit the risk of progression and death. Between optimal and failure, there is an intermediate zone, which was previously referred to as “suboptimal” and is now designated as “warning.” Warning implies that the characteristics of the disease and the response to treatment require more frequent monitoring to permit timely changes in therapy in case of treatment failure.

In the definition of response, a controversial point is the value of early molecular response, particularly after 3 months of treatment. A BCR-ABL1 transcripts level $>10\%$ was reported to be prognostically significant in several studies. However, the conclusion of the panel is that a single measurement of BCR-ABL1 transcripts level is not sufficient to define as failure necessitating a change of treatment, whereas 2 tests (at 3 and 6 months) and supplementary tests in between provide more support for the decision to change the treatment. Failures must be distinguished as either primary (failure to achieve a given response at a given time) or secondary (loss of response) (Table 5).

The definitions of the response to second-line treatment, based on the same concepts, are shown in Table 6. They are limited to dasatinib and nilotinib but until more data become available, they may provisionally serve also for the other TKIs. These definitions have profound therapeutic implications because they mark the difficult and critical boundaries between TKIs and alloSCT.

Treatment recommendations

It is recommended that in practice outside of clinical trials, the first-line treatment of CP CML can be any of the 3 TKIs that have been approved for this indication and are available nearly worldwide, namely imatinib (400 mg once daily), nilotinib (300 mg twice daily), and dasatinib (100 mg once daily). These 3 TKIs can also be used in second or subsequent lines, at the standard or at a higher dose (400 mg twice daily for imatinib, 400 mg twice daily for nilotinib, and 70 mg twice daily or 140 mg once daily for dasatinib). Bosutinib (500 mg once daily) has been approved by the FDA and EMA for patients resistant or intolerant to prior therapy. Ponatinib (45 mg once daily) has also been approved by the FDA for patients resistant or intolerant to prior TKI therapy. Also approved, for patients in whom prior TKI therapy fails, are radotinib, which is available in Korea, and omacetaxine, which is a non-TKI drug approved by the US FDA.

Busulfan is not recommended. Hydroxyurea can be used for a short time before initiating a TKI, until the diagnosis of CML has been confirmed. rIFNα alone is recommended only in the rare circumstances in which a TKI cannot be used. The combinations of TKIs and rIFNα are potentially useful but still investigational. Cytotoxic chemotherapy is never recommended in CP but may be useful to control BP and to prepare BP patients for alloSCT.

Treatment recommendations for CP are proposed in Table 7. These recommendations are based on a critical evaluation of efficacy, but it is acknowledged and recommended that the choice of the TKI must take into account tolerability and safety, as well as patient characteristics, particularly age and comorbidities, which may be predictive of particular toxicities with the different TKIs. In all cases of “warning,” research and investigational studies are warranted and should be encouraged to improve treatment results.
AlloSCT will continue to be an important treatment of patients who fail to respond durably to TKIs. Over the last 14 years, the timing of transplant has changed to third or fourth line after failure of the second-line TKIs. However, the current situation is more complex given that patients can be treated up front with different TKIs. It seems reasonable that for patients in CP, transplants should be reserved for those who are resistant or intolerant to at least one second-generation TKI. The nature of conditioning therapy is controversial because in CP there is no evidence at present that myeloablative conditioning offers any advantage over reduced-intensity preparative regimens. Patients should be monitored after transplant by RQ-PCR and treated with donor lymphocyte infusion and/or TKI as clinically appropriate. Patients in BP should receive intensive chemotherapy with or without a TKI, with the intention of proceeding to allo-SCT if a second chronic phase can be established. The value of using a TKI as maintenance after alloSCT is not proven but seems intuitively logical. Transplant conditioning should be myeloablative where possible. Patients in AP should be considered for alloSCT unless they achieve an optimal response to second-line therapy in case of failure of imatinib.

