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Brief report

Early prediction of response in patients with relapsed or refractory Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph\textsuperscript{+} ALL) treated with imatinib

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Imatinib has pronounced but brief antileukemic activity in advanced Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph\textsuperscript{+} ALL). We assessed the prognostic impact of pretreatment disease features and the early bone marrow (BM) response in 68 consecutive patients with Ph\textsuperscript{+} ALL receiving imatinib salvage therapy. A complete hematologic or marrow response was achieved by 92% of patients with BM blasts below 5% on day 14, whereas 62.5% of patients with more than 5% BM blasts on day 14 were nonresponders. Similarly, time to progression (TTP) was superior in patients with a good day 14 response (5.2 versus 0.9 months; \( P < .0001 \)). Prior complete remission of less than 6 months, white blood cell count of more than 10 \( \times 10^9 \)/L, circulating peripheral blood blasts at diagnosis, additional Philadelphia chromosomes, or at least 2 Bcr-Abl fusion signals were associated with significantly inferior remission rate and response duration. In patients without poor prognostic features, single-agent imatinib may be appropriate before transplant salvage therapy. Conversely, patients with clinically or cytogenetically defined poor-risk features are candidates for trials of upfront imatinib in combination with other agents. (Blood. 2004;103:1495-1498)

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Introduction

The prognosis of patients with Philadelphia chromosome–positive acute lymphoblastic leukemia (ALL) is poor.\textsuperscript{1-3} Allogeneic stem cell transplantation (alloSCT) in first complete remission (CR) is potentially curative, but is rarely successful after failure of first-line therapy.\textsuperscript{1,4-7} Imatinib (Glivec; Novartis, Basel, Switzerland) has significant antileukemic activity and a favorable toxicity profile in advanced Ph\textsuperscript{+} ALL.\textsuperscript{8,10} and results of alloSCT during imatinib-induced remission are encouraging. Conversely, outcome in patients resistant to imatinib is extremely poor.\textsuperscript{11} As up to 30% of patients are primary refractory and disease progression occurs after a median of only 2.2 months,\textsuperscript{12} prediction of response and response duration would be valuable to guide treatment. We identified clinical and laboratory parameters that permit prediction of the probability of remission and allow an estimate of the response duration.

Study design

Imatinib therapy

We analyzed 68 patients with relapsed or refractory Ph\textsuperscript{+} ALL (n = 66) or minimal residual disease (n = 2) who were enrolled in 2 multicenter phase 2 studies of imatinib. The design of study 109 (n = 14) has been described previously,\textsuperscript{10} and is comparable to the expanded-access study 114 (n = 54; Table 1). Initial imatinib doses were 600 mg (n = 63), 400 mg (n = 4), or 300 mg (n = 1). Allogeneic or autologous SCT had been performed in 20 (29%) and 4 (6%) patients, respectively. Cytogenetic and interphase fluorescence in situ hybridization (FISH) analyses were performed by standard techniques. Complex chromosomal aberrations were defined as 3 or more abnormalities in addition to the Philadelphia chromosome. Quantitative real-time polymerase chain reaction (PCR; Taqman; Perkin Elmer Applied Biosciences, Weiterstadt, Germany) and “nested PCR” analysis were performed as previously published.\textsuperscript{12,13} Approval for the studies was obtained from the Ethics Committee of the Johann Wolfgang Goethe-Universität, Frankfurt, Germany. Informed consent was provided according to the Declaration of Helsinki.

Statistical analysis

Follow-up has been updated to December 1, 2002. Kaplan-Meier analyses and log rank test were performed using the GraphPad Prism software package (GraphPad Software, San Diego, CA). For the TTP analysis, patients undergoing SCT were censored at the time of transplantation. The Fisher exact test (2-sided) was performed using the BIAS statistical software program (Dr Hans Ackermann, Frankfurt/Main, Germany).
and C indicates the 50% level.

Extra Ph chromosomes and/or Bcr-Abl signals in more than 20% of nuclei had a significantly inferior TTP and OS (1 month and 4.4 months, respectively). The fitted line in panels A and C indicates the 50% level.

Results and discussion

Efficacy and safety

The overall hematologic response rate in these 68 patients was 70%, with 30% in complete hematologic remission (CHR), 29% in marrow CR, and 11% in partial remission (PR), consistent with previous reports. Twenty patients (30%) were refractory to imatinib. Blast clearance from PB occurred after a median of 9 days (range 3-21 days) in 37 (90%) of 41 patients, including 14 patients (38%) without a marrow response. Imatinib was discontinued because of disease progression (n = 53; 78%), transfer to alloSCT while in CR (n = 10; 15%), and patient decision (n = 1).

