Targeted Therapies in the Treatment of Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia

Dieter Hoelzer, Nicola Gökte, and Oliver G. Ottmann

Imatinib mesylate (Gleevec, Novartis Pharmaceuticals Corp, East Hanover, NJ; Glivec, Novartis Pharma AG, Basel, Switzerland), a signal transduction inhibitor with preferential effects against the tyrosine kinase activity of the protein product of the ABL proto-oncogene, induced hematologic responses in >90% of patients with chronic-phase chronic myeloid leukemia (CML). In Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL), the BCR-ABL translocation is the main transforming event, making it another hematologic malignancy targeted by this ABL-tyrosine kinase inhibitor. In an international multicenter phase II trial, imatinib-induced hematologic responses (typically brief) were achieved in 60% of patients with relapsed or refractory Ph+ ALL. Subsequently, the German Multicenter Study Group for Adult ALL (GMALL) analyzed 59 patients treated in two successive nonrandomized phase II trials of imatinib in patients with relapsed or refractory Ph+ ALL. Peripheral blood blasts cell clearance occurred within 8 to 14 days in most patients. However, in a significant proportion, blast counts subsequently increased 16 to 50 days after treatment onset. Imatinib mesylate was particularly effective in patients with relapse after stem cell transplantation (SCT); 75% of patients achieved complete leukemia response. Rapid development of resistance during treatment with imatinib mesylate remains a major problem. Further research efforts should explore the mechanisms of resistance to imatinib mesylate; effectiveness of other targeted therapies (eg, farnesyl transferase inhibitors [FTIs]); combination therapies; and inclusion of strategies for immune response modification (eg, donor lymphocyte infusions, interferon-α) for Ph/BCR-ABL–positive leukemias.

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survival rates, improved therapies clearly are needed for patients with Ph⁺ ALL.¹⁵

Clinical Studies of Imatinib Mesylate in Ph⁺ ALL

International STI571 Study Group Experience

A large international phase II study evaluated imatinib mesylate in patients with Ph⁺ ALL or CML in lymphoid blast crisis (CML-LBC).¹⁶ To be eligible, patients were required to be experiencing either (1) first relapse following standard chemotherapy or SCT, or (2) refractory disease after more than two chemotherapy cycles.¹⁶ Imatinib mesylate was administered at a daily dose of 400 to 600 mg, without any additional cytoreductive therapy.¹⁶ Hematologic response was the primary end point.¹ Patients were categorized as responders if they met one of the following three criteria: complete hematologic response (ie, < 5% bone marrow blasts) with full peripheral blood recovery; complete hematologic response with incomplete peripheral blood recovery (ie, absolute neutrophil count ≥ 1,000 µL, but platelets ≥ 20,000 µL.), or partial hematologic response (ie, < 15% blasts in bone marrow and peripheral blood).¹ Preliminary analysis of the Ph⁺ ALL subset demonstrates that 29 of 48 patients (60%) achieved a hematologic response after 4 weeks of therapy.¹⁶ This response rate of 60% is notable when considering the usual outcome of relapsed Ph⁺ ALL with conventional treatment.

The German Multicenter Study Group for Adult ALL Experience

Because of these promising findings from the international study, a similar phase II trial was initiated as part of an expanded access program. Recruitment into this study enabled the German Multicenter Study Group for Adult ALL (GMALL) to more thoroughly investigate imatinib mesylate in the Ph⁺ ALL setting based on a larger patient cohort.

Overall population. At an interim analysis, 59 patients with relapsed or refractory Ph⁺ ALL, most of whom had refractory disease at study entry, have been enrolled into this nonrandomized phase II trial. Baseline demographic and disease characteristics are presented in Table 3. Of note, 19 of the patients had relapsed after an allogeneic SCT.

Clinical response data for this GMALL study have not yet been published. Importantly, most patients—even those with leukocyte counts of 100,000/µL to 200,000/µL—exhibited a decrease in peripheral blood blasts within 8 to 14 days of initiating imatinib mesylate, as shown for a subset of patients in Fig 3.

