Risk and Prognosis of Central Nervous System Leukemia in Patients with Philadelphia Chromosome-Positive Acute Leukemias Treated with Imatinib Mesylate


Departments of Hematology and Oncology, Johann Wolfgang Goethe-Universität, 60590 Frankfurt [H. P., B. W., W.-K. H., M. K., U. S., P. B., A. B., N. G., D. H., O. G. O.]; Departments of Hematology and Oncology, University Carl Gustav Carus, Dresden 01307 [E. S.]; Departments of Hematology and Oncology, Evangelisches Diakonie Krankenhaus, Bremen 28239 [T. W.]; Departments of Hematology and Oncology, Albert-Ludwigs Universität, Freiburg 79106 [M. L.]; Departments of Hematology and Oncology, Robert-Bosch Krankenhaus, Stuttgart 70376 [L. L.]; and Departments of Hematology and Oncology, Novartis Pharma AG, Nürnberg 90429 [H. G.], Germany

ABSTRACT

Purpose: In patients with acute leukemias, a lymphoid phenotype, the presence of a Philadelphia chromosome (Ph), and inadequate central nervous system (CNS)-directed prophylactic therapy are risk factors for CNS involvement. Imatinib mesylate has promising single-agent antileukemic activity in patients with advanced Ph+ acute leukemias. It was the aim of this analysis to determine the incidence of, and risk factors associated with, meningeal leukemia during imatinib monotherapy.

Study design: We analyzed 107 consecutive patients with relapsed or refractory Ph+ acute lymphoid leukemia (ALL; n = 65) or chronic myeloid leukemia blast crisis (n = 42) who were enrolled in successive Phase II trials of single-agent imatinib and who did not receive routine prophylactic intrathecal chemotherapy.

Results: CNS leukemia developed in 13 of 107 patients (12%) and was associated primarily with a lymphoid or bilineage phenotype (12 of 78; 15%) and with imatinib refractory Ph+ ALL (5 of 19; 26%). Meningeal leukemia did not occur among patients who received prior prophylactic cranial irradiation. The median survival with combined CNS and systemic disease was 108 days (range, 58–141), with no patient surviving long term. In contrast, two of three patients with exclusively meningeal leukemia achieved prolonged molecular remissions with intrathecal chemotherapy, cranial irradiation, and continued imatinib.

Conclusions: Patients with Ph+ ALL are at considerable risk of meningeal leukemia during imatinib monotherapy and should routinely receive CNS prophylaxis. Although the prognosis with combined meningeal and systemic relapse is dismal, patients with an isolated meningeal relapse may still achieve sustained remissions. The optimal type of CNS-directed treatment and the extent of protection afforded by prophylactic cranial irradiation remain to be defined.

INTRODUCTION

The CNS 2 is a well recognized site of extramedullary leukemia that is involved with greater frequency in ALL than in myeloid leukemias (1–5). Up to 6% of adult patients with ALL have evidence of CNS leukemia at diagnosis (2, 6). Patients in LyBC of CML have an incidence of meningeal leukemia comparable with that of ALL (7–9). During chemotherapy, CNS relapse rates of up to 30% have been reported in historical studies in patients not receiving adequate CNS prophylaxis (3, 10). With routine CNS-directed prophylactic therapy, the risk of CNS relapse in patients with ALL has decreased to <5–10%. This has had a significant impact on overall treatment outcome because of the poor prognosis associated with CNS recurrence (3, 11–14). Risk factors for development of CNS leukemia include a high initial WBC count, bone marrow cellularity ≥95%, extramedullary involvement, advanced disease stage, and the Ph (1, 2, 11, 15).

Imatinib mesylate (Glivec, formerly STI571), a selective inhibitor of the ABL, c-kit, platelet-derived growth factor receptor and ARG tyrosine kinases (16–18), has shown significant antileukemic activity in patients with CML-BC (19–21).

2 The abbreviations used are: CNS, central nervous system; ALL, acute lymphoid leukemia; LyBC, lymphoid blast crisis; CML, chronic myeloid leukemia; BC, blast crisis; CSF, cerebrospinal fluid; Ph, Philadelphia chromosome; marrow-CR, complete marrow response; CHR, complete hematological response; HPLC, high-performance liquid chromatography; GMALL, German Multicenter Study Group for Adult ALL; LDH, lactate dehydrogenase; gDNA, genomic DNA.
and Ph⁺ ALL (22) in recent clinical Phase II trials. Rapid relapse limits the value of imatinib in patients with advanced Ph⁺ leukemias, however, even if they achieved a complete bone marrow and peripheral blood response (21, 22). In the initial Phase I and II studies, the simultaneous administration of imatinib and cytotoxic agents including prophylactic CNS-directed therapy was not permitted, because of the lack of safety data. In a recent preliminary report involving a small number of patients (23), 20% of imatinib-treated patients with either lymphoid or bilineage CML-BC or Ph⁺ ALL experienced a CNS relapse. This study and two recent case reports (24, 25) indicate that poor penetration of imatinib into the CSF may be associated with an elevated risk of CNS relapse if no additional prophylaxis is given.

We analyzed the data of 107 consecutive patients with relapsed or refractory Ph⁺ ALL or CML blastic phase who were enrolled in Phase II studies of imatinib to determine the incidence of, and risk factors associated with, leukemic CNS involvement during treatment with single-agent imatinib.

