Imatinib mesylate is the sole BCR–ABL tyrosine kinase inhibitor approved as first-line treatment of accelerated-phase (AP) chronic myeloid leukemia (CML). Indication was based on the STI571 0109 study, in which imatinib favorably compared to historical treatments in patients failing prior therapies. The relevance of these results to currently newly diagnosed AP-CML patients remains unknown. We evaluated the benefit of imatinib in 42 newly diagnosed AP-CML patients. In all, 16 patients had hematological acceleration without chromosomal abnormalities in addition to the Philadelphia chromosome (ACAs; HEM-AP), 16 solely had ACAs (ACA-AP) and 10 had hematological acceleration plus ACAs (HEM-AP + ACA). Major cytogenetic responses were achieved in 93.7% of HEM-AP patients, 75% of patients with ACA-AP ($P = NS$) and 40% of patients with HEM-AP + ACA ($P = 0.0053$). The 24-month failure-free survival rate was 87.5% in HEM-AP patients, 43.8% in ACA-AP patients and 15% in HEM-AP + ACA patients ($P = 0.022$). The 24-month estimate of progression-free survival was 100% in HEM-AP patients, 92.8% in ACA-AP patients and 58.3% in HEM-AP + ACA patients ($P = 0.0052$). In conclusion, frontline imatinib allows favorable outcomes in HEM-AP and ACA-AP patients but appears insufficient for patients with HEM-AP + ACA. Broader-target and/or more potent BCR–ABL tyrosine kinase inhibitors alone or in combination may be considered in this setting.

Keywords: frontline imatinib; accelerated-phase; chronic myeloid leukemia

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm caused by a specific chromosomal rearrangement in hematopoietic stem cells, the Philadelphia chromosome (Ph1). Ph1 results from a balanced reciprocal translocation t(9;22)(q34;q11), leading to the formation of an abnormal fusion gene, BCR–ABL. This gene encodes the BCR–ABL oncoprotein with deregulated tyrosine kinase activity, which has a crucial role in CML pathogenesis.

The natural history of CML most commonly includes a chronic phase at diagnosis. In the absence of appropriate disease control, CML progresses towards an accelerated phase (AP) followed by a rapidly fatal blast crisis (BC). Up to 15% of patients with CML are already in AP at the time of diagnosis. Acceleration is thought to depend on the acquisition of genetic aberrations in addition to the BCR–ABL fusion gene, leading to an impaired differentiation potential of leukemic hematopoietic stem cells and a decreased responsiveness to therapy.

From 2001 onwards, imatinib mesylate, the first ATP-competitive inhibitor of the BCR–ABL oncoprotein, became the best initial treatment against CML due to its remarkable rate of responses at all disease stages and improved progression-free and overall survival (OS) compared with the previous treatment options. The STI571 0109 study, an international multicenter phase 2 open-label non-randomized trial, formed the basis for imatinib approval in AP-CML. Complete hematologic responses (CHR), major cytogenetic responses (MCyR) and complete cytogenetic responses (CCyR) were reported for 53%, 24% and 17% of patients, respectively, and estimated OS rate at 12 months was 74%. An independent analysis demonstrated the survival advantage conferred by imatinib compared with historical treatments in AP-CML patients. However, a long-term survey of the STI571 0109 trial indicated that 82% of patients were withdrawn from imatinib mainly because of unsatisfactory response or progression to BC, toning down the enthusiasm initial results had generated. It is important to underline that in this trial, patients were enrolled regardless of their prior disease and treatment history. As a result, the relevance of the results from the STI571 0109 trial to the current newly diagnosed AP-CML patients who are being offered imatinib frontline is somewhat difficult to define.

This gap in our knowledge about the outcome of imatinib-treated newly diagnosed AP-CML patients urged us to evaluate the benefit of the drug in the context of a retrospective multicenter analysis.