<table>
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<tr>
<th>Table 1. Rationale for Therapeutic Intervention With ABL Tyrosine Kinase Inhibitors in Ph/BCR-ABL–Positive Leukemias</th>
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<tr>
<td><strong>BCR-ABL</strong> is considered the decisive initiating factor in the pathogenesis of Ph⁺ leukemias</td>
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<tr>
<td>Hybrid <strong>BCR-ABL</strong> genes code for fusion proteins (p210<strong>bcr-abl</strong> or p190<strong>bcr-abl</strong>) with dysregulated tyrosine kinase activity</td>
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<td>Overexpression of ABL-tyrosine kinase is essential to induce and maintain the transformed phenotype of <strong>BCR-ABL</strong> cells</td>
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Abbreviations: Ph, Philadelphia chromosome.

Table 2. Treatment Modalities and Outcome in Ph⁺ ALL

<table>
<thead>
<tr>
<th>Treatment Approach</th>
<th>No. of Studies</th>
<th>No. of Patients</th>
<th>3-Year LFS</th>
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<tr>
<td>Conventional chemotherapy</td>
<td>8</td>
<td>282</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>Intensive chemotherapy, including high-dose methotrexate and high-dose cytarabine</td>
<td>4</td>
<td>300</td>
<td>10%-20%</td>
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<tr>
<td>Autologous SCT</td>
<td>10</td>
<td>96</td>
<td>27%</td>
</tr>
<tr>
<td>Allogeneic SCT</td>
<td>9</td>
<td>162</td>
<td>41%</td>
</tr>
<tr>
<td>Matched unrelated donor SCT</td>
<td>5</td>
<td>115</td>
<td>41%</td>
</tr>
</tbody>
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Abbreviations: Ph⁺ ALL, Philadelphia chromosome-positive acute lymphoblastic leukemia; SCT, stem cell transplantation; LFS, leukemia-free survival.
A substantial proportion of patients, however, experienced a subsequent increase in peripheral blood blasts as early as 16 days after the initiation of therapy.

**Subset analyses.** This study included two patient cohorts in whom imatinib mesylate was particularly effective: (1) patients who received imatinib mesylate prior to SCT, and (2) patients treated with imatinib mesylate at the time of relapse after SCT.

**Imatinib mesylate prior to SCT.** Twenty-three patients were considered eligible for allogeneic SCT. Their median age was 35 years (range, 18 to 58 years). Ten patients were in first (n = 6) or second (n = 4) relapse. Thirteen patients had refractory disease.\(^\text{17}\) As a result of repeated chemotherapy cycles, half of these patients had a history of grade 3/4 infectious complications, including *Aspergillus* infection of the lung/brain, *Candida* infection of the lung/liver, or bacterial sepsis. In 20 patients a donor was available and 14 patients actually underwent allogeneic SCT. Transplant-related mortality was within the expected range, primarily attributed to graft-versus-host disease and infectious complications. Despite the high-risk status of these patients, seven of 14 remained in continuous complete remission after SCT with a median follow-up of 156 days.\(^\text{17}\) In a small proportion of patients, minimal residual disease negativity (defined as the absence of BCR-ABL\(^+\) cells) appears to be achievable. It became evident, however, that the interval between the start of imatinib mesylate treatment and SCT has to be short because of the development of resistance.

**Imatinib mesylate for relapse after SCT.** This second cohort consists of 20 patients who received imatinib mesylate for relapse after allogeneic SCT, two of whom had prior exposure to imatinib mesylate.\(^\text{18}\) As in the first cohort, a good clinical response was observed in this subset. Complete remission with peripheral blood recovery was documented in 11 patients (55%), and four additional patients (20%) achieved complete remission with persistent cytopenias.\(^\text{18}\) Thus, the clinical response rate was 75% among patients treated with imatinib mesylate for relapse after an allogeneic SCT.\(^\text{18}\) Among these responders, median donor chimerism levels in the peripheral blood increased from 83% at pretreatment to 98% within 4 weeks of initiating imatinib mesylate, with a concomitant increase from 64% to 98% in the bone marrow.\(^\text{18}\) Of the 15 responding patients, four (27%) are in an ongoing complete remission after 6, 10, 46, and 78 weeks of therapy; 10 (67%) have

