Multicenter Independent Assessment of Outcomes in Chronic Myeloid Leukemia Patients Treated With Imatinib

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Background
Imatinib slows development of chronic myeloid leukemia (CML). However, available information on morbidity and mortality is largely based on sponsored trials, whereas independent long-term field studies are lacking.

Patients and Methods
Consecutive CML patients who started imatinib treatment before 2005 and who were in complete cytogenetic remission (CCyR) after 2 years (±3 months) were eligible for enrollment in the independent multicenter Imatinib Long-Term (Side) Effects (ILTE) study. Incidence of the first serious and nonserious adverse events and loss of CCyR were estimated according to the Kaplan–Meier method and compared with the standard log-rank test. Attainment of negative Philadelphia chromosome hematopoiesis was assessed with cytogenetics and quantitative polymerase chain reaction. Cumulative incidence of death related or unrelated to CML progression was estimated, accounting for competing risks, according to the Kalbkleisch–Prentice method. Standardized incidence ratios were calculated based on population rates specific for sex and age classes. Confidence intervals were calculated by the exact method based on the χ² distribution. All statistical tests were two-sided.

Results
A total of 832 patients who were treated for a median of 5.8 years were enrolled. There were 139 recorded serious adverse events, of which 19.4% were imatinib-related. A total of 830 nonserious adverse events were observed in 53% of patients; 560 (68%) were imatinib-related. The most frequent were muscle cramps, asthenia, edema, skin fragility, diarrhea, tendon, or ligament lesions. Nineteen patients (2.3%) discontinued imatinib because of drug-related toxic effects. Forty-five patients lost CCyR, at a rate of 1.4 per 100 person-years. Durable (>1 year) negative Philadelphia chromosome hematopoiesis was attained by 179 patients. Twenty deaths were observed, with a 4.8% mortality incidence rate (standardized incidence ratio = 0.7; 95% confidence interval = 0.40 to 1.10, P = .08), with only six (30%) associated with CML progression.

Conclusions
In this study, CML-related deaths were uncommon in CML patients who were in CCyR 2 years after starting imatinib, and survival was not statistically significantly different from that of the general population.

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The development of imatinib and other tyrosine kinase inhibitors (TKIs) for the treatment of chronic myeloid leukemia (CML) radically changed CML treatment (1–7). Imatinib, which slows or prevents the evolution of CML, resulting in a possibly indefinite chronic phase, rapidly gained regulatory approval after its introduction in 1998 and is now used as first-line therapy for CML throughout the world, limited only by drug availability.

The Philadelphia (Ph) chromosome, which results from a chromosome 9;22 translocation that fuses the breakpoint cluster region (BCR) and c-abl oncogene 1, nonreceptor tyrosine kinase (ABL1) genes (8), represents the genetic basis of the disease, and its detection is essential to establish the diagnosis of CML. Despite the restoration of negative Philadelphia (Ph−) chromosome hematopoiesis, sensitive polymerase chain reaction (PCR) assays continue to detect the BCR-ABL1 fusion transcripts in most patients, indicating the presence of residual leukemic cells. It has been estimated that as many as 10⁶ residual leukemic cells might persist in patients who test negative by PCR (9). Thus, although the incidence of PCR negativity appears to increase over time (6), the current treatment recommendations for CML are that treatment should be continued “indefinitely” (10). Fortunately, the reported safety profile of imatinib is benign, peripheral edema and muscle cramps being the most frequent side effects. However, the bulk of available data on imatinib is derived from industry-sponsored clinical studies that were performed in selected research-intensive institutions,
**CONTEXTS AND CAVEATS**

**Prior knowledge**

Imatinib, which slows or prevents the development of chronic myeloid leukemia (CML), is now used as first-line therapy for CML, but no independent long-term field studies have assessed morbidity and mortality for imatinib-treated CML patients.

**Study design**

In the multicenter Imatinib Long Term Effects (ILTE) study, data on CML and non-CML-related toxic events, loss of complete cytogenetic remission, and cumulative incidence of death were assessed in 832 CML patients who were in complete cytogenetic remission after approximately 2 years of imatinib treatment.

**Contribution**

Long-term toxic effects associated with imatinib treatment were modest. At 6 years from the start of imatinib treatment, almost 95% of patients maintained their complete cytogenetic remission, and at 8 years, CML-related deaths accounted for only 1% of CML patients.

