Sensitivity to imatinib but low frequency of the TEL/PDGFRβ fusion protein in chronic myelomonocytic leukemia

ROSALIND HELEN GUNBY, GIOVANNI CAZZANIGA, ELENA TASSI, PHILIPP LE COUTRE, ENRICO POGLIANI, GIORGINA SPECCHIA, ANDREA BIONDI, CARLO GAMBAROTI-PASSERINI

Background and Objectives. Chronic myelomonocytic leukemia (CMML) is a myelodysplastic syndrome that has been associated with the expression of platelet-derived growth factor β receptor (PDGFRβ) fusion proteins, namely TEL/PDGFRβ. These fusion proteins possess a constitutive PDGFRβ tyrosine kinase activity, leading to aberrant PDGFRβ signaling and cellular transformation. The expression of PDGFRβ fusions in CMML could have therapeutic relevance, as PDGFRβ is inhibited by the selective tyrosine kinase inhibitor, imatinib. Here, we investigated the possibility of employing imatinib to treat CMML.

Design and Methods. We assessed the effect of imatinib on TEL/PDGFRβ-transformed cells in terms of proliferation, by trypan blue exclusion and 3H-thymidine uptake, and TEL/PDGFRβ autophosphorylation by anti-phosphotyrosine immunoblotting. TEL/PDGFRβ expression in mononuclear cells from the peripheral blood of 27 clinically diagnosed CMML patients was determined by reverse transcriptase-polymerase chain reaction.

Results. Imatinib potently inhibited the proliferation of TEL/PDGFRβ-transformed cells (IC50=7.5 nM), and TEL/PDGFRβ kinase activity. However, TEL/PDGFRβ expression was detected in only 1 of 27 CMML patients (4%, confidence intervals: 0-13%). Additionally, another PDGFRβ fusion protein, Hip1/PDGFRβ, had a similarly low incidence in the same samples: 1 of 25 (4%, confidence intervals: 0-14%).

Interpretation and Conclusions. Although imatinib represents an attractive therapeutic agent for neoplasias associated with abnormal PDGFRβ signaling, the low frequency of the TEL/PDGFRβ and Hip1/PDGFRβ fusion proteins in CMML suggests that its application to this disease may be limited. Detection of PDGFRβ fusion genes in individual patients is necessary in order to employ this drug rationally in CMML.

Key words: CMML, imatinib, TEL/PDGFRβ, leukemia therapy, oncogenic fusion proteins.

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Phase I and II clinical trials have since demonstrated that imatinib is a highly effective treatment for CML, with few associated side effects.\textsuperscript{15} Given the promising results of imatinib clinical trials and the fact that imatinib also inhibits PDGFR\textsubscript{β}, it is possible that this drug will serve as an effective treatment for CMML. This paper investigates the feasibility of using imatinib as a treatment for CMML. The effect of imatinib on the transforming activity of TEL/PDGFR\textsubscript{β} was assessed using an \textit{in vitro} cell model system of TEL/PDGFR\textsubscript{β}-transformed cells. Furthermore, the prevalence of the TEL/PDGFR\textsubscript{β} fusion protein in CMML was determined in 27 patients by reverse transcriptase-polymerase chain reaction (RT-PCR) analysis.

**Design and Methods**

**Cell culture and imatinib treatment**

BaF3 is a murine progenitor cell line possessing characteristics of immature B-cells. Derivatives of this cell line, expressing the oncogenic fusion pro-

teins NPM/ALK (BaF3-N/A) and TEL/PDGFR\textsubscript{β} (BaF3-T/P) were generated as described previously,\textsuperscript{6,16} and kindly supplied, respectively, by Dr. Stephen W. Morris (St. Jude Children’s Hospital, Memphis, Tennessee, USA) and Dr. Martin Carroll (University of Pennsylvania, Philadelphia, PA, USA). All cell lines were grown in RPMI 1640 media (BioWhittaker Europe, Verviers, Belgium), supplemented with 10% FBS, 2 mM L-glutamine, 100 U/mL penicillin G, 80 µg/mL gentamycin, and 20 mM HEPES, in a humidified atmosphere at 37°C and 5% CO\textsubscript{2}.