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ORIGINAL ARTICLE

First-line imatinib mesylate in patients with newly diagnosed accelerated phase-chronic myeloid leukemia

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Keywords: frontline imatinib; accelerated-phase; chronic myeloid leukemia
PATIENTS AND METHODS

Patients

Forty-two patients of at least 18 years of age meeting criteria for AP-CML at diagnosis and treated with first-line imatinib were included in this analysis. Hematological criteria of acceleration were those selected by the European LeukemiaNet. They were identified by Kantarjian et al. before the imatinib era and adopted in the STI571 0109 registration trial. They proved to retain their validity in patients treated with imatinib. Hematological acceleration was defined by any of the following features: at least 15 to less than 30% blasts in peripheral blood or bone marrow, more than 30% blasts plus promyelocytes provided that less than 30% blasts are present, at least 20% peripheral blood basophils or platelets less than \(100 \times 10^9/l\) unrelated to therapy. We decided to also include patients with chromosomal abnormalities in addition to the Ph1 (ACAs) at diagnosis but without cytological feature of AP. Indeed, ACAs used to be recognized as a key factor of disease acceleration at diagnosis and remain an important adverse prognostic feature in the imatinib era.

Cytogenetic analyses

Analysis of karyotypes from bone marrow cells was based on 20 metaphases or more. Results were interpreted according to the International System for Human Cytogenetic Nomenclature. In brief, an abnormality was considered clonal when at least two metaphases carried the same aberration in case of a structural abnormality or an extra chromosome. In case of a monosomy, it had to be present in at least three metaphases. Ph1 variant translocation and constitutional cytogenetic abnormalities were excluded from ACA definition.

Evaluation of responses

A CHR corresponded to the absence of extramedullary involvement together with normal platelets and leukocytes differential counts.

Table 1. Acceleration features at diagnosis and initial imatinib treatment

<table>
<thead>
<tr>
<th></th>
<th>All, n (%)</th>
<th>ACAs only</th>
<th>Hematological acceleration only</th>
<th>Hematological acceleration + ACAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PB(^a); or marrow blasts 15–29(^b)</td>
<td>42</td>
<td>16</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>PB or marrow blasts + promyelocytes (\geq 30%) and blasts &lt; 30%</td>
<td>14 (33%)</td>
<td>0</td>
<td>7 (43%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>PB basophils (\geq 20%)</td>
<td>3 (7%)</td>
<td>0</td>
<td>3 (18%)</td>
<td>0</td>
</tr>
<tr>
<td>Platelets (&lt;100 \times 10^9/l) unrelated to therapy(^b)</td>
<td>6 (14%)</td>
<td>0</td>
<td>6 (37%)</td>
<td>0</td>
</tr>
<tr>
<td>ACAs</td>
<td>5 (12%)</td>
<td>0</td>
<td>2 (12%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td></td>
<td>26 (62%)</td>
<td>16 (100%)</td>
<td>0</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Imatinib starting dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>600 mg/d</td>
<td>14 (33%)</td>
<td>11 (69%)</td>
<td>2 (12%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td></td>
<td>28 (67%)</td>
<td>5 (31%)</td>
<td>14 (88%)</td>
<td>9 (90%)</td>
</tr>
</tbody>
</table>

Abbreviation: ACAs, additional chromosomal abnormalities. \(^a\)Peripheral blood. \(^b\)One patient harbored both basophils \(\geq 20\%\) and PB or marrow blasts between 15 and 29\% at diagnosis and another had platelet counts \(<100 \times 10^9/l\) unrelated to therapy and PB or marrow blasts between 15 and 29\% at diagnosis.

Table 2. Additional chromosomal abnormalities (ACAs) at diagnosis (n = 26)

<table>
<thead>
<tr>
<th>ACs</th>
<th>Isolated</th>
<th>+ Others</th>
<th>Total (%)</th>
<th>Isolated</th>
<th>+ Others</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 8</td>
<td>4</td>
<td>1(^a)</td>
<td>5 (31%)</td>
<td>0</td>
<td>1</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Ph1 duplication</td>
<td>3</td>
<td>1(^a)</td>
<td>4 (25%)</td>
<td>2</td>
<td>0</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Chromosome 6 abnormalities</td>
<td>3</td>
<td>1(^a)</td>
<td>4 (25%)</td>
<td>1</td>
<td>0</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Del(20q)</td>
<td>0</td>
<td>1</td>
<td>1 (6%)</td>
<td>0</td>
<td>1</td>
<td>0 (10%)</td>
</tr>
<tr>
<td>Monosomy 7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0 (10%)</td>
</tr>
<tr>
<td>Del(5q)</td>
<td>1</td>
<td>0</td>
<td>1 (6%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>t(3;21)(q26;q22)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1(^b)</td>
<td>0 (10%)</td>
</tr>
<tr>
<td>Chromosome 17 abnormalities</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1(^b)</td>
<td>0 (10%)</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>5</td>
<td>7 (43%)</td>
<td>2</td>
<td>4</td>
<td>6 (60%)</td>
</tr>
</tbody>
</table>

\(^a\)One patient carried five ACAs including trisomies of chromosomes 6, 8, 10, 11, 19 together with a double Ph1. \(^b\)Additional material on the long arm of chromosome 17, together with a monosomy 19.