**PATIENTS AND METHODS**

**Patients and Imatinib Treatment.** We studied 107 patients with relapsed or refractory Ph⁺ ALL (n = 65) or CML in BC (n = 42) who were enrolled in successive multicenter Phase II studies of imatinib (International STI571 Study Group trials CSTI571 102, 109, 114, and 115). Details of study procedures were published previously (21, 22). Patients with Ph⁺ ALL resistant to at least two cycles of chemotherapy or with relapsed disease and patients with CML in previously treated or untreated BC were eligible.

The BCR-ABL rearrangement was confirmed in all patients by RT-PCR and/or fluorescence in situ hybridization analysis. Bilineage BC was defined by coexpression of >30% of myeloid and lymphoid markers.

Patients with an Eastern Cooperative Oncology Group Performance Score >3, active CNS disease, or any other serious concomitant medical condition were excluded. Patient characteristics at the start of imatinib therapy are detailed in Table 1. Imatinib was started as a single daily oral dose of 600 mg in 103 patients, 400 mg in 3 patients, and 300 mg in 1 patient, mostly on an outpatient basis. Treatment was continued until severe adverse effects or disease progression occurred or the patient was transferred to stem cell transplantation. The studies were approved by the local ethics committee, and all patients gave prior written informed consent.

**Assessment of Response and CNS Involvement.** The definitions of CHR, marrow-CR, and partial response were used as published previously (21, 22). Relapse was defined as disease recurrence with bone marrow blasts exceeding 5% or reappearance of peripheral blood blasts in a patient who had achieved a CHR or marrow-CR (21, 22).

**Table 1** Patient characteristics at the start of imatinib therapy

<table>
<thead>
<tr>
<th></th>
<th>Ph⁺ ALL</th>
<th>CML BC</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>65 (61)</td>
<td>42 (39)</td>
<td>107</td>
</tr>
<tr>
<td>Age (median, range)</td>
<td>49 (18–76)</td>
<td>52 (20–74)</td>
<td>51 (18–76)</td>
</tr>
<tr>
<td>Sex</td>
<td>37 (57)</td>
<td>22 (52)</td>
<td>59 (55)</td>
</tr>
<tr>
<td>Disease status at imatinib start</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st relapse:</td>
<td>27 (41.5)</td>
<td>13 (20)</td>
<td></td>
</tr>
<tr>
<td>≥2nd relapse:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated:</td>
<td>12 (29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>48 (45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extramedullary diseaseb</td>
<td>2 (4.6)</td>
<td>3 (7)</td>
<td>5 (4.7)</td>
</tr>
<tr>
<td>WBC &gt;30/μl</td>
<td>9 (14)</td>
<td>11/39 (28)</td>
<td>20/104 (19)</td>
</tr>
<tr>
<td>Peripheral blood blasts</td>
<td>40 (61.5)</td>
<td>34/40 (85)</td>
<td>74/105 (70.5)</td>
</tr>
<tr>
<td>Elevated LDH (&gt;200 U/liter)</td>
<td>33/51 (65)</td>
<td>29/36 (81)</td>
<td>62/87 (71)</td>
</tr>
<tr>
<td>Breakpoint</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M-bcr-abl</td>
<td>18 (26)</td>
<td>26 (62)</td>
<td></td>
</tr>
<tr>
<td>m-bcr-abl</td>
<td>46 (70.7)</td>
<td>1 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Complex karyotypec</td>
<td>22/51 (45)</td>
<td>13 (31)</td>
<td>36/87 (41)</td>
</tr>
<tr>
<td>Prior SCTa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allogeneic SCT</td>
<td>20 (31)</td>
<td>14 (33)</td>
<td>34 (32)</td>
</tr>
<tr>
<td>Autologous SCT</td>
<td>3 (5)</td>
<td>3 (7)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>TBI-containing conditioninga</td>
<td>15 (23)</td>
<td>6 (14)</td>
<td>21 (19.6)</td>
</tr>
<tr>
<td>Prior CNS leukemia</td>
<td>2 (3)</td>
<td>1 (2.4)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Prior CNS irradiation</td>
<td>29 (45)</td>
<td>0</td>
<td>29 (27.1)</td>
</tr>
</tbody>
</table>

a MRD, minimal residual disease; SCT, stem cell transplantation; TBI, total body irradiation.
b Involvement of bone, tests, or skin.
c Defined as 3 or more cytogenic aberrations in addition to the Philadelphia chromosome.

on September 22, 2017. © 2003 American Association for Cancer Research.
CNS Relapse in Ph+ Leukemia during Imatinib

was based on typical findings on cranial computed tomography/magnetic resonance imaging in conjunction with neurological signs and symptoms. Routine safety assessments included clinical evaluation with documentation of adverse events and hematological and biochemical laboratory tests. Toxicity was graded according to the Common Toxicity Criteria of the National Cancer Institute.

**Imatinib Concentration in Serum and CSF.** The newly developed HPLC method for analyzing imatinib and N-desmethyl-STI is described in detail elsewhere. Briefly, a ZirChrom analytical HPLC column (3 μm, PDB-ZrO2, 3% carbon, 50 × 4 × 6 mm) with a precolumn of the same solid phase specificity was used as the analytical column. The system was designed as an online-enrichment system with another PDB-ZrO2 precolumn as enrichment column. Plasma and liquor samples were deproteinized by perchloric acid and diluted, and an aliquot of up to 200 μl was injected into the HPLC. Flow was set on 0.4 ml/min at room temperature in the analytical part and on 2 ml/min at room temperature in the enrichment part. The analytical eluate consisted of 600 ml of 0.01 m KH2PO4/0.09 m K2HP04 + 400 ml of methanol/liter (v/v), whereas the enrichment eluate was prepared with 450 ml of 0.1 m KH2PO4 + 350 ml of H2O + 200 ml of CH3OH (v/v). Quantitation was performed by means of UV detection at 260 nm using the external standard method.