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**Table 3.** German Multicenter Study Group for Adult ALL (GMALL) Experience With Imatinib Mesylate in Relapsed/Refractory Ph\(^+\) ALL: Patient Characteristics (N = 59)

<table>
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<tr>
<th>Stage of disease, n (%)</th>
<th>Median age (range), yr</th>
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<tr>
<td>Refractory</td>
<td>47 (17-76)</td>
</tr>
<tr>
<td>1st relapse</td>
<td>34 (25)</td>
</tr>
<tr>
<td>≥2nd relapse</td>
<td>23 (39)</td>
</tr>
<tr>
<td>Molecular/cytogenetic relapse</td>
<td>12 (20)</td>
</tr>
<tr>
<td>Relapse after allogeneic SCT, n (%)</td>
<td>3 (5)</td>
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Abbreviations: Ph\(^+\) ALL, Philadelphia chromosome-positive acute lymphoblastic leukemia; SCT, stem cell transplantation.
Molecular complete remission, as determined by quantitative polymerase chain reaction (PCR) analysis, has been sustained in a patient who thus far has received a 78-week course of imatinib mesylate.\textsuperscript{18} Imatinib mesylate was compatible with the prophylactic regimens for graft-versus-host disease, including immunosuppressive, antiviral, and antifungal agents.\textsuperscript{18} It also was determined that imatinib mesylate and donor lymphocyte infusions can be given concurrently. Overall, in relapse after allogeneic SCT, imatinib mesylate was highly effective in inducing leukemia remissions and reestablished full donor chimerism in responding patients.\textsuperscript{18} Prolonged clinical complete remission and molecular complete remission (albeit rare) has occurred in a small subset of patients.\textsuperscript{18}

In summary, in each patient cohort, imatinib mesylate produced a high initial response rate that was, however, followed by rapid development of resistance in a substantial number of patients. Thus, imatinib mesylate monotherapy appears to be insufficient for treating patients with relapsed/refractory \( \text{Ph}^+ \) ALL.

**Future Strategies for Imatinib Mesylate Therapy in the Treatment of \( \text{Ph}^+ \) ALL Combination Therapies**

When considering future directions for imatinib mesylate in the treatment of \( \text{Ph}^+ \) ALL, prospective studies of this ABL tyrosine kinase inhibitor plus traditional cytotoxic chemotherapy regimens are a rational next step. Thus, the GMALL has started a randomized trial in elderly patients (> 65 years) with de novo \( \text{Ph}^+ \) ALL. Imatinib mesylate as single drug induction is being compared with conventional dose-reduced induction chemotherapy. After induction therapy all patients receive imatinib mesylate alternating with and/or parallel to consolidation chemotherapy. The aim is to improve the remission rate and remission duration in elderly patients, in whom intensification of conventional chemotherapy is not possible. In future studies, imatinib mesylate might be combined with novel therapeutics. For example, targeted therapies such as monoclonal antibodies (eg, anti-CD20) or, in SCT recipients, immune response modification with donor lymphocyte infusions or with interferon-\( \alpha \) could be studied.

Farnesyl transferase inhibitors (FTIs), a new class of signal transduction modulators that target Ras and several other pathways, also may be suitable candidates.\textsuperscript{19} In another article in this supplement, Kurzrock et al review the antitumor activity of two FTIs, Zarnestra (R115777; Johnson & Johnson Pharmaceutical Research & Development, L.L.C., San Diego, CA) and BMS 214662 (Bristol-Myers Squibb, Princeton, NJ), in patients with relapsed or refractory acute leukemias and myelodysplastic syndrome. Combining imatinib mesylate with an FTI—agents with distinct, targeted mechanisms of action and single-agent activity against \( \text{Ph}^+ \) leukemia—is an intriguing approach to treating \( \text{Ph}^+ \) ALL. Furthermore, there are preclinical data to indicate that FTIs are effective against imatinib mesylate–resistant cell lines, thereby suggesting a potential role for FTIs in \( \text{Ph}^+ \) ALL patients who become resistant to imatinib mesylate.