Imatinib was supplied by Novartis Inc. (Basel, Switzerland). Stock solutions of 10 mM were prepared in distilled water, then filtered and stored at −20°C. The effect of imatinib on proliferation of BaF3 cell lines was determined using trypan blue exclusion and \textsuperscript{3}H-thymidine uptake assays. For the trypan blue exclusion assay, cells were seeded at approximately 2×10\textsuperscript{5} cells/mL and then treated with 10 and 100 nM imatinib for 72 hours. Controls were treated with the appropriate volume of distilled water alone. Trypan blue viable cells were counted every 24 hours by mixing an equal volume of cells with 0.1% trypan blue (Sigma-Aldrich Co. Ltd. Irvine, UK) and using a hemocytometer. For the thymidine uptake assay, cells were plated in a 96-well plate (10\textsuperscript{4}/well) and treated with imatinib at various concentrations, ranging from 0.001 to 10 mM, for 72 hours before labeling with \textsuperscript{3}H-thymidine for 16 h (1 µCi/well). Control samples received an equivalent volume of water alone. The 50% inhibitory concentration (IC\textsubscript{50}) of imatinib was defined as the concentration that gave a 50% decrease in \textsuperscript{3}H-thymidine uptake from that in controls.

**Immunoblotting**

BaF3-T/P cells were treated with 1 µM imatinib for 1 min, 1.5 h or 5.5 h or left untreated in the control sample. Cells were then washed in ice cold PBS and lysed in SDS-loading buffer (50 mM Tris-HCl pH 6.8, SDS 2%, bromophenol blue 0.1%, β-mercaptoethanol 5%). Cell lysates corresponding to 2.5×10\textsuperscript{6} cells were resolved on a 6% SDS-polyacrylamide gel and transferred to a nitrocellulose membrane (Hybond Super-C, Amersham). Tyrosine phosphorylated proteins were detected using an anti-phosphotyrosine antibody (clone 4G10, Upstate Biotechnology Inc.) and the TEL/PDGFR\textsubscript{β} (LBD – ligand binding domain; TKD – tyrosine kinase domain; TM – transmembrane) proteins. The HLH domain of TEL and the TM and TKD of PDGFR\textsubscript{β} fuse to form the TEL/PDGFR\textsubscript{β} fusion protein.

**Patients’ samples**

Mononuclear cells were isolated by Ficoll sedimentation from the peripheral blood of 27 CMML patients

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**Figure 1.** (A) Ideograms of the chromosomes involved in the t(5;12)(q33;p13) chromosomal translocation. Chromosomal bands involved in the rearrangement are shown in frame on the normal chromosomes (chr) 5 and 12. Jagged lines indicate the break/fusion points. The TEL/PDGFR\textsubscript{β} fusion gene is created on the derivative chromosome (der) 5. (B) Schematic representation of TEL (HLH – helix-loop-helix; DBD – DNA binding domain), TEL/PDGFR\textsubscript{β}, and PDGFR\textsubscript{β} (LBD – ligand binding domain; TKD – tyrosine kinase domain; TM – transmembrane) proteins. The HLH domain of TEL and the TM and TKD of PDGFR\textsubscript{β} fuse to form the TEL/PDGFR\textsubscript{β} fusion protein.
patients in various stages of disease, referred from three different Italian hospitals. All samples contained more than 1000 monocytes/mm³. Informed consent was obtained from all patients. All diagnostic slides were reviewed by the same pathologist to reduce variability. After Ficoll separation, cells were resuspended in RPMI 1640 supplemented with 10% FBS and 10% DMSO and stored at -80°C until use.