A complete cytogenetic remission was induced in the majority of CHR (16 of 18; 89%) and marrow CR patients (10 of 13; 77%) with sufficient cytogenetic and/or FISH data. Bcr-Abl transcripts became undetectable by quantitative reverse transcriptase (RT)-PCR on at least one occasion in 10 (28%) of 36 CHR or marrow CR patients. Molecular and cytogenetic remissions were rarely sustained, and relapse occurred after a median of 4 months (range, 0.5-5.0 months). Four patients are in ongoing CHR (n = 3) or marrow CR (n = 1) a median of 21 months (range, 12.5-33.7) months after starting imatinib. Progression-free survival is 22.8% ± 5.8% at 6 months. Overall survival (OS) of all patients is 33.3% ± 5.8% at 12 months and 22.6% ± 5.4% at 18 months (Figure 1A).

Median TTP in patients with CHR (n = 20) was 5.4 months, compared with 2.9 months in patients achieving a marrow CR (n = 19; P = .07), 1.7 months in patients with a PR (n = 7; P < .0001), and 0.7 months in imatinib refractory patients (n = 20; P < .0001). Extending previous reports, only patients achieving a CHR are likely to have a clinically meaningful longer window of opportunity for undergoing alloSCT compared with overall TTP of 2 months (range, 0.1-14.9 months).

Adverse events attributed to imatinib were grade II/III nausea and vomiting, fluid retention, and muscle cramps. Grade III/IV neutropenia or thrombocytopenia developed in 50% and 19% of patients, respectively. Bifrontal cerebral hygromas developed in 2 patients with grades III-IV thrombocytopenia. More than 80% of patients were treated either exclusively (40 of 68; 59%) or

Table 1. Patient characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (range)</td>
<td>48 (17.7-60)</td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td>Male 37 (54.4), Female 31 (45.6)</td>
</tr>
<tr>
<td>Disease status, no. (%)</td>
<td>First relapse 28 (41), Second or later relapse 13 (19), Primary refractory 25 (37), CR1 2 (3)</td>
</tr>
<tr>
<td>Subtype of ALL, no. (%)</td>
<td>c-ALL 49 (72), Pre-B-ALL 14 (21), BIPH 12 (18), NA 3 (4)</td>
</tr>
</tbody>
</table>
| Subtype of ALL, no. (%) | Complex karyotype 22 (34), No. of prior chemotherapy cycles, median (range) 3 (1-10), Prior CNS irradiation, no. (%) 29 (43), No. of prior chemotherapy cycles, median (range) 3 (1-10), Prior CNS irradiation, no. (%) 29 (43), Prior infectious complications of grade III or IV, no. (%) 6 (9), Fungal infections 13 (19), Septicemia 12 (18), Prior SCT, no. (%) 20 (29), AutoLOGous 4 (6), Median time from diagnosis to study entry, mo (range) 7 (2-66), Median duration of CR1, mo (range) 7 (1-44), Median WBC count, × 10^9/L (range) 6.1 (0.2-176), WBC count of at least 10 × 10^9/L, no. (%) 24 (35.3), Median % of blasts in bone marrow (range) 84 (5-99), Median platelets, × 10^9/L (range) 63 (11-472), Blast clearance from PB occurred after a median of 9 days (range 3-21 days) in 37 (90%) of 41 patients, including 14 patients (38%) without a marrow response. Imatinib was discontinued because of disease progression (n = 53; 78%), transfer to alloSCT while in CR (n = 10; 15%), and patient decision (n = 1). A complete cytogenetic remission was induced in the majority of CHR (16 of 18; 89%) and marrow CR patients (10 of 13; 77%) with sufficient cytogenetic and/or FISH data. Bcr-Abl transcripts became undetectable by quantitative reverse transcriptase (RT)-PCR on at least one occasion in 10 (28%) of 36 CHR or marrow CR patients. Molecular and cytogenetic remissions were rarely sustained, and relapse occurred after a median of 4 months (range, 0.5-5.0 months). Four patients are in ongoing CHR (n = 3) or marrow CR (n = 1) a median of 21 months (range, 12.5-33.7) months after starting imatinib. Progression-free survival is 22.8% ± 5.8% at 6 months. Overall survival (OS) of all patients is 33.3% ± 5.8% at 12 months and 22.6% ± 5.4% at 18 months (Figure 1A).