Other examples of targeted therapies for \( \text{Ph}^+ \) leukemias, which are receiving increased attention in preclinical settings, include (1) inhibition of \( \text{BCR-ABL} \) gene expression by antisense oligodeoxynucleotides or ribozymes, and (2) tumor vaccination targeting \( \text{BCR-ABL} \) sequences.

**Monitoring of Minimal Residual Disease**

Detection of minimal residual disease allows clinicians to monitor treatment response to imatinib mesylate and provides the option of evaluating the effectiveness of any of the above-mentioned treatment options on short notice. In 38 patients with \( \text{Ph}^+ \) ALL treated within the above-mentioned GMALL trials, the quantitative \( \text{BCR-ABL} \) level 4 weeks after the start of treatment with imatinib mesylate (measured by PCR) was significantly associated with outcome.\textsuperscript{20} On this basis, the minimal residual disease–guided protocol illustrated in Fig 4 was adopted by the GMALL study group. Eligible patients will receive conventional chemotherapy induction. Minimal residual disease status is assessed at day 44 of the study, ie, at the end of induction therapy, and patients who

![Figure 4. German Multicenter Study Group for Adult ALL (GMALL) protocol: minimal residual disease–guided imatinib mesylate therapy in Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL); MRD, minimal residual disease; SC, stem cell; SCT, stem cell transplantation.](image-url)
are positive (nearly all patients) receive imatinib mesylate monotherapy for 4 weeks. After consolidation, 4 additional weeks of imatinib mesylate may be given. Finally, those with minimal residual disease after allogeneic or autologous SCT or after additional consolidation (in patients in whom SCT cannot be performed) may receive further treatment with imatinib mesylate until BCR-ABL is no longer detectable.

The primary aim of this minimal residual disease–guided study is to explore the rate and durability of cytogenetic or molecular complete remissions when imatinib mesylate is used after chemotherapy and SCT for Ph+ ALL. Of particular interest is whether minimal residual disease after clinical complete remission can be eradicated. In addition, this study and others will determine the feasibility of selecting a higher proportion of BCR-ABL negative stem cells during apheresis following pretreatment with imatinib mesylate.

Identifying and Overcoming Resistance Mechanisms

One of the most important avenues of investigation will be to identify the mechanisms underlying resistance to imatinib mesylate and interventions capable of overcoming the key resistance mechanism(s). In fact, a variety of resistance mechanisms have already been proposed, including (1) clonal evolution, (2) inactivating point mutations, (3) amplification of BCR-ABL at the genomic or transcriptional level, (4) upregulation of multidrug resistance proteins (eg, Pgp-1), and (5) functional inactivation of imatinib mesylate by binding to the acute-phase protein α1 acid glycoprotein. As part of the GMALL phase II trial of imatinib mesylate for Ph+ ALL, 30 complementary DNAs (including nine matched samples) were extracted from the bone marrow samples of 21 patients in an attempt to identify resistance mechanisms. Analysis of the nucleotide sequence that encodes the ATP-binding site revealed a unique point mutation, Glu255Lys, in six of nine patients (67%) that is seen after, but not prior to, treatment with imatinib mesylate.

STI571 analogs are being developed in an attempt to circumvent resistance due to inactivating point mutations. The clinical merits of this class of agents are under investigation.

Conclusions

The development of the ABL-tyrosine kinase inhibitor imatinib mesylate, a paradigm for molecular targeting, is offering new possibilities for the treatment of Ph+ ALL. Imatinib mesylate has demonstrated pronounced antileukemic activity in patients with Ph+ ALL, including those treated for relapse after allogeneic SCT. There is now the need for well-designed studies to identify optimal timing and the best combination for achieving a real cure—or at least a significant improvement—in Ph/BCR-ABL–positive leukemias with an otherwise dismal prognosis. Characterization of the resistance mechanisms that result in relatively short response durations will be invaluable to the continued clinical development of imatinib mesylate for acute and chronic leukemias.

References

17. Wassmann B, Atta J, Pfeifer H, et al: STI571 (Glivec) to enable allogeneic stem cell transplantation (SCT) in relapsed or refractory Philadelphia-chromosome positive acute lymphoblastic leukemia (Ph+ ALL). Onkologie 23:18, 2001 (abstr 64)