**Mutation Analysis.** gDNA was extracted from CSF-derived blast cells using Trizol (Life Technologies, Inc., Grand Island, NY) according to standard protocols. Twenty nanograms of gDNA were used as a template for PCR amplification. To detect the most common point mutations of ABL, three primer pairs for amplification of exons 4, 6, and 7 (GI 22046769) were designed as: exon 4, 176-bp fragment, forward 5′-GGGAGATGGAACGGCAGGAC-3′, reverse 5′-AATGCCCAGACGCTTGTG-3′; exon 6, 207-bp fragment, forward 5′-GGGTCTGCACC-3′, reverse 5′-GGGAGATGGGTCTGCACC-3′; exon 7, 135-bp fragment, forward 5′-GCCGGAAACTGCGGCTTGTA-3′, reverse 5′-GGTCTCGGTTGCAGCTCAT-3′. PCR was performed as described previously (26) using an annealing temperature of 55°C. PCR products were separated on a 2% agarose gel containing 0.3 mg/ml ethidium bromide and purified using the QIAquick purification system (Qiagen, Valencia, CA) according to the manufacturer’s protocol. The purified DNA was directly sequenced in both sense and antisense direction by the ABI PRISM dye terminator cycle sequencing reaction (Perkin-Elmer, Foster, CA).

**Statistical Analysis.** Follow-up has been updated to January 1, 2003. Kaplan-Meier analyses and the log rank test were used for comparison of survival curves with documentation of adverse events and hematological and biochemical laboratory tests. Toxicity was graded according to the Common Toxicity Criteria of the National Cancer Institute.

**RESULTS**

**CNS Relapse.** CNS relapse occurred in 13 of 107 patients (12%) within 11–274 (median, 84) days since start of imatinib therapy. Details and outcome of patients developing CNS leukemia are given in Tables 2 and 3. None of the 13 patients had a history of prior CNS leukemia. Twelve of 13 CNS relapses (92%) occurred in leukemias displaying a lymphoid or bilineage phenotype (Ph+ ALL, 8 of 65 patients; LyBC, 4 of 13 patients), resulting in a frequency of CNS leukemia in this patient subgroup of 15%. Only one of 29 patients with CML in myeloid BC had evidence of leukemic CNS involvement during imatinib treatment. This preponderance of CNS involvement in leukemias with lymphoid as opposed to myeloid phenotype was not statistically significant (P = 0.18) because of the relatively small number of events. Neurological signs and symptoms at the time of CNS relapse included severe headache (n = 8), nausea and vomiting (n = 2), facial nerve palsy (n = 1), moderate vision impairment (n = 2), complete unilateral loss of vision (n = 1), meningism (n = 1), vertigo (n = 1), myoclonic epilepsy (n = 2), and coma (n = 1). Nine of the 13 patients who eventually developed CNS leukemia had received intrathecal chemotherapy immediately before imatinib, but only one patient during imatinib treatment.

**Protective Effect of Prophylactic Cranial Irradiation.** Of the 13 patients who developed CNS leukemia, none had received prior prophylactic cranial or craniospinal irradiation. Conversely, none of the 29 patients previously treated with prophylactic cranial irradiation (all with Ph+ ALL) developed CNS leukemia during imatinib therapy for subsequent relapse or refractory disease. The protective effect of prophylactic cranial irradiation was statistically significant (P = 0.018) and was apparent irrespective of the patients response to imatinib. Reasons for withholding cranial irradiation during GMALL first-line therapy (only ALLs considered) were refractoriness to induction chemotherapy in eight patients or treatment outside of the GMALL protocol for a variety of reasons (n = 28). The protective effect of prior cranial irradiation seemed to be independent of the patient’s initial response to induction chemotherapy: of the 19 patients with Ph+ ALL who failed initial induction chemotherapy, 11 had received prophylactic cranial irradiation, none of whom developed CNS relapse.

**Risk of CNS Leukemia in Relation to Systemic Imatinib Response.** When we assessed the probability of CNS involvement by imatinib response in patients with lymphoid or bilineage leukemia, the incidence of meningeal leukemia in patients refractory to imatinib (5 of 30; 17%) was not significantly different from that in patients achieving a complete remission (8 of 48; 17%; P = 0.44). Five of eight imatinib responders presented with isolated CNS leukemia, whereas three patients developed simultaneous CNS and bone marrow relapse. Median time from the start of imatinib treatment to CNS relapse was 190 (range, 41–290) days in cases of isolated CNS relapse and 84 (range, 75–89) days in simultaneous relapse. The highest incidence of CNS leukemia was seen in the subset of Ph+ ALL refractory to imatinib (5 of 19; 26%), whereas none of the 12 CML patients with refractory myeloid (n = 10) or lymphoid (n = 2) BC developed CNS leukemia. CNS involvement in the five patients with imatinib-refractory Ph+ ALL developed within the first month of imatinib treatment in three patients (1, 2, and 5) and within 2 months after its discontinuation in two patients (3 and 4).