Sustained CHR was defined as a CHR lasting for at least 4 weeks. CyRs were measured every 3–6 months until a CCyR was obtained. CyRs were categorized as follows: complete (CCyR: Ph1 0%), partial (partial CyR: Ph1 1–35%) or major (MCyR: Ph1 0–35%). Molecular responses were monitored every 3–6 months by real-time quantitative PCR on peripheral blood, although molecular follow-up on peripheral blood should be interpreted with caution in advanced phase CML. A major molecular response was defined as a BCR–ABL/control gene IS ratio equal or less than 0.1%, provided that the breakpoint in the BCR gene occurred in the major (M) breakpoint cluster region. Imatinib failure referred to treatment discontinuation owing to the lack of a CHR by 3 months, the absence of a MCyR by 6 months or no CCyR by 12 months (primary failure), a loss of previous CHR or MCyR at anytime during treatment (secondary failure), progression to BC or death. Disease progression was defined as treatment discontinuation owing to the transformation to BC or death.

Statistical analyses

Differences in rates of responses and treatment failure were analyzed with the Fisher’s exact test using two-tailed P values. Survival analyses were estimated by the Kaplan–Meier method and compared by the log-rank test. Failure-free survival (FFS) was calculated from the start of imatinib therapy to drug withdrawal due to treatment failure. Progression-free survival (PFS) was calculated from the start of imatinib therapy to drug withdrawal due to the occurrence of BC or death. FFS was also analyzed based on the presence or absence of a MCyR at 6 months. For this landmark analysis, patients had to be treated with imatinib up to or beyond the 6-month time point, thus patients who discontinued imatinib owing to treatment failure before the 6-month time point were excluded. OS was calculated as the time from imatinib treatment start to the date or death from any cause.

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RESULTS

Patients’ characteristics

Forty-two patients diagnosed with AP-CML entered this multicenter retrospective analysis. In all, 31 patients (74%) were males and 11 (26%) were females. The median age at diagnosis was 46 years (range, 19–67). A total of 26 patients (62%) met criteria for hematological acceleration and 16 (38%) solely had cytogenetic acceleration (Table 1). In those patients with hematological acceleration, the presence of ACAs was a common feature at diagnosis, with an observed frequency of 38.4% (10/26). The median percentage of metaphases with ACAs was 84% (range, 8–100). ACAs most commonly involved trisomy 8, a Ph1 duplication, or abnormalities in chromosome 6 (Table 2). Fusion transcripts were of the M-BCR–ABL type in all patients but one with an e19a2 transcript variant. Imatinib was initiated after a median time since CML diagnosis of 16 days (1–79). The starting dose of imatinib was 600 mg daily in 28/42 (67%) patients, 400 mg daily in 14 (33%) of the remaining patients. The majority (11/14) of patients in the latter dose group had ACAs without hematological acceleration (Table 1). Median imatinib treatment duration was 24 months (range, 1–95) and median follow-up since imatinib initiation was 39 months (8–107).

Overall responses to imatinib

Overall, 38/42 (90.5%) patients achieved a CHR on at least one occasion, and 36/42 (87.5%) had a CHR sustained for at least 4 weeks. The median time to achieve a sustained CHR was 38 days (0–151). A MCyR was obtained by 31/42 (74%) patients and the CyR was complete in 25 (60%). The median time to obtain a MCyR or CyR was 6 months (3–13). Seventy-five percent of patients with a CCyR also gained a major molecular response and the median time to the major molecular response was 9 months (6–34).