**Table 6. Definitions of the response to second-line therapy in case of failure of imatinib**

<table>
<thead>
<tr>
<th>Time</th>
<th>Optimal Response</th>
<th>Warning</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>NA</td>
<td>No CHR or loss of CHR on imatinib or lack of CyR to first-line TKI or high risk</td>
<td>NA</td>
</tr>
<tr>
<td>3 mo</td>
<td>BCR-ABL1 ≤10% and/or Ph+ &lt; 65%</td>
<td>BCR-ABL1 &gt;10% and/or Ph+ 65-95%</td>
<td>No CHR or Ph+ &gt;95% or new mutations</td>
</tr>
<tr>
<td>6 mo</td>
<td>BCR-ABL1 ≤10% and/or Ph+ &lt; 35%</td>
<td>Ph+ 35-65%</td>
<td>BCR-ABL1 &gt;10% and/or Ph+ &gt;65% or new mutations</td>
</tr>
<tr>
<td>12 mo</td>
<td>BCR-ABL1 &lt;1% and/or Ph+ 1-35%</td>
<td>BCR-ABL1 1-10% and/or Ph+ &gt;35%</td>
<td>BCR-ABL1 &gt;10% and/or Ph+ &gt;35% or new mutations</td>
</tr>
<tr>
<td>Then, and at any time</td>
<td>BCR-ABL1 ≤0.1%</td>
<td>CCA/Ph− (−7 or 7q−) or BCR-ABL1 &gt;0.1%</td>
<td>Loss of CHR or loss of CyR or PCyR</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
<td>New mutations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Confirmed loss of MMR*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CCA/Ph−</td>
</tr>
</tbody>
</table>

*In 2 consecutive tests, of which one with a BCR-ABL transcripts level ≥1%.

Treatment discontinuation, pregnancy

Currently, we recommend that a patient with CML who is responding optimally to treatment continues indefinitely at the standard recommended dose. There have been controlled attempts to discontinue imatinib in some patients who were in sustained, deep MR (MR4 or better).^{26-29} Approximately 40% of them maintained the same degree of response, with a follow-up of 1 to 4 years. Almost all of those who had a molecular recurrence achieved again the same level of deep response when treatment with imatinib was resumed. These data provide a proof-of-principle for the hypothesis that TKI treatment can be discontinued safely, even though some BCR-ABL1+ cells always remain detectable.^{130-132} However, the data are still insufficient to make recommendations about discontinuing treatment outside of well-designed, prospective, controlled studies. One such study (EUROSKI), sponsored by ELN, is in progress. Alternatives to discontinuation, such as the intermittent administration of imatinib,
Table 8. Treatment strategy recommendations for CML in AP or BP

| AP and BP in newly diagnosed, TKI-naive patients | Imatinib 400 mg twice daily or dasatinib 70 mg twice daily or 140 mg once daily Stem cell donor search. Then, alloSCT is recommended for all BP patients and for the AP patients who do not achieve an optimal response. Chemotherapy may be required before alloSCT, to control the disease. |
| AP and BP as a progression from CP in TKI-pretreated patients | Anyone of the TKIs that were not used before progression (ponatinib in case of T315I mutation), then alloSCT in all patients. Chemotherapy is frequently required to make patients eligible for alloSCT. |

In treatment-naive patients, AP is believed to be close to high-risk CP, so that TKIs have priority. In patients who progress to AP or BP during TKI therapy, the response to any subsequent treatment is poorer, and less durable, so that alloSCT is recommended for all patients who are eligible for the procedure. However, in these patients, not only TKIs but also cytotoxic chemotherapy may be necessary to reinsert some degree of remission to permit alloSCT. In case of uncontrolled, resistant BP, alloSCT is not recommended. All recommendations for alloSCT imply that the patient is eligible for that procedure. Note that nilotinib was tested, but not approved, for the treatment of BP.4,121,122

Warning Molecular and cytogenetic tests to be performed by conventional Sanger sequencing is recommended in case of progression, failure, or cryptic translocations.

In case of warning, it is recommended to repeat all tests, cytogenetic and molecular, more frequently, even monthly.

In case of treatment failure or of progression to AP or BP, cytogenetics of marrow cell metaphases, PCR, and mutational analysis should be performed.

If dysplastic morphology or other indications of myelodysplasia develop, such as unexplained or prolonged cytopenia, histopathologic and cytogenetic studies of bone marrow are recommended. Clonal chromosome abnormalities in Ph− cells, which may develop in up to 10% of responders, are a warning only in case of chromosome 7 involvement.