**Risk of CNS Leukemia in Relation to Pretreatment Features.** The incidence of CNS leukemia did not differ significantly between patients with a high (>30 × 10⁹/liter) WBC (2 of 20 versus 11 of 84; P = 0.52), presence of blasts in
Table 2  Baseline characteristics of patients developing CNS leukemia

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Breakpoint</th>
<th>Prior chemotherapy</th>
<th>Prior intrathecal therapy</th>
<th>Prior SCT/conditioning</th>
<th>Parameters at start imatinib</th>
<th>WBC $\times 10^9$</th>
<th>PB blasts (%)</th>
<th>LDH (units/liter)</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>F</td>
<td>Ph + ALL, prim.refr.</td>
<td>e1a2</td>
<td>Ind.I, Cy + dexta.</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>10.6</td>
<td>57</td>
<td>172</td>
<td>t(9;22)</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>F</td>
<td>Ph + ALL, 1st rel.</td>
<td>b3a2</td>
<td>Ind.I + II, HD AraC/ Mitox., Idas, Ind.II, HDAraC/Mitox.</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>11.0</td>
<td>31</td>
<td>196</td>
<td>t(9;22)</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>F</td>
<td>Ph + ALL, prim.refr.</td>
<td>n.a.</td>
<td>Ind.I, HDAraC/Mitox., HDMTX/Cy x3</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>54.8</td>
<td>78</td>
<td>1031</td>
<td>t(9;22)</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>M</td>
<td>Ph + ALL, prim.refr.</td>
<td>e1a2</td>
<td>Ind.I, HDAraC/Mitox., HDMTX, 6-MP</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>2.3</td>
<td>67</td>
<td>n.a.</td>
<td>t(9;22), complex</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>M</td>
<td>Ph + ALL, 2nd rel.</td>
<td>e1a2</td>
<td>BFM05/93, 2xHD AraC/Mitox., Ind.I + II</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>2.9</td>
<td>64</td>
<td>318</td>
<td>t(9;22), −Y, +8</td>
</tr>
<tr>
<td>6</td>
<td>66</td>
<td>M</td>
<td>Ph + ALL, 1st rel.</td>
<td>e1a2</td>
<td>Ind.I, 6-MP/MTX</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>4.2</td>
<td>0</td>
<td>189</td>
<td>n.a.</td>
</tr>
<tr>
<td>7</td>
<td>42</td>
<td>M</td>
<td>Treated bilin. BC</td>
<td>e1a2</td>
<td>2xHDAraC/Mitox.</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>3.3</td>
<td>0</td>
<td>242</td>
<td>46, XYb</td>
</tr>
<tr>
<td>8</td>
<td>66</td>
<td>M</td>
<td>Untreated MyBC</td>
<td>b3a2</td>
<td>HU, IFN-α</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>67.8</td>
<td>65</td>
<td>249</td>
<td>t(9;22)</td>
</tr>
<tr>
<td>9</td>
<td>19</td>
<td>M</td>
<td>Treated bilin. BC</td>
<td>b3a2</td>
<td>HU, imatinib</td>
<td>N</td>
<td>Y</td>
<td>MFD/TBI + Cy + VP16, TCD</td>
<td>10.1</td>
<td>0</td>
<td>268</td>
<td>Complex</td>
</tr>
<tr>
<td>10</td>
<td>68</td>
<td>M</td>
<td>Untreated LyBC</td>
<td>b2a2</td>
<td>HU, IFN-α</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>24.9</td>
<td>53</td>
<td>484</td>
<td>t(9;22)</td>
</tr>
<tr>
<td>11</td>
<td>47</td>
<td>F</td>
<td>Ph + ALL, 1st rel.</td>
<td>e1a2</td>
<td>Ind.I, imatinib</td>
<td>N</td>
<td>Y</td>
<td>MFD/RIT + TBI + Cy, TCD</td>
<td>5.6</td>
<td>0</td>
<td>188</td>
<td>Normal</td>
</tr>
<tr>
<td>12</td>
<td>45</td>
<td>M</td>
<td>Treated bilin. BC</td>
<td>b3a2</td>
<td>HU, IFN-α, VCR + Pred</td>
<td>N</td>
<td>N</td>
<td>MMUD/Flu + BU</td>
<td>1.7</td>
<td>0</td>
<td>148</td>
<td>t(9;22)</td>
</tr>
<tr>
<td>13</td>
<td>74</td>
<td>M</td>
<td>Ph + ALL, CR1, MRD +</td>
<td>c1a2</td>
<td>Ind.I</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>7.0</td>
<td>0</td>
<td>150</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

Median 46

Notes: Female; M, male; N, no; Y, yes; n.a., not applicable; prim.refr., primary refractory; rel., relapse; bilin., bilineage; Ind.I + II, induction I + II according to GMALL study protocol; Cy, cyclophosphamide; dexta, dexamethasone; HDAraC/Mitox., high-dose AraC/mitoxantrone; HDMTX, high-dose methotrexate; HU, hydroxyurea; VCR, vincristine; MFD, matched family donor; RIT, radioimmunotherapy; TBI, total body irradiation; TCD, T-cell depletion; MMUD, mismatched unrelated donor; 6-MP, 6-mercaptopurine; Pred, prednisone; IFN-α, interferon-α; Flu, fludarabine; BU, busulfan; n.a., not available.

b Transplanted from male donor.
## Table 3  Treatment and outcome of patients developing CNS-leukemia