Reverse transcriptase polymerase chain reaction assay

Mononuclear cells stored at -80°C were washed twice in 0.9% NaCl solution and resuspended in guanidinium isothiocyanate. Total RNA was extracted using a standard cesium chloride gradient purification. cDNA was synthesized from 1.0 µg of total RNA using Superscript II Reverse Transcriptase enzyme (Gibco BRL) in a final volume of 20 µL. Samples were then analyzed for the presence of the TEL/PDGFRβ fusion gene product. PCR was performed as follows: 50 µL of PCR mixture containing 2 µL of cDNA, 1.5 mM MgCl₂, 50 mM KCl, 10 mM Tris–HCl pH 8.3, 200 µM dNTP, 1.0 U of Taq DNA Polymerase (Boehringer) and 15 pmoles of primers. The amplification primers for the 5' region of TEL not involved in t(5;12) using the CACGTAGATGT-3' for PDGFRβ, GAAGACTCG-3' for TEL and 5'-CTGCATGGGGTGCTACGCTAGATGT-3' were used. After an initial denaturation at 94°C for 2 minutes, 35 cycles of amplification were performed (94°C for 30 seconds, 60°C for 30 seconds and 72°C for 30 seconds) on a DNA Thermal Cycler (Perkin-Elmer-Cetus). The amplification primers for the TEL/PDGFRβ product were 5'-CGCTCAAGGATGGAGGAAGACTCG-3' for TEL and 5'-CTGCATGGGGTGCTACGCTAGATGT-3' for PDGFRβ. The cDNA quality was assessed for each sample by amplification of a 5' region of TEL not involved in t(5;12) using the following primers: 5'-GGGTTGGGGAAGGAAAGGG-3' and 5'-TGCGCTTAAGAAAAACTATTATTTT-3'. After amplification, PCR products were run on a 2.5% agarose gel, stained with ethidium bromide and visualized under a UV lamp. Representative PCR products were cloned into the plasmid vector pMOS (Amerham, Buckinghamshire, UK) and sequenced by the dideoxynucleotide chain termination method modified for use with double-stranded DNA templates.

Results

Imatinib inhibits TEL/PDGFRβ function in an in vitro cell model system

The effect of imatinib on the transforming activity of TEL/PDGFRβ was assessed in BaF3 cells stably transfected with this fusion protein (BaF3-T/P). In order to assess specificity of imatinib, its effect on NPM/ALK transformed cells was also assessed (BaF3-N/A). NPM/ALK is an oncogenic fusion protein which, like TEL/PDGFRβ, possesses a constitutive tyrosine kinase activity. It arises from the t(2;5)(p23;q35) chromosomal translocation and is responsible for approximately 50% of cases of anaplastic large cell lymphoma. BaF3 is a murine, pro-B cell line, which is dependent on IL-3 for growth and survival. Transfection of these cells with the oncogenic fusion proteins, TEL/PDGFRβ and NPM/ALK, renders cells IL-3-independent and fusion protein-dependent. Therefore, interruption of oncogenic fusion protein signaling should result in the death of these cells.

The effect of imatinib on proliferation of BaF3-T/P and BaF3-N/A cells was investigated. Cells were treated with various concentrations of imatinib for 72 hours and proliferation was measured using the trypan blue exclusion and 3H-thymidine uptake assays. Imatinib was shown to inhibit proliferation of BaF3-T/P cells at both 10 and 100 nM assessed by trypan blue exclusion, whilst BaF3-N/A cells were unaffected (Figures 2a and b). Similarly, using the 3H-thymidine uptake assay, imatinib was shown to potently inhibit proliferation of BaF3-T/P cells, with a greater than 30% inhibition relative to the control observed at 3 nM and a complete inhibition observed at 30 nM (Figure 2c). The IC₅₀ for inhibition of proliferation was approximately 7.5 nM. In comparison, imatinib had a much less potent effect on the proliferation of BaF3-N/A cells (Figure 2d). No effect on proliferation was observed at concentrations of imatinib up to 300 nM, and only a 25% inhibition was observed at 3 µM. At 10 µM, an almost complete inhibition of proliferation was observed. This may be due to a non-specific effect of imatinib on other kinases within the cell.