Several factors were evaluated for possible association with the achievement of responses. Best rates of CHR, MCyR and CCyR did not significantly differ between patients from the 400 and 600 mg-dose groups (not shown). However, it should be noted that 9/14 (64.3%) patients who started imatinib at 400 mg/d underwent dose escalation to 600 mg daily, including 7 patients with ACAs in the absence of hematological acceleration and 2 patients with hematological acceleration and no ACAs. Similar rates of CHR, MCyR and CCyR during imatinib therapy were obtained in patients with hematological acceleration and in those solely harboring ACAs at diagnosis (Figure 1a). Baseline hematological parameters such as platelet count, basophils and blasts percentage failed to affect responses, perhaps due to small sample size in our subgroup analysis (not shown). Interestingly, a trend toward inferior MCyR and CCyR rates was noted in patients with ACAs compared with those without ACAs (Figure 1b). Patients were thus divided into three categories according to disease characteristics at diagnosis: one with hematological acceleration features but no evidence of ACAs (HEM-AP, n = 16), a second category with ACAs only (ACA-AP, n = 16) and a third category with hematological acceleration plus ACAs (HEM-AP + ACA, n = 10). In all, 15 (93.7%) of 16 HEM-AP patients obtained a sustained CHR, compared with 14 (87.5%) of 16 ACA-AP patients and 7 of 10 (70%) patients with HEM-AP + ACA, and CHR rates did not significantly differ among the three subgroups (Figure 1c). MCyR occurred in 15/16 (93.7%) HEM-AP patients, compared with 12/16 (75%) ACA-AP patients (P = NS) and 4/10 (40%) patients with HEM-AP + ACA (P = 0.0053; Figure 1c). CCyR was seen in 13/16 (81.2%) patients with HEM-AP, compared with 9/16 (56.2%) patients with ACA-AP (P = NS) and 3/10 (30%) patients with HEM-AP + ACA (P = 0.0152; Figure 1c).

Treatment outcome and survival

In all, 22 out of 42 (52.4%) patients stopped imatinib after a median time on the drug of 9 months (1–91) owing to imatinib failure in 19/42 (45.2%), prolonged grade 1–2 non-hematological adverse events in 2/42 (4.8%) or enrollment in an imatinib-discontinuation trial in 1/42 (2.4%). Reasons for failure were lack or loss of an appropriate response (n = 14) or progression to BC (n = 5) while on imatinib. Patients who failed stopped therapy after a median time of 8 months (1–24) and were offered varying therapeutic options including second generation tyrosine kinase inhibitors alone or in combination with high dose chemotherapy, allogeneic hematopoietic stem cell transplantation or omacetaxine. At the time of imatinib discontinuation, new ACAs had emerged in 3/19 patients and BCR–ABL mutations were identified in 6/16
(37.5%) patients (1/2 HEM-AP, 3/7 ACA-AP and 2/7 HEM-AP + ACA) in whom BCR-ABL mutational assessment data were available, including an E255K in 4 cases, an E355G in 1 case and a T315I in 1 case.

Overall, the estimated 24-month FFS rate was 54.2% (95% CI, 39–69.5%; Figure 2a). Highest 24-month FFS rate, 85.7% (95% CI, 71.3–100%), was observed in HEM-AP patients, compared with 43.8% (95% CI, 19.5–68.1%) in ACA-AP patients and 15% (95% CI, 0–40.2%) in patients with HEM-AP + ACA (P = 0.022; Figure 2b). Patients with HEM-AP had a significantly better FFS than patients with ACA-AP and HEM-AP + ACA (P = 0.0164 and P = 0.0004, respectively), whereas there was no significant difference between these two latter sub-groups. In the ACA-AP subgroup, trisomy 8 and chromosome 6 abnormalities seemed particularly associated to treatment failure (not shown). The overall estimated 24-month PFS rate was 87.2% (95% CI, 76.6–97.7%; Figure 3a). Highest 24-month PFS rates, 100%, were seen in HEM-AP patients, compared with 92.8% (95% CI, 79.3–100%) in the ACA-AP subgroup and 58.3% (95% CI, 26.7–89.9%) in patients with HEM-AP + ACA (P = 0.0052; Figure 3b). Patients from both HEM-AP and ACA-AP subgroups had a significantly better PFS than patients with HEM-AP + ACA (P = 0.04 and P = 0.0059, respectively), whereas there was no significant difference between these two former sub-groups. PFS was also evaluated by CyR category at a 6-month landmark. Early CyRs revealed predictive of outcome as patients without a CyR at 6 months had a significantly lower 24-month PFS rate 76.2% (95% CI, 55.2–100%) than patients who achieved a MCyR at 6 months (100%, P = 0.0131; Figure 4). In all, 7 out of 42 (16.7%) patients died following discontinuation of imatinib, among whom 4 had progressed to BC while on the drug and 3 had failed imatinib. Four of these patients belonged to the HEM-AP + ACA category and three had ACA-AP. The main cause of death was BC (n = 6). Overall, the estimated 24-month OS rate was 87.8% (95% CI, 77.8–97.8%; Figure 5a), 100% in HEM-AP patients, 86.6% (95% CI, 69.4–100%) in ACA-AP patients and 57.1% (95% CI, 25–89.2%) in patients with HEM-AP + ACA (P = 0.0157; Figure 5b).