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Duration (day)</th>
<th>Best response</th>
<th>Type of relapse</th>
<th>Onset of CNS relapse after start of imatinib (day)</th>
<th>Symptoms of CNS relapse</th>
<th>Time of relapse (during/after imatinib)</th>
<th>Treatment of CNS relapse</th>
<th>Imatinib continued</th>
<th>OS (day)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>Fail</td>
<td>ref.; disease + CNS</td>
<td>26</td>
<td>Headache, facial nerve palsy, vomiting</td>
<td>During</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>Fail</td>
<td>ref.; disease + CNS</td>
<td>13</td>
<td>Myoclonic epilepsy, status</td>
<td>During</td>
<td>Y</td>
<td>N</td>
<td>Y, temp.</td>
<td>127</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>Fail</td>
<td>ref.; disease + CNS</td>
<td>59</td>
<td>Na</td>
<td>Post</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>124</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>Fail</td>
<td>ref.; disease + CNS</td>
<td>110</td>
<td>Headache</td>
<td>Post</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>133</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>Fail</td>
<td>ref.; disease + CNS</td>
<td>11</td>
<td>Headache, dizziness, nausea, vomiting</td>
<td>During</td>
<td>Y</td>
<td>N</td>
<td>Y, temp.</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>99</td>
<td>CHR</td>
<td>CNS + BM</td>
<td>84</td>
<td>Tinnitus, vertigo</td>
<td>During</td>
<td>Y</td>
<td>N</td>
<td>Y, temp.</td>
<td>141</td>
</tr>
<tr>
<td>7</td>
<td>92</td>
<td>CHR</td>
<td>CNS + BM</td>
<td>89</td>
<td>Coma</td>
<td>During</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>75</td>
<td>CHR</td>
<td>CNS + BM</td>
<td>75</td>
<td>Myoclonic epilepsy, status</td>
<td>During</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>83</td>
</tr>
<tr>
<td>9</td>
<td>131</td>
<td>Marrow-CR</td>
<td>Isolated CNS, later BM</td>
<td>41</td>
<td>Headache, nausea, vomiting, meningism</td>
<td>During</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>172</td>
</tr>
<tr>
<td>10</td>
<td>109</td>
<td>CHR</td>
<td>Isolated CNS, later BM</td>
<td>139</td>
<td>Headache, diploic images</td>
<td>Post</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>188</td>
</tr>
<tr>
<td>11</td>
<td>556+</td>
<td>Marrow-CR</td>
<td>Isolated CNS</td>
<td>190</td>
<td>Headache, blurred vision</td>
<td>During</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>556+</td>
</tr>
<tr>
<td>12</td>
<td>617+</td>
<td>Marrow-CR</td>
<td>Isolated CNS</td>
<td>191</td>
<td>Headache, hearing loss</td>
<td>During</td>
<td>Y</td>
<td>Y”</td>
<td>Y</td>
<td>617+</td>
</tr>
<tr>
<td>13</td>
<td>562+</td>
<td>CHR</td>
<td>Isolated CNS</td>
<td>274</td>
<td>Headache, loss of vision</td>
<td>During</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>133</td>
</tr>
</tbody>
</table>

Median 92 (26–617)

84 (11–274)

\( a \) CNS irradiation discontinued because of pancytopenia.

\( b \) ref., refractory; BM, bone marrow, n.a., not available; MRD, minimal residual disease; OS, overall survival; temp., temporary; PD, progressive disease.

### DISCUSSION

Our analysis of 107 consecutive patients treated with single-agent imatinib for relapsed or refractory Ph+ ALL or CML in the subset of patients with a lymphoid or bilineage phenotype. In most cases, CNS and systemic relapse was observed concurrently, and isolated meningeal relapse occurred only rarely.

### Mutation Analysis of CSF Blasts

DNA was isolated from leukemic blast cells of two patients with isolated CNS relapse. The samples were analyzed for mutations in the BCR-ABL1 gene. Two of these patients with isolated CNS relapse (patients 11, 12, and 13) received additional imatinib therapy. The third patient (no. 12) received imatinib after diagnosis of isolated CNS relapse. All patients were resistant to imatinib with no signs of CNS leukemia. The risk of leukemia was not statistically significant (\( P = 0.5 \)).

### Imatinib Concentrations in CSF and Serum

Imatinib concentrations in CSF and serum were measured by HPLC in 25 paired plasma and CSF samples collected from a total of 11 patients. Three of the four patients with isolated CNS relapse (patients 11, 12, and 13) received imatinib after diagnosis of isolated CNS relapse (patients 11, 12, and 13). Although imatinib concentrations in plasma and CSF were not significantly different (\( P = 0.9 \)), the CSF concentrations were lower than the plasma concentrations. The median plasma concentration was 1983.2 (mean, 1452.1) ng/ml, while the median CSF concentration was 570.3 (mean, 32.4) ng/ml. These results are not significant regarding plasma to CSF ratios (Ref. 27).

### Treatment and Outcome of CNS Relapse

All patients with isolated CNS relapse received treatment, and none died of progressive disease. One patient (no. 11) died of progressive disease within 4 months. Similarly, all patients who developed combined CNS and bone marrow relapse experienced prolonged survival. These patients received treatment and are in ongoing complete molecular remission.

<table>
<thead>
<tr>
<th>CSF</th>
<th>Serum</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.11</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>0.12</td>
<td>0.2</td>
</tr>
<tr>
<td>3</td>
<td>0.13</td>
<td>0.2</td>
</tr>
<tr>
<td>4</td>
<td>0.14</td>
<td>0.2</td>
</tr>
</tbody>
</table>

### In-vitro Studies

In-vitro studies were performed on leukemic cell lines and patient samples. The results showed that Imatinib concentrations in CSF were lower than in serum, with a median ratio of 0.5. CNS leukemia was not statistically significant (\( P = 0.5 \)).
uncommon (3%) in myeloid BC, irrespective of the response to imatinib. These findings are consistent with the propensity of ALL to present with meningeal disease if no adequate CNS prophylaxis is administered, (4, 5, 30, 31) and are consistent with preliminary evidence that imatinib affords insufficient protection from CNS relapse (23–25). Our results confirm that imatinib penetration into the CSF is poor, resulting in drug levels below those needed to inhibit bcr/abl kinase activity (32, 33). Recently, limited distribution of imatinib to the brain has been attributed to p-glycoprotein-mediated efflux in mice (34). Furthermore, we demonstrate that the imatinib concentration in the CSF of both patients with and without meningeal leukemia is not significantly different (mean, 32.4 ng/ml versus 39.8 ng/ml; \( P < 0.9 \)), although the ratio of CSF to plasma imatinib concentration was slightly higher in patients analyzed at the time of leukemic meningeal involvement (2.45% versus 1.51%). This difference was not statistically significant, however \( (P = 0.06) \). Thus, the presence of meningeal leukemia does not affect penetration of the CSF by imatinib in a clinically meaningful manner.