**Implications**

The overall survival of this population of CML patients was not statistically significantly different from that of the general population, in contrast to survival after other therapies such as bone marrow transplantation.

**Limitations**

Differences in the schedule of cytogenetic testing among centers could cause some variation in the annual rates of complete cytogenetic remission loss.

*From the Editors*

whereas independent long-term field studies are generally lacking.

The Imatinib Long-Term Side Effects (ILTE) study (www.ilte-cml.org) was conceived as an independent multicenter trial, aimed at evaluating the long-term effects of imatinib in a population of CML patients in stable cytogenetic remission. Although supported by Italian public funds, ILTE includes 27 active centers located on five continents (see Supplementary Table 1, available online).

The ILTE study enrolled patients who were in complete cytogenetic remission (CCyR) after 2 years (±3 months) of imatinib treatment. The objective was to focus on long-term effects, excluding the initial treatment period in which the risk of relapse/resistance or of acute toxicity is highest.

**Patients and Methods**

**Study Patients**

Consenting eligible patients were at least 18 years old, had chronic phase CML, started oral imatinib between September 1, 1999, and December 31, 2004, and were in CCyR after 2 years (±3 months). All patients signed an informed consent approved by local institutional review boards (www.ilte-cml.org). Centers were reminded regularly to check their databases for all eligible consenting patients. Patients were considered as “first line” if imatinib was started within 6 months of diagnosis and no other treatment except hydroxyurea was administered. Cytogenetics was performed between 1 and 2 times per year, depending on the center and the year; in 2008, some centers (# 2, 4, 7, 18, and 23) elected to stop cytogenetic analysis in patients with PCR values for BCR-ABL1 less than 0.1%. PCR analysis was performed between two and three times per year; center number 33 did not have access to PCR.

CCyR was defined as the lack of Ph+ metaphases in a sample of at least 20 metaphases. In some instances, and only during follow-up, fewer than 2% BCR-ABL1 positive cells, as assessed by fluorescence in situ hybridization or quantitative PCR calibrated to the international scale, were considered equivalent to CCyR.

PCR for BCR-ABL1 was performed according to the local laboratory (for methods used, see Supplementary Table 1, available online); the sensitivity of the quantitative assay was stated to range between 1 and 5 × 10⁻⁴. Loss of CCyR was defined as the presence of any positive metaphases on two different occasions or a single value of more than 10%. Loss of partial cytogenetic response was defined as the presence of more than 35% Ph+ metaphases.

**Study Protocol**

The protocol was approved by the local institutional review boards. The long-term follow-up of CML patients assessed side effects, cytogenetics/PCR status, tolerability, and survival. The study was presented to centers through letters of invitation and advertised in the journal Blood. A total of 38 centers were initially included. However, 11 centers were subsequently excluded because of no response or center refusal (nine centers) or failure to obtain protocol approval or administrative problems (two centers), leaving 27 active centers (see Supplementary Table 1, available online). The centers are located in 12 different countries on five continents; 11 centers do not belong to academic or research institutions; two centers did not enroll patients. Although the patient population was from selected centers, it constituted a representative sample of CML care as it is provided worldwide.

Patient data were collected by local investigators and transferred to electronic case report forms. Up to December 31, 2006, data were collected retrospectively, whereas those obtained after January 1, 2007, were prospectively entered up to December 31, 2008. The following data were collected: dose of imatinib, time to CCyR, cytogenetic and molecular response, serious adverse events (SAEs), including deaths and second cancers, adverse events not qualifying as SAE, but judged by treating physicians to have a substantial impact on the patient’s quality of life (nonserious adverse events, NSAEs). SAE and NSAE incidences refer only to the period following the first 2 years of imatinib treatment. Because NSAEs were reported by physicians and not patients, the NSAEs reported during 2008 at center number 1 were cross-validated. At the beginning of 2009, patients were administered a brief questionnaire in which they were asked whether imatinib treatment had interfered in a substantial way with their quality of life during the preceding year and in what respect.