Side effects

The TKIs have different patterns of side effects, and this should be considered when choosing among these drugs. Side effects can be divided into 3 general categories. The first includes major, grade 3/4, side effects that typically occur during the first phase of treatment, are manageable, but require temporary treatment discontinuation and dose reduction, and can lead to treatment discontinuation in about 10% of patients.4,5,10,13,15,20,21,24,26-30,33,34,38,42,136,137 The second category includes minor, grade 1/2, side effects that begin early during treatment and can persist forever and become chronic. They are also manageable and tolerable, in principle, but negatively affect the quality of life and are a cause of decreased treatment compliance.

Table 9. Recommendations for cytogenetic and molecular monitoring

| At diagnosis | Chromosome banding analysis (CBA) of marrow cell metaphases FISH in case of Ph negativity to identify variant, cryptic translocations Qualitative PCR (identification of transcript type) |
| During treatment | Quantitative real-time PCR (RQ-PCR) for the determination of BCR-ABL transcripts level on the international scale, to be performed every 3 months until an MMR (BCR-ABL ≤0.1%, or MR50) has been achieved, then every 3 to 6 months and/or CBA of marrow cell metaphases (at least 20 banded metaphases), to be performed at 3, 6, and 12 months until a CCyR has been achieved, then every 12 months. Once a CCyR is achieved, FISH on blood cells can be done. If adequate molecular monitoring can be ensured, cytogenetics can be spared. |
| Warning | Molecular and cytogenetic tests to be performed more frequently. CBA of marrow cell metaphases recommended in case of myelodysplasia or CCA/Ph− with chromosome 7 involvement. |

The responses can be assessed either with molecular tests alone or with cytogenetic tests alone, depending on the local laboratory facilities, but whenever possible, both cytogenetic and molecular tests are recommended until a CCyR and an MMR are achieved. Then RQ-PCR alone may be sufficient. Mutational analysis by conventional Sanger sequencing is recommended in case of progression, failure, and warning.55 In case of failure, warning, and development of myelodysplastic features (unexpected leucopenia, thrombocytopenia, or anemia), CBA of marrow cell metaphases is recommended.

FISH, fluorescence in situ hybridization; CCA/Ph−, clonal chromosome abnormalities in Ph− cells.
compliance, which is a major cause of failure.\textsuperscript{4,5,18,19,28-31,42,136-143} Many of these side effects are common to all TKIs, with some differences in frequency and severity, so that several patients can benefit from changing the TKI. The third category includes late, so-called “off-target” complications, which can affect the cardiovascular system, heart and blood vessels, the respiratory system, liver, pancreas, the immune defense, second malignancies, calcium, glucose, and lipid metabolism, etc.\textsuperscript{144-159} All TKIs can be toxic to the heart and should be used with great caution in patients with heart failure. Nilotinib has been reported to be associated particularly with the heart and should be used with great caution in patients with heart failure. Bosutinib has been reported to be associated particularly with arterial pathology, both peripheral and coronary. Dasatinib has been reported to be associated particularly with pleura and lung complications. Data on bosutinib and ponatinib are scanty. Overall, the long-term, so-called “late” or “off-target” complications of second-generation TKIs are not yet fully understood and evaluable. Because these complications are a potential cause of morbidity and mortality, continued clinical monitoring of all patients is required.

### Discussion

These recommendations are based primarily on the antileukemic efficacy of TKIs, but it should not be overlooked that the choice of the treatment depends also on other important variables, which affect the quality of life and life itself, including side effects, serious adverse events, and late “off-target” complications. The evaluation of therapeutic efficacy must be based on the clinical outcomes (PFS and OS), but because the data of clinical outcomes require a long observation time, the evaluation is influenced by the so-called early surrogate markers, namely the molecular and the cytogenetic response. However, as was already pointed out elsewhere,\textsuperscript{160,161} survival data should also be interpreted carefully because different definitions of progression and failure were used in different studies, and even deaths were counted in different ways, whether they had occurred during the so-called core study treatment, or at any time, or whether they were regarded as “related” or “unrelated” to CML.\textsuperscript{15-18,21,24,26,28,29,31,35-39}