Interestingly, CNS leukemia occurred in none of the patients who received prophylactic cranial irradiation during ALL induction therapy. Because cranial irradiation is delayed in patients who do not achieve a complete response with GMALL induction chemotherapy, this finding could potentially reflect a bias resulting from the predominance of induction failures among the patients not given prophylactic cranial irradiation. The protective effect of cranial irradiation, however, was independent of the patient’s response to initial induction chemotherapy, because none of the 11 Ph\(^+\) ALL patients who failed induction chemotherapy, but nevertheless received prophylactic cranial irradiation, developed leptomeningeal relapse. These data imply that prophylactic cranial irradiation effectively reduces the risk of CNS leukemia in patients with acute Ph\(^+\) lymphoid leukemias who receive imatinib without additional CNS-directed treatment. The clinical settings in which prophylactic cranial irradiation reliably abrogates the need for additional CNS prophylaxis during imatinib-based therapy remain to be determined. Conversely, our data do not indicate whether prophylactic cranial irradiation will have an impact on the frequency of meningeal relapse if patients receive prophylactic intrathecal chemotherapy together with imatinib-based therapy. It is also uncertain to what degree the results obtained in relapsed or refractory Ph\(^+\) ALL can be extrapolated to patients with chemosensitive \textit{de novo} Ph\(^+\) ALL.

Taken together, our results underscore the importance of CNS-directed therapy in all patients receiving imatinib for Ph\(^+\) lymphoid or bilineage leukemia, although the optimal treatment modalities and schedules remain to be established (3, 10, 11, 32). In view of the often brief interval between commencing imatinib and occurrence of CNS leukemia, CNS prophylaxis should be initiated early (3). Identification of factors predictive of meningeal relapse in individual patients could conceivably restrict additional CNS-directed treatment to patients at risk, but this goal has thus far proven elusive. In our present analysis, factors previously reported as prognostically relevant in pediatric and adult patients with ALL \( (e.g., \) high WBC, marrow infiltration \( >95\%), \) elevated LDH, or more advanced disease; Refs. 2 and 11) were not significantly associated with a higher risk of meningeal relapse.

A substantial proportion of Ph\(^+\) ALL and LyBC patients with acquired resistance to imatinib develop a point mutation of \( \text{bcr/abl} \) that inactivates imatinib by causing a conformational change either in the ATP binding site or the activation loop of ABL (27–29). Using the same experimental approach previously used to identify point mutations in secondary resistant Ph\(^+\) ALL bone marrow cells (26), we were unable to detect any mutations in the blasts obtained from the CSF at the time of isolated CNS relapse. In these patients, administration of imatinib is likely to exert systemic antileukemic activity and should.

### Table 4 Measurement by HPLC of Imatinib concentrations in simultaneously collected plasma and CSF samples from patients receiving imatinib

<table>
<thead>
<tr>
<th></th>
<th>Imatinib concentration (ng/ml)</th>
<th>Ratio CSF:plasma (%)</th>
<th>Time since imatinib administration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CSF</td>
<td>Plasma</td>
<td></td>
</tr>
<tr>
<td>Paired samples ( (n = 18) ) from nonmeningeosis patients(^a)</td>
<td>Mean</td>
<td>39.8</td>
<td>2965.6</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>22.4</td>
<td>1288.3</td>
</tr>
<tr>
<td></td>
<td>VC in %</td>
<td>56.2</td>
<td>43.4</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>9.9–84.2</td>
<td>632.5–5249.7</td>
</tr>
<tr>
<td>Paired samples ( (n = 7) ) from patients with meningeal relapse(^b)</td>
<td>Mean</td>
<td>32.4</td>
<td>1452.13</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>21.8</td>
<td>487.08</td>
</tr>
<tr>
<td></td>
<td>VC in %</td>
<td>88.5</td>
<td>33.54</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>15.4–80.1</td>
<td>570.3–1983.2</td>
</tr>
<tr>
<td>All samples ( (n = 25) )</td>
<td>Mean</td>
<td>37.7</td>
<td>2570.8</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>22.0</td>
<td>1312.5</td>
</tr>
<tr>
<td></td>
<td>VC in %</td>
<td>58.2</td>
<td>51.1</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>9.9–84.2</td>
<td>570.3–5249.7</td>
</tr>
</tbody>
</table>

\(^a\) The time interval between different measurements in individual patients was several weeks to months.

\(^b\) Eighteen paired CSF and plasma samples were obtained from seven patients with no evidence of meningeal leukemia undergoing routine lumbar puncture for prophylactic intrathecal chemotherapy.

\(^c\) Seven samples from four patients were collected at the time of proven meningeal leukemia.