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Figure 1. Response to imatinib treatment by Kaplan-Meier analyses. (A) Time to progression (TTP) and overall survival (OS) calculated from the start of imatinib treatment for all 68 patients. Ten patients discontinued therapy to undergo alloSCT. All patients were followed up until October 2003, and the median duration of follow-up was 12 months (range, 0.5-33.7 months). The estimated survival rates for all patients were 51% at 12 months and 57% at 18 months without censoring at the time of transplantation. The overall hematologic response rate in these 68 patients was 70%, with 30% in complete hematologic remission (CHR), 29% in marrow CR, and 11% in partial remission (PR), consistent with previous reports. Twenty patients (30%) were refractory to imatinib. Blast clearance from PB occurred after a median of 9 days (range 3-21 days) in 37 (90%) of 41 patients, including 14 patients (38%) without a marrow response. Imatinib was discontinued because of disease progression (n = 53; 78%), transfer to alloSCT while in CR (n = 10; 15%), and patient decision (n = 1).

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predominantly (17 of 68; 25%) on an outpatient basis for the duration of imatinib treatment.

Remission rate and duration in relation to early imatinib response

We found the response kinetics, assessed by day 14 BM cytology, to be predictive of remission rate and response duration. Marrow blasts were reduced to less than 5% in 26 (52%) of 50 evaluable patients, with a subsequent CHR (16 of 26 patients) or marrow CR (8 of 26 patients) rate of 92%. In contrast, 15 (62.5%) of 24 patients with day 14 BM blasts of more than 5% were refractory to imatinib; only 9 patients eventually achieved a CHR (n = 3; 12.5%), marrow CR (n = 3; 12.5%), or PR (n = 3; 12.5%). Moreover, TTP was significantly longer in patients with fewer than 5% day 14 BM blasts (5.2 months [range, 0.7-14.9 months] versus 0.9 months [range 0.4-5.0 months]; P < .0001; Figure 1B). Day 14 BM cytology therefore reflects the leukemic blast’s sensitivity to imatinib, analogous to the early steroid response in childhood ALL, and is a good clinical predictor of imatinib response. Notably, day 14 BM cytology correlated significantly (P = .02; Fisher exact test) with the results of microarray analysis previously shown by us to predict responsiveness to imatinib (data not shown).

Pretreatment parameters and response to imatinib

Genomic amplification of Bcr-Abl may lead to imatinib resistance in chronic myeloid leukemia (CML), but its role in Ph−ALL is unclear. A double Philadelphia chromosome or up to 2 additional Bcr-Abl fusion signals were detected in leukemic cells from 23 (36%) of 64 patients. This was predictive of a low probability of CHR (13% versus 39%; P = .04), shorter TTP (1.6 months versus 3.2 months; P = .006), and inferior OS (5.2 months versus 9.6 months; P = .01; Figure 1C). Bcr-Abl amplification may thus contribute to primary refractoriness of Ph−ALL to imatinib, whereas point mutations of Bcr-Abl are the primary cause of secondary resistance. Complex chromosomal aberrations alone were not associated with an inferior response.

The probability of achieving a CHR was higher in patients with a baseline WBC count of less than 10 × 10^9/L (41% versus 12.5%; P = .025), no circulating blasts pretreatment (50% versus 18%; P = .005), and a prior CR of at least 6 months (35% versus 12.5%; P = not significant). Similarly, TTP was significantly longer in patients with a lower WBC count (2.3 months versus 1.6 months; P = .03), no initial peripheral blood (PB) blasts (3.2 months versus 1.7 months; P = .05), and longer (≥ 6 months) CR1 (2.9 months versus 1.4 months; P = .008). Disease status at study start did not affect the probability of achieving a CHR or marrow CR, although OS was longer in patients in first as opposed to at least second relapse (6.9 months versus 3.0 months; P = .002). Remission rates and outcome did not differ significantly between patients with p190Bcr−Abl and p210Bcr−Abl expressing Ph−ALL, despite suggestions of a more aggressive clinical course of p190Bcr−Abl.21,22 Age, gender, immunologic subtype, and previous chemotherapy did not influence remission rate or outcome.

In advanced Ph−ALL, it is essential that alloSCT be performed as early as possible. Imatinib is attractive as salvage therapy preceding alloSCT because of its favorable toxicity profile, but its value is profoundly limited by a 30% primary resistance rate and rapid development of acquired resistance. Since alloSCT yields promising results only if performed during CR, single-agent imatinib is inappropriate in patients likely to have an insufficient response. We show that the day 14 marrow with a cutoff at 5% blasts is predictive of a patient’s response to imatinib and survival. Pretreatment variables including bcr abl amplification, high WBC count, and circulating blasts are as important in predicting imatinib response as the day 14 marrow and may be more clinically relevant, as they enable identification of patients unlikely to benefit from single-agent imatinib. These prognostic parameters are valuable for decisions regarding imatinib-based pretransplantation treatment of patients with advanced Ph−ALL.

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References