The definition of response has an important operational value because it is the basis of continuing or changing the treatment. Two points are particularly controversial. One point is the choice of the first TKI,\textsuperscript{162-164} two trials have shown an initial superiority of second-generation TKIs vs imatinib, with significant differences in response but not yet in outcome.\textsuperscript{9-13} They justify placing nilotinib and dasatinib in the front-line setting but do not justify the exclusion of imatinib. The second point is the prognostic value of the depth of molecular response at 3 months. Many studies, with imatinib, nilotinib, dasatinib, and bosutinib, both as first-line and second-line treatments, reported that the 10% BCR-ABL1 transcripts level was prognostically significant.\textsuperscript{93-103} Therefore, why should 10% or more BCR-ABL1 transcripts at 3 months not be considered a treatment failure, leading to a recommendation to change therapy? The conclusion of the panel was mainly based on the recognition that there are no studies showing that the outcome of such patients would be improved, and if so how much, if therapy was changed at 3 months. It should also be noted that in all but one of the studies, the difference in OS and PFS, though significant, was of the magnitude of about 10% (survival was about 95% in case of BCR-ABL1 <10% vs about 85% in case of >10%), making it problematic to recommend switching all patients to benefit a minority. Also, it should be considered that all of the data supporting the prognostic value of the 10% cutoff value at 3 months were derived from retrospective analyses of subgroups that had not been predefined in the original study protocols, and that the molecular assays were performed in one or few reference laboratories that may not yet represent the typical standard of molecular testing, worldwide. Therefore, the panel has considered that a single molecular test cannot be sufficient to take such an important decision as the change of treatment. Two tests, at 3 and 6 months, and, even better, a supplementary test between 3 and 6 months, as it is recommended in case of “warning,” provide a sounder basis for treatment decisions. The issue of very early change is still investigational. The patients not achieving <10% after 6 months of therapy are more clearly in need of a change of therapy.\textsuperscript{94,96,99,100,102,103}

Efficacy is important, but treatment choice does not depend only on efficacy. The introduction of imatinib was celebrated as the beginning of a new era of cancer treatment, in which therapy was finally nontoxic, safe, and well-tolerated. After more than 10 years, these promises were largely fulfilled because the side effects of imatinib are usually mild, with only rare severe, life-threatening complications.\textsuperscript{4,5,42,136,137} The side effects of second-generation TKIs are somewhat different from those of imatinib, but overall the tolerability profile is comparable. However, the sensitivity and tolerance of patients is changing, not only because of the chronicity of the treatment, but also because the availability of other TKIs makes changes possible and easier. Even low-grade side effects affect quality of life and compliance,\textsuperscript{137-143} and they can justify a change of drug even though there is a therapeutic response.

The problems of late, so-called “off-target,” complications, are more difficult to evaluate and manage because the information is still inadequate and the follow-up is still short, particularly for second-generation TKIs. If the phase of the disease is advanced and the major threat is the disease itself, these considerations may have less value, but for patients in CP, where a normal duration of life is the goal, these considerations are very important, compete with efficacy data, and may deserve priority. The adaptation of the treatment to the clinical conditions, a careful attention to the health state of the patients, and the timely reporting of any severe complication are recommended. The ELN panel has appointed a committee for a detailed and careful analysis and discussion of the side effects of TKIs that will be the subject of a separate report.

The quality of life is also affected by the very fact that living together with a potentially fatal disease—CML is a cancer, after all—has emotional and social consequences affecting family and career planning and is accompanied by a variable level of uncertainty and fear. It was not surprising that both physical and mental health were reported to be better and closer to normal in the older than in the younger patients, because younger have more and different expectations, not only of a normal life, but also of a life free from leukemia and from treatment.\textsuperscript{144} Currently, the major goal of therapy is survival, but it is acknowledged that living without treatment and without detectable leukemia will be a major issue for clinical investigation, requiring the achievement of a deeper molecular response.\textsuperscript{2,3,93,94,96,100,102,126-129} These findings underscore the importance of age. The problem of children and adolescents, and also of young adults, is of particular concern. It is believed and recommended\textsuperscript{165-167} that children must be managed and treated like adults, but specific data are limited and more information pertaining to these particular age groups is necessary.

The current cost of TKIs is high, particularly because therapy needs to be continued for life.\textsuperscript{168,169} Depending on the country, costs are determined through negotiations among several partners, so that the cost of the same drug can vary from one country to another. In many countries, the costs are not completely reimbursable, or some
TKIs are not even available. The ELN expert panel has appointed a committee to study and to report soon on the pharmacoeconomic and ethical implications of the treatment of CML, because it is now time to draw attention to the problem and to call for a public debate.

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