The study was monitored by a dedicated research nurse. Five centers were visited, accounting for 25% of enrolled patients. Biannual meetings were held with investigators to present available results and to discuss emerging problems. Some of the meeting minutes are available on the ILTE Web site (www.ilte-cml.org). In addition, each submission of information was reviewed by the statistical unit and by the Chairman. Side effects or other events that were unclear or not sufficiently described generated a query to the local investigator.
Statistical Analysis

Descriptive statistics were used to present the data, and the test for proportions was applied for comparisons. Event rates per 100 person-years were estimated with 95% asymmetrical confidence intervals (CIs) based on logarithmic transformation and asymptotic derivation of the standard errors. Both events and person-years were calculated for the time under observation following the initial 2 years of imatinib treatment. The total observed number of events was used to calculate event rates of SAE and NSAE, even though a patient could experience more than one event.

Standard incidence ratios of death and second neoplasias were calculated based on population rates specific for sex and age classes provided by the Italian National Institute of Statistics (ISTAT) (11), updated in 2004, and by the International Agency for Research on Cancer (IARC), updated in 1997 (12). The expected number of events was calculated by multiplying the number of person-years observed in each age class by the corresponding population rate. Confidence intervals for the standard incidence ratios were obtained by the exact method (13). The incidence of the first SAE or NSAE in an individual patient and of the loss of CCyR were estimated according to the Kaplan–Meier method. Comparisons were performed by the standard log-rank test, and hazard ratios were estimated with the Cox proportional hazards model (13). Asymmetrical confidence intervals were provided based on the Greenwood formula for estimation of the variance (14).

The overall survival probability was estimated according to the Kaplan–Meier method. The cumulative incidence of death, that is, the complement to survival probability, was broken down into incidence of death related or unrelated to CML, accounting for competing risks, according to the Kalbfeisch–Prentice estimator (14). All statistical tests were two-sided, and P values were based on the difference. SAS software (SAS Institute Inc., 100 SAS Campus Drive Cary, NC 27513-2414, USA) (15) was used for data management and analysis. Graphics were obtained using R software (The R Foundation for Statistical Computing c/o Institute for Statistics and Mathematics, Wirtschaftsuniversität Wien, Augasse 2–6 1090 Vienna, Austria) (16).

Results

Study Participants

A total of 832 patients were enrolled with a median treatment duration of 5.8 years. A total of 948 patients were initially included in the ILTE database. A cross-check of the eligibility criteria performed by the statistical unit or by the research nurse during audits confirmed the eligibility of 832 patients (97.8%). Most excluded patients were considered ineligible because of the lack of a cytogenetic assessment after 2 years (±3 months) of imatinib treatment. Numbers of eligible patients entered by each center ranged from 3 to 128 (Supplementary Table 1, available online). Imatinib represented first-line treatment for 354 patients, whereas it was second-line treatment for 478 patients; in this latter population, the median time between diagnosis and imatinib start was 1.7 years, and 89.5% of these patients had previously received interferon.

The median age at registration was 51 years (range 18–94 years). Fifty-nine percent of patients were men and 74.5% were of white European descent. This relatively “young” age can be attributed in part to the inclusion in the ILTE study of patients from Mexico, Nigeria, and Korea, which have a younger population than more developed countries. Comorbidities were recorded in 49.5% of patients, with cardiovascular comorbidities being the most common (18.0%, mostly hypertension; Supplementary Table 2, available online). Notably, the prevalence of cardiovascular comorbidities in Korean patients was much lower than all other groups (3.9% vs 20.9%, P < .001), despite a comparable median age (45 years). Forty-seven patients (5.6%) had a history of malignancy, with breast cancer accounting for 38.3% of these malignancies (Supplementary Table 3, available online).

Median duration of study follow-up was 3.8 years (range 0.5–7.1 years), corresponding to 5.8 years (range 2.5–9.1 years) from the start of imatinib treatment. A total of 3247 person-years were available for analysis. The median duration of treatment was longer (6.3 years) in patients who received imatinib as a second-line therapy than in those who received it as first-line therapy (4.9 years). The median dose of imatinib was 400 mg/d at all years of follow-up, with mean doses ranging from 420 to 464 mg/d between registration and the latest follow-up. Patients receiving less than 400 mg/d (generally 300) ranged from 2% to 7%, whereas 11% to 23% were treated with more than 400 mg/d (generally 600). The median time to CCyR after starting imatinib was 6.5 months.