The effect of imatinib on the kinase activity of TEL/PDGFRβ was investigated by assessing autophosphorylation in BaF3-T/P cells. Cells were treated with 1 µM imatinib for 1 min, 1.5 and 5.5 h or left untreated in the control sample. Autophosphorylation of TEL/PDGFRβ was assessed by immunoblotting with an anti-phosphotyrosine antibody (Figure 3a). A reduction in tyrosine phosphorylation was apparent after only 1 min of treatment with 1 µM imatinib, and an almost complete inhibition was observed after 5.5 h. The total amount of TEL/PDGFRβ protein did not change throughout the time course, indicating that the reduction in tyrosine phosphorylation was not due to unequal loading of protein (Figure 3b). Treatment with imatinib also inhibited the tyrosine phosphorylation of other cellular proteins, observed as bands above and below the T/P band in the anti-phosphotyrosine immunoblot (Figure 3a), which likely represent substrates of TEL/PDGFRβ as has previously been described with BCR/ABL expressing cells treated with imatinib. Together these results suggest that imatinib can specifically inhibit the kinase activity of TEL/PDGFRβ in BaF3 cells, resulting in an inhibition of TEL/PDGFRβ – mediated proliferative signals.
Low frequency of the TEL/PDGFRβ fusion protein in CMML patients

The frequency of TEL/PDGFRβ in patients clinically diagnosed with CMML was determined by screening mononuclear cells from the peripheral blood of 27 patients, whose characteristics are presented in Table 1. All patients were receiving hydroxyurea. Cytogenetics was informative in 13 patients, one of whom had a t(5;12) chromosomal translocation. In 14 patients no cytogenetic information could be obtained, mostly because of a lack of evaluable metaphases. RT-PCR was performed with primers designed to fall on either side of the TEL/PDGFRβ fusion site, resulting in an amplified DNA fragment of 533 bp (Figure 4A). The sensitivity of the RT-PCR assay was evaluated by serially diluting RNA extracted from BaF3-T/P cells in RNA extracted from healthy donor cells, and was found to be in the range of 10⁻⁵⁻⁶ (Figure 4B). From the 27 samples, only one (patient E.L., in whom the t(5;12) translocation was detected by cytogenetics) was found to be positive for the TEL/PDGFRβ fusion, giving rise to the 533 bp DNA fragment, which was also detected in the BaF3-T/P positive control (Figure 4C). To verify the quality of cDNA in these samples a portion of the TEL wild type gene present in TEL/PDGFRβ, but not involved in the translocation, was amplified (Figure 4A). The resulting 308 bp DNA fragment was detected in all samples and the positive BaF3-T/P control, confirming the quality of the cDNA (data not shown). These results indicate a frequency of 1 in 27 for the TEL/PDGFRβ fusion in patients clinically diagnosed with CMML, i.e. 4% (95% confidence intervals: 0-
Figure 3. Time course of the inhibition of TEL/PDGFRβ tyrosine kinase activity by imatinib. BaF3-T/P cells were incubated in the presence of 1 μM imatinib for 1 min, 1.5 h and 5.5 h or left untreated in the control sample (con). Cells were lysed and equal amounts of lysate were analyzed by immunoblotting with an anti-phosphotyrosine antibody (A) and an anti-PDGFR antibody that recognizes the TEL/PDGFRβ fusion protein (B). TEL/PDGFRβ (T/P) is indicated with a complete arrow and other cellular proteins, possibly substrates of T/P, are indicated with arrowheads.

Table 1. Clinical characteristics of the patients studied.

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</tr>
<tr>
<td>Number of patients with dysplastic CMML</td>
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<td></td>
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<td>0–11</td>
</tr>
<tr>
<td>% Monocytes</td>
<td>35% *</td>
<td>7–64%</td>
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(*Median value; WBC: white blood count.)

Figure 4. Screening of CMML patients for the presence of the TEL/PDGFRβ fusion transcript by RT-PCR. A) Schematic representation of the position of the PCR primers (arrow) within the TEL/PDGFRβ fusion protein. B) RT-PCR sensitivity assay: RNA extracted from BaF3-T/P cells, was serially diluted (10⁻¹ to 10⁻⁷) in RNA extracted from healthy donors. cDNA synthesis and the PCR reaction were performed as described in design and methods. An amplified fragment of the expected size (533 bp) was visible in the undiluted sample (U) and samples diluted up to 10⁻⁴. No band was observed in the water only control (C). C) Twenty-seven patients were screened for the TEL/PDGFRβ fusion by RT-PCR. The gel shows a TEL/PDGFRβ positive patient (E.L.), a negative sample from a patient, the BaF3-T/P positive control and a water only control (C).
13%). Furthermore, using the RT-PCR assay we were able to test samples in which cytogenetic analysis was not informative.