\(^d\) Variation coefficient.
therefore, be continued, whereas patients with a combined sys-
temic and CNS relapse are unlikely to benefit from continued
imatinib treatment. This is supported by the observation that
three of our patients with an isolated CNS relapse experienced
prolonged benefit from aggressive CNS-directed therapy ac-
companying continued imatinib, with survival of 11, 14, and 16
months after the first isolated CNS relapse. Remarkably, two of
these patients are in confirmed and ongoing complete molecular
remission, whereas none of the patients with a combined me-
ingeal and systemic relapse survived. This latter result mirrors
the experience with chemotherapy in adult ALL, in which CNS
relapse heralds systemic recurrence and only 5–10% of patients
survive long term, despite initial response rates of up to 60%
with intrathecal chemotherapy (2, 3).

In conclusion, CNS-directed prophylactic therapy is an
important element of imatinib-based treatment of patients with
acute Ph+ lymphoid or bilineage leukemia. The most effective
types of prophylaxis (e.g., cranial irradiation or intrathecal
chemotherapy), as well as their optimal scheduling, remain to
be elucidated.

ACKNOWLEDGMENTS

We are indebted to Brigitte Gehrke, Anja Goodwin, Heike Nün-
berger, Martine Pape, Rabea El Kalaaoui, and Sandra Wagner for
invaluable technical assistance and to S. Kriener, M.D., for the pa-
thological review of marrow histologies.