Safety Profile of Imatinib

Long-term toxic effects associated with imatinib appeared to be modest. Imatinib was discontinued in 75 patients (9.0%) because of side effects (19 patients, 2.3%), relapse or insufficient response (22 patients, 2.6%), or persistent PCR negativity (20 patients, 2.4%). Infrequent causes for permanent discontinuation were diagnosis of a second malignancy (three patients, 0.4%), enrollment in another research study (four patients, 0.5%), or financial or other reasons (seven patients, 0.8%). Among the 19 patients who discontinued treatment because of side effects, there were three patients with muscle cramps, two each with edema, skin toxicity, diarrhea, arthritis, cardiovascular events linked to therapy (one cerebral hemorrhage and one peripheral arteriopathy), and recurrent scleral hemorrhages, and one each with liver toxicity, pancreatitis, varicocele, and severe asthenia. The rate of imatinib discontinuation because of side effects was 0.6 per 100 person-years and appeared lower in the third and fourth year of treatment than in subsequent years (0.1 vs 1.2 per 100 person-years).

A total of 139 SAEs were reported (Supplementary Table 4, available online), with only 27 (19.4% of SAEs, 3.2% of patients) considered at least possibly linked to imatinib (Table 1), including seven patients (26% of these 27 SAEs) with gastrointestinal toxicity (diarrhea, esophagitis, gastritis, pancreatitis and liver toxicity), five patients (18.5%) with cardiovascular events (angina, heart failure and myocardial infarction), three with tendon or ligament lesions (11.1%), four with infections (14.8%), two with fever (7.4%), and one with skin rash (3.7%). The gastric surgery for weight gain by one patient was also linked to imatinib use. Thirty second cancers were reported, prostate and breast cancers being most common (Supplementary Table 5, available online). This incidence is comparable to the expected incidence of 28.6 cases.
based on the age and sex distribution of the population from worldwide cancer registries, although these results must be considered preliminary, given the available follow-up.

A total of 830 NSAEs were observed in 53% of the patients. The majority of NSAEs (560, 68%) were considered at least possibly related to imatinib (Table 2 and Supplementary Table 6, available online). As expected, patients developed the known side effects of imatinib, including edema, muscle cramps, and gastrointestinal disturbances (diarrhea and abdominal pain or distention). Other notable NSAEs were asthenia (4.8%), skin rash or fragility (4.6%), osteoarticular pain and tendon or ligament lesions (4.3%), conjunctivitis or scleral hemorrhages (3.7%), and a hazard ratio of men vs women equal to 0.71 (95% CI = 0.56 to 0.90). There were no differences according to age or the line of treatment (34.3%, 95% CI = 30.6% to 37.9%) increased to 32.6% (95% CI = 45.3% to 58.9%) after 8 years (Figure 1, A), with higher values in women (χ² statistic for standard log-rank test = 8.4, P = .004) and a hazard ratio of men vs women equal to 0.71 (95% CI = 0.56 to 0.90). There were no differences according to age or the line of therapy (data not shown). This pattern was maintained when the analysis was restricted to patients treated with 400 mg/d of imatinib.

In the NSAE cross-validation, patients were asked whether imatinib treatment had interfered in a substantial way with their quality of life during the preceding year. Fifty-two percent of patients answered positively to this question, whereas physicians reported NSAEs in 61.2% for patients. In 78% of the validated NSAEs (49 of 63), the evaluations of NSAE reports were concordant between patients and physicians. In 88% of the 49 concordant evaluations, patients and health professionals agreed on the specific type of NSAE. Thus, 68% of NSAE evaluations were concordant between patients and physicians in both specific type and occurrence of the NSAE.

Response to Imatinib
The majority of patients with stable CCyR after approximately 2 years of imatinib treatment maintained long-term CCyR with continued treatment. At 6 years from the start of treatment with imatinib, 94.9% (95% CI = 93.1% to 96.6%) of patients maintained their CCyR (Figure 1, B); this value decreased only moderately (89.5%, 95% CI = 85.4% to 93.8%) at 8 years.
A total of 45 patients lost CCyR during the observation period, corresponding to an overall rate of 1.4 per 100 person-years. Of those patients who started imatinib as first-line treatment, 15 lost CCyR, corresponding to a rate of 1.3 per 100 person-years (95% CI = 0.8 to 2.2) compared with 1.5 (95% CI = 1.0 to 2.1) in patients given imatinib as second-line therapy. The median time to loss of CCyR was 2.6 years (corresponding to 4.6 years of treatment). Similar values for loss of partial cytogenetic response (defined as >35% of Ph+ metaphases) were obtained, with a total rate of 0.9 per 100 person-years (1.0 per 100 person-years for imatinib as first-line therapy and 0.9 for second-line therapy).