**DISCUSSION**

Our study is the first to specifically focus on newly diagnosed AP-CML as imatinib has entered the realm of daily clinical practice. Results demonstrated a substantial effectiveness of frontline imatinib treatment in AP-CML patients, with CHR, MCyR and CCyR in 87.2%, 74% and 60% of patients, respectively. These response rates were consistent whether or not patients with ACAs as the sole criteria for acceleration were included in the analyses. These rates of response favorably compared with the range of 34–80% of CHR, 24–35% of MCyR and 17–24% of CCyR reported in three previous studies including the STI571 0109 trial, a study from the
First-line imatinib mesylate in patients with AP-CML

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MD Anderson Cancer Center and an independent prospective trial from the GIMEMA CML working party. A key difference between our study and historical data lies in the fact that only newly diagnosed AP-CML patients were taken into account in our series while the vast majority of populations enrolled in clinical trials had evolved to AP after failure of at least one line of therapy such as interferon or cytarabine. Thus, despite the retrospective nature of our work, we can reasonably conclude that imatinib in AP-CML appears more efficient in the frontline setting than in ‘late’ AP, and this observation parallels that made in the chronic phase. In addition, the prognosis of patients markedly differed according to disease characteristics at diagnosis. Patients with exclusive HEM-AP fared best, with highest response rates, FFS, PFS and OS. Although ACA-AP patients showed response rates similar to those of HEM-AP patients, we found that their outcome was markedly less favorable due to a reduced FFS. This result was fairly unexpected because ACAs alone at diagnosis are no longer regarded as a major factor of disease acceleration as imatinib has entered the therapeutic arsenal against CML. Instead, they are simply considered as a ‘warning’ feature within the chronic phase of the disease. 

Frontline imatinib in AP-CML was obviously associated with favorable outcomes, as attested by 24-month rates of OS, PFS and FFS of 87.8%, 87.2% and 54.2%, respectively. As previously reported in AP-CML patients who received imatinib after failure of other therapies, early CyR to imatinib was predictive of outcome, a finding that may be used to identify those patients who may benefit from a change in therapy. In addition, the prognosis of patients markedly differed according to disease characteristics at diagnosis. Patients with exclusive HEM-AP fared best, with highest response rates, FFS, PFS and OS. Although ACA-AP patients showed response rates similar to those of HEM-AP patients, we found that their outcome was markedly less favorable due to a reduced FFS. This result was fairly unexpected because ACAs alone at diagnosis are no longer regarded as a major factor of disease acceleration. In the Chronic phase of the disease. 

As a result, most ACA-AP patients of our series simply considered as a ‘warning’ feature within the chronic phase criteria for acceleration. To conclude, frontline imatinib for CML patients with disease acceleration is a valuable option but ACAs at diagnosis remain as an unfavorable prognostic feature, especially when hematological criteria for acceleration are also present. To date, AP-CML patients may benefit from the highly potent second generation tyrosine kinase inhibitors dasatinib or nilotinib only if they develop intolerance or resistance to imatinib. Because the recent approval of these compounds in the frontline setting is exclusively reserved for chronic phase-CML. Further clinical trials are warranted in newly diagnosed AP-CML patients in order to assess the benefit of broader-targeted and/or more potent BCR-ABL tyrosine kinase inhibitors alone or as part as combination strategies.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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REFERENCES

Figure 5. Overall survival of first-line imatinib-treated AP-CML patients. For the total AP-CML population (n = 42, 36 censored observations) (a) and for patients with HEM-AP, ACA-AP and HEM-AP + ACA (b).