The excellent cooperation with the referring physicians from the
following centers is gratefully acknowledged: Department of Hemat-
ology, University Hospital, Amsterdam (Dr. C. Hollak); II. Medizinische
Klinik, Zentralklinikum Augsburg, Augsburg (Prof. Dr. B. Schlimmck); Medizinische Klinik III, Uni-
viersität-Klinikum Benjamin Franklin, Berlin (Prof. Dr. E. Thiel, Prof. Dr. W.-U. Knauf); II. Innere Abteilung,
Krankenhaus Neukölln, Berlin (Dr. A. C. Mayr, Dr. A. Grüniesen);
Campus Virchow-Klinikum, Charité, Berlin (Prof. Dr. B. Dörken, PD Dr. P. le Couture); Medizinische Klinik, Städtisches Klinikum, Braung-
schweig (Prof. Dr. B. Wörmann, Dr. A. Pies); Medizinische Klinik, Ev.
Diakonissenanstalt, Bremen (Prof. Dr. K. H. Pführer, Dr. T. Wolff); Medizinische Klinik, St. Joseph Hospital, Bremerhaven (PD Dr. H.-H.
Heidtmann, Dr. A. Pott); Krankenhaus Küchengarten, Klinikum ГЋklini,
Chemnitz (Dr. F. Fiedler, Dr. K. Trol); Klinikum Carl Gustav Carus der
Technische Universität, Dresden (Prof. Dr. G. Ehninger, Dr. R. Naum-
nann); Medizinische Klinik II, St. Johannes-Hospital, Duisburg (Prof.
Dr. C. Aul, Dr. A. Giagounidis); Klinik f. hämatologie, Onkologie
Univ. Klinik, Düsseldorf (Prof. Dr. R. Haas, Dr. G. Meckenstock); Med.
Klinik III, Friedrich-Alexander-Universität, Erlangen (Prof. Dr. J. R.
Kalden, Prof. Dr. M. Gramatzi); Innere Medizin, Med. Klinik u.
Poliklin. der GHS, Essen (Prof. Dr. U. Dührsen, Dr. C. Rosenthal);
Hämatoonkologie, Ev. Krankenhaus, Essen-Werden (Prof. Dr. W.
Heit, OA Dr. Bau); Schwerpunktpraxis Hämatologie und Onkologie,
Frankfurt (Dr. J. Cordes); Abt. für Innere Medizin I, Universitätsklini-
kum, Freiburg (Prof. Dr. R. Mertelsmann, OA Dr. M. Lübbert); Mediz-
inische Klinik III, Städt. Klinikum, Fulda (Dr. G. Höffkes, Dr. M. Ar-
land); Schwerpunktpraxis Hämatologie und Onkologie, Gießen (Dr. A.
Kabisch); Zentrum für Innere Medizin, Universitätsklinikum, Gießen
(Prof. Dr. H. Pralle, Dr. A. Matzdorff); Zentrum für Innere Medizin,
Universitätsklinikum, Göttingen (Prof. Dr. L. Trümper, PD Dr. F.
Griesinger); Medizinische Fakultät, Ernst-Moritz-Arndt-Universität,
Greifswald (Prof. Dr. G. Dölkem, Dr. M. Schwenke); Abt. Innere Medi-
zein II, Katholisches Krankenhaus, Hagen (Dr. H. Einemacher, Dr. V.
Rethwisch); II. Med. Klinik, Univ. Krankenhaus Eppendorf, Hamburg
(Prof. Dr. D. K. Hossfeld, Dr. M. de Wit); Medizinische Klinik, Ev.
Krankenhaus, Hamm (Prof. Dr. L. Ballesen, Dr. A. Grote-Methe); Abt.
Hämologie u. Onkologie, Med. Hochschule, Hannover (Prof. Dr. A.
Ganser, Dr. H. Diedrich); Medizinische Poliklinik V, Universitätsklini-
kum, Heidelberg (Prof. Dr. A. Ho, Dr. G. Egerer); Innere Med. I, Med.
Universität klinik und Poliklinik, Homburg/Saar (Prof. Dr. M. Pfeund-
shuch, PD Dr. F. Hartmann); Klinik f. KMT u. Hämatologie/Onkologie
GmbH, Idar-Oberstein (Prof. Dr. A. A. Fauser, Dr. M. Koldehoff);
Standort I, Westfälisch Klinikum, Kaiserslautern (Prof. Dr. H. Link, Dr.
F.-G. Hagmann); II. Medizinische Klinik, Städt. Klinikum Karlsruhe,
Stuttgart (Prof. Dr. J. T. Fischer, Dr. S. Wilhelm); II. Medizinische
Klinik, Städtisches Krankenhaus, Kiel (Prof. Dr. M. Kneba, Dr. T.
Raff); Med. Klinik II/Hämatologie, Universitätsklinik, Köln (Dr. D.
Voliotis, Dr. P. Staub); Medizinische Klinik II, Klinikum Krefeld
Krefeld (Prof. Dr. T. Frieling, Dr. M. Planker); Medizinische Klinik II,
Klinikum Lippe-Lemgo, Lemgo (Prof. Dr. H.-P. Lohrman, Dr. H.
Meckende); Universitätsklinikum, Linz (Dr. O. Krieger, Prof. Dr. Lutz);
Med. Klinik A, Städt. Klinikum, Ludwigshafen am Rhein (PD Dr. M.
Üppenkamp, Dr. B. Claus); Otto v. Guericke Univ. Klinik für Hämato-
logie, Magdeburg (Dr. H. H. Wolf, Prof. Dr. A. Franke); III. Medizi-
nische Klinik, Universitätsklinik, Mainz (Prof. Dr. C. Huber, Dr. J.
Beck); III. Medizinische Klinik, Klinikum der Stadt, Mannheim (Prof.
Dr. R. Hehlmann, OA Dr. A. Weiss); Zentrum der Inneren Medizin,
Klinikum Lahnerbe, Marburg (Prof. Dr. A. Neuhauer, Dr. M. Jianke); I.
Med. Abt., Krankenhaus München-Schwabing, München (Prof. Dr. C.
Neri, Dr. T. Lipp); Klinikum Rechts der Isar der TU München, München
(Prof. Dr. C. Peschel, Dr. F. Schneller); Medizinische Klinik III, Univ.
Klinikum Großhadern, München (Dr. M. Schleuning, PD Dr. T. Ha-
erlach); Schwerpunktpraxis Hämatologie und Onkologie, Münster
(Dr. R. Kriebel-Schmitt, Dr. V. Burstedde); Innere Medizin A, Uni-
viersitätsklinik, Münster (Prof. Dr. W. E. Berdel, Dr. M. Stelljes); Mediz-
inische Klinik 5, Klinikum Nürnberg Nord, Nürnberg (Prof. Dr. W. M.
Gallmeier, PD Dr. H. Wandt); Innere Medizin II, Städt. Kliniken,
Oldenburg (Prof. Dr. H. J. Illiger, Dr. B. Metzner); Klinik f. Hämatologie/
Hämatologie, Städt. Klinikum, Osnabrück (Prof. Dr. H. Hartlapp, Dr.
T. Hegge); Innere Medizin I, Universitätsklinik, Regensburg (Prof.
Dr. R. Andreessen, Dr. M. Gnad); Medizinische Fakultät, Universität Rostock,
Rostock (Prof. Dr. M. Freund, Dr. A. Leithäuser); Innere Abteilung,
Diakonie-Krankenhaus, Schwäbisch-Hall (Prof. Dr. H. Heiljmeyer, OA
Dr. T. G. Medizinische Klinik III, St. Marien-Krankenhaus, Siegen
(Prof. Dr. W. Gäßmann, Dr. M. Winkemann); Medizinische Klinik,
Klinikum der Hansestadt, Stralsund (Prof. Dr. T. H. Ittel, Dr. U.
Gerecke); Innere Abteilung II, Robert Bosch-Krankenhaus, Stuttgart
(Prof. Dr. W. Aulitzky, Dr. B. Löffler); Medizinische Klinik I, Bürger-
hospital, Stuttgart (Prof. Dr. H. C. Benöhr, Dr. W. Grimminger); Med.
Abteilung I, Mutterhaus der Borromäerinnen, Trier (Prof. Dr. M.
Clements, Dr. R. Mahler); Innere Med. II/Hämatologie, Universitäts-
klinikum, Tübingen (Prof. Dr. L. Kanz, Dr. M. Schmalzing); Innere Med.
III, Medizinische Universitätsklinik, Ulm (Prof. Dr. H. Döhrer, Dr. M.
Schmid); I. Medizinische Abteilung Univ., Wilhelminenspital, Wien
(Prof. Dr. H. Ludwig, Doz. Dr. J. Meran); Deutsche Klinik für Diag-
nostik, Wiesbaden (PD Dr. R. Schwedtfeiger, Dr. M. Purnbaum); Innere Med. III, Dr.-Hoest-Schmidt-Klinikum, Wiesbaden (Prof. Dr. N.
Fröchhofer, Dr. H.-G. Fuhr); Medizinische Poliklinik der Universität, Würzburg (Prof. Dr. K. Wilms, PD Dr. M. Wilhelm).

REFERENCES

High peripheral blast count in adult acute myelogenous leukemia is a

2. Cortes, J. Central nervous system involvement in adult acute lympho-

3. Gökbuget, N., and Hoezer, D. Meningeosis leukaemia in adult acute


Risk and Prognosis of Central Nervous System Leukemia in Patients with Philadelphia Chromosome-Positive Acute Leukemias Treated with Imatinib Mesylate


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/9/13/4674

Cited articles
This article cites 32 articles, 15 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/9/13/4674.full#ref-list-1

Citing articles
This article has been cited by 12 HighWire-hosted articles. Access the articles at:
http://clincancerres.aacrjournals.org/content/9/13/4674.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.