The annual rate of CCyR loss for patients who received imatinib as first-line treatment was 0.6 (95% CI = 0.1 to 2.2), 1.5 (95% CI = 0.6 to 3.5), and 2.6 (95% CI = 1.1 to 5.6) in the third, fourth, and fifth year of imatinib treatment, respectively, whereas in the sixth year, no CCyR loss was reported. Analysis of annual rates of CCyR loss indicated that CCyR is very durable in this population, without major differences between patients treated with imatinib as first-line vs second-line therapy (Table 3).

Survival
CML-related deaths were uncommon in CML patients who were in CCyR 2 years after starting imatinib. A comparison of the observed mortality rate in CML patients with the rate in the general Italian population showed no excess mortality (Table 4). Twenty deaths were observed, with a 4.8% mortality incidence rate (standardized incidence ratio = 0.7; 95% CI = 0.40 to 1.10, \( P = 0.08 \)). Only six out of the 20 observed deaths were attributable to CML progression (Table 4). Estimated survival at 6 and 8 years was 97.7% (95% CI = 96.6% to 98.9%) and 95.2% (95% CI = 92.5% to 98.1%), respectively (Figure 1, C). The CML-related mortality accounted for only 1.0%, out of the 4.8% mortality incidence at 8 years (Figure 1, D). Thus, patients in this population are more likely to die of causes unrelated to CML. The mortality rates of the Italian centers were also compared with general population mortality rates in Italy, and no statistically significant differences were observed (data not shown).

Achievement of PCR Negativity
It is known that PCR represents a more sensitive assay than cytogenetics; thus it can be expected that a portion of patients in CCyR would also test negative by PCR (complete molecular
responders). A total of 733 patients had at least one PCR result available, with a median number of 2.0 PCR tests per person-year. By December 31, 2008, 179 patients (24.4% of the 733 patients, or 21.5% of all eligible patients) had been in complete molecular response for at least 1 year, including 125 patients with at least 2 years of negativity. Therefore, after a median treatment of almost 6 years, approximately 25% of patients were in durable complete molecular response, as assessed in their own centers.

### Racial and Ethnic Differences

The ILTE study cohort encompassed different racial and ethnic groups, including 128 Asian patients who differed from patients of other racial and ethnic groups (almost all of European origin).

### Table 3. Loss of complete cytogenetic remission during the Imatinib Long-Term Effects study follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median follow-up, y</th>
<th>Third</th>
<th>Fourth</th>
<th>Fifth</th>
<th>Sixth</th>
<th>Seventh</th>
<th>Eighth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib therapy†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-line</td>
<td>2.9</td>
<td>353.0 (0.6)</td>
<td>342.0 (1.5)</td>
<td>234.9 (2.6)</td>
<td>108.0 (0.0)</td>
<td>42.5 (2.4)</td>
<td>12.3 (0.0)</td>
</tr>
<tr>
<td>Second-line</td>
<td>4.3</td>
<td>474.0 (1.3)</td>
<td>469.1 (0.6)</td>
<td>436.0 (1.1)</td>
<td>364.6 (1.9)</td>
<td>215.7 (2.8)</td>
<td>103.4 (2.9)</td>
</tr>
<tr>
<td>Total</td>
<td>3.7</td>
<td>827.0 (1.0)</td>
<td>811.1 (1.0)</td>
<td>670.9 (1.6)</td>
<td>472.6 (1.5)</td>
<td>258.2 (2.7)</td>
<td>115.7 (2.6)</td>
</tr>
<tr>
<td>Age, y‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50</td>
<td>3.6</td>
<td>401.4 (1.0)</td>
<td>392.9 (0.8)</td>
<td>314.1 (2.2)</td>
<td>213.8 (1.9)</td>
<td>110.9 (1.8)</td>
<td>43.2 (0.0)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>3.9</td>
<td>426.6 (0.9)</td>
<td>418.2 (1.2)</td>
<td>356.8 (1.1)</td>
<td>258.8 (1.2)</td>
<td>147.3 (3.4)</td>
<td>72.4 (4.1)</td>
</tr>
<tr>
<td>Total</td>
<td>3.7</td>
<td>827.0 (1.0)</td>
<td>811.1 (1.0)</td>
<td>670.9 (1.6)</td>
<td>472.6 (1.5)</td>
<td>258.2 (2.7)</td>
<td>115.7 (2.6)</td>
</tr>
</tbody>
</table>

* Expressed as events per 100 person-years.
† Rates per year based on line of therapy.
‡ Rates per year based on age.