**Discussion**

The selective tyrosine kinase inhibitor, imatinib, has recently been shown to be a highly effective treatment for BCR/ABL positive CML and ALL, with relatively few associated side effects assessed over a three-year period. As imatinib inhibits other tyrosine kinases, namely c-Kit and PDGFRβ, it might be effective against cancers which possess aberrant signaling from these receptors. Indeed, imatinib has recently been demonstrated to be highly effective against gastrointestinal stromal tumors (GIST), in which elevated c-Kit activity is commonly observed. Furthermore, a recent study has investigated whether imatinib could be effective against CMML, which has been associated with the COL1A1/PDGFβ rearrangement, both in vitro and in vivo. This rearrangement results in the deregulated expression of PDGFB, and consequently an autocrine stimulation of the PDGFRβ leading to malignant transformation. Our study indicates whether imatinib could be effective against CMML, which has been associated with PDGFRβ fusion proteins, such as TEL/PDGFRβ and HIP1/PDGFRβ.

Using an in vitro cell model system, we show that the kinase activity of TEL/PDGFRβ and the proliferation of TEL/PDGFRβ transformed BaF3 cells are potently inhibited by imatinib with an IC50 of approximately 7.5 nM. In contrast, NPM/ALK transformed BaF3 cells were more resistant to imatinib, requiring doses in the micromolar range to have any effect on cell proliferation. Presumably, the effects observed at these higher concentrations are due to non-specific actions of imatinib. These data support previously published results showing that imatinib is able to inhibit TEL/PDGFRβ autophosphorylation and reduce viability of TEL/PDGFRβ transformed BaF3 cells. However, the IC50 of TEL/PDGFRβ inhibition was reported to be 150 nM, 20-fold greater than our findings. This result probably differs from ours because it was based on the inhibition of autophosphorylation as opposed to inhibition of proliferation. Recently, it has also been demonstrated that imatinib inhibits growth of BaF3 cells transformed with a novel PDGFRβ fusion protein involving rabaptin-5 (rab5/PDGFRβ). Together these results indicate that imatinib could potentially be used as a treatment for CMML. In fact, two recent publications have reported that imatinib was effective in the treatment of patients with PDGFRβ fusion protein-positive myeloproliferative disorders. In total, five patients were treated, three possessing the TEL/PDGFRβ fusion, one with the rab5/PDGFRβ fusion and one with an unidentified PDGFRβ fusion protein. Two of the patients were newly diagnosed and had not received previous treatment, while the remaining three patients had all undergone extensive treatment prior to administration of imatinib. All patients responded rapidly to the treatment, with cell counts and cytogenetics returning to normal and in some cases a complete molecular remission was achieved. It should be noted however that only one of these patients was diagnosed as having CMML.

Although CMML is known to be associated with TEL/PDGFRβ, the frequency with which this fusion protein occurs is unknown. In order to evaluate the potential impact of imatinib on CMML treatment, the proportion of CMML patients expressing TEL/PDGFRβ was determined by RT-PCR. Of the 27 clinically confirmed CMML patients screened, only one (patient E.L.) was found to be positive for TEL/PDGFRβ (4%, confidence intervals 0–13%). Retrospective review of cytogenetic information confirmed the presence of the t(5;12) translocation in this patient. Patient E.L. had undergone an allogeneic stem cell transplantation, but had relapsed with a white blood cell count of 35×10^3/mm³ at the time of sampling. Unfortunately, at that time (December 1999) it was not possible to treat this patient with imatinib, hence the patient decided to undergo a second allogeneic stem cell transplantation but died soon after.

A preliminary screen for another PDGFRβ fusion protein associated with CMML, HIP1/PDGFRβ (H/P), has been performed using the same samples as for TEL/PDGFRβ. One positive patient was identified from 25 tested by RT-PCR, again