### Table 4. Deaths during Imatinib Long-Term Effects study follow-up and comparison with available rates in the Italian population*

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age at imatinib start, y</td>
<td>Time to death, y†</td>
</tr>
<tr>
<td>Surgery: post cholecystectomy complications</td>
<td>64</td>
<td>7.4</td>
</tr>
<tr>
<td>Second cancer</td>
<td>50</td>
<td>4.3</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>69</td>
<td>3.3</td>
</tr>
<tr>
<td>Complications after vascular surgery</td>
<td>69</td>
<td>3.5</td>
</tr>
<tr>
<td>CML progression</td>
<td>68</td>
<td>6.3</td>
</tr>
<tr>
<td>Motorcycle accident</td>
<td>77</td>
<td>5.1</td>
</tr>
<tr>
<td>Pneumonia unrelated to CML</td>
<td>65</td>
<td>5.1</td>
</tr>
<tr>
<td>Cardiac insufficiency</td>
<td>41</td>
<td>7.6</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>72</td>
<td>5.1</td>
</tr>
<tr>
<td>Malaria</td>
<td>68</td>
<td>5.5</td>
</tr>
<tr>
<td>Median time to death overall, y†</td>
<td>44</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Deaths

<table>
<thead>
<tr>
<th>Observed</th>
<th>Expected</th>
<th>SIR (95% CI) §</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>21.05</td>
<td>0.52 (0.26 to 0.94)</td>
</tr>
<tr>
<td>9</td>
<td>9.39</td>
<td>0.96 (0.44 to 1.82)</td>
</tr>
<tr>
<td>20</td>
<td>30.44</td>
<td>0.70 (0.40 to 1.10)</td>
</tr>
</tbody>
</table>

† From start of imatinib.
‡ Pneumonia with pleural effusion.
§ SIRs were calculated by dividing the observed number of events by the expected ones. The expected number of events was calculated by multiplying the number of person-years observed in each age class by the corresponding population rate. Confidence intervals for the SIR were obtained by the exact method. Two-sided P values.
in terms of cardiovascular comorbidities (Supplementary Table 2, available online). Therefore, Asian patients were compared with non-Asian ones on several parameters, including imatinib dose, CCyR loss, SAEs and NSAEs, second cancers, and survival. Only imatinib–related SAEs (Supplementary Figure 1, available online) were statistically significantly different in Asian patients (6.8% vs 2.6% at 6 years, P = .035), with a higher cumulative incidence of SAEs in Asian patients, possibly because of a trend toward higher imatinib plasma levels observed in Asian patients (18).

Discussion

The results presented here indicate that CML-related deaths are uncommon in CML patients who are in CCyR 2 years after starting imatinib and show, to our knowledge for the first time, that the overall survival of this population is not statistically significantly different from that of the general population, in contrast to survival after other therapies such as bone marrow transplantation (19,20). Notably, no statistically significant differences were noted between patients who received imatinib as first- or second-line therapy, further supporting the concept that once a stable CCyR is obtained, its duration becomes independent of known prognostic factors such as the line of treatment or the Sokal score (4). These data are consistent with data from several registries such as the Surveillance, Epidemiology, and End Results (SEER) database and show the extent to which imatinib reduced CML mortality and improved prognosis (Figure 2). The impact of imatinib treatment on CML survival observed in the ILTE study is probably greater than estimated. The conventional notion that in the preimatinib era the median duration of chronic phase-CML was 5 years (21), derived mostly from registration studies performed on very select patient populations and thus is probably overestimated. A recent analysis of the Swedish National Cancer Registry estimated that median survival of CML patients diagnosed from 1970 to 1995 ranged from 2 to 3 years (22).

The ILTE study represents, to our knowledge, the first independent assessment of imatinib long term effects in a global population of CML patients. Features that distinguish the ILTE from other studies are the focus on patients in CCyR after approximately 2 years of imatinib treatment, the participation of academic and nonacademic centers, and independent financial support. Other independent studies performed in single centers focused on efficacy, with a shorter follow-up (23,24).

The first 2 years of treatment represent the period in which the risk of relapse is the highest, presumably because of the selection of resistant cells already present at the time of treatment initiation. Moreover, severe toxic effects that mandate discontinuation of therapy tend to develop early in the course of therapy. The fact that ILTE patients were enrolled after these initial 2 years allowed us to focus on long-term effects, in terms of both toxic effects and response.

Approximately 25% of ILTE patients reside outside of Western Europe and North America, thus facilitating a global assessment of CML therapy and allowing the analysis of differences attributable to race, ethnicity, or lifestyle. The inclusion of 11 nonacademic centers in ILTE (accounting for 33% of all eligible patients) allowed a more realistic appraisal of CML management worldwide.

This study had several limitations. The ILTE study was not designed as an experimental protocol and therefore the management of patients was left to each participating center. Thus, differences in the schedule of cytogenetic and PCR testing among centers could cause some variation in the yearly rates of events (eg, the loss of CCyR) but should not affect the overall rates. The fluctuations of the yearly rates could, however, be attributable to the limited number of events when a year by year analysis was undertaken; this fact was also observed in experimental protocols such as the International Randomized Study of Interferon and STI571 (IRIS) study (6).

Independence from pharmaceutical companies is also an important consideration for clinical studies. Whereas initial registration trials are efficiently surveyed by the sponsoring companies, the reporting of adverse events (including second cancers) in patients who receive treatment outside of a clinical trial is notoriously
inefficient. In other cases, monitoring by the sponsor is discontinued after a few years, although many side effects may require a considerable length of time to develop and can only be captured with surveys. The example of Rofecoxib (VIOXX) (25) shows the importance of independent studies and researchers in analyzing the safety of medications (26). The results produced by the ILTE study will also be useful for sponsored studies because the credibility of their results will be enhanced by the existence of independent studies.

In 22 of 45 instances of CCyR loss by patients, imatinib was permanently discontinued, whereas in the remaining patients, imatinib dose increases controlled the disease at least temporarily. Although we do not have complete information on further treatments in the 23 patients who discontinued imatinib because of loss of CCyR, second-line TKIs were used for at least 15 patients, and their use probably contributed to minimization of CML-related mortality.

Long-term toxic effects associated with imatinib appeared to be modest because only 2.3% of patients stopped imatinib because of side effects (corresponding to a discontinuation rate of 0.6 per 100 person-years). It is important to note that the discontinuation rate is also affected by the availability of second-line TKIs. In fact, at least half the patients who discontinued imatinib for side effects did so for non-life-threatening toxic effects and switched to second-line TKIs. This type of discontinuation occurred only after 2006, the year in which dasatinib was approved as the first second-line TKI (http://www.cancer.gov/cancertopics/druginfo /ida-dasatinib).

NSAEs related to treatment were frequent events, with more than 50% of patients having at least one NSAE after 8 years of treatment, suggesting that patients treated with imatinib, although not experiencing severe toxic effects, frequently suffer from side effects that, although not serious, can reduce quality of life. The occurrence of NSAEs emphasizes the importance of a good provider–patient relationship, in which side effects are easily communicated and addressed to reduce or avoid noncompliance (27). Such relationships will require constant attention on the part of physicians who need to devote sufficient time to the seemingly unproblematic CML patients. A recent study found that the two main variables associated with treatment adherence in a group of CML patients were the number of CML patients seen at that center (and thus the probable existence of a dedicated CML clinic) and the duration of the first visit (27).

Approximately 25% of patients in the ILTE cohort were durably negative for the BCR-ABL1 fusion (as assessed by PCR) at 6 years of therapy. This rate is lower than those reported in several other cohorts, including the IRIS study (6), despite the fact that the ILTE cohort was selected on the basis of CCyR at 2 years. A possible reason for this discrepancy is that ILTE comprises a more realistic patient population that more adequately reflects the current state of CML therapy in the community. It is also important to remember that, because ILTE was a nonregistration trial, no centralization of PCR assays was performed, with single centers being free to participate (or not) in standardization programs.

The ILTE study results showing that the survival of this cohort of CML patients is not different from that of the general population are the indication of how profoundly imatinib has changed the clinical course of CML. These data may help physicians to advise CML patients about their prognosis on imatinib.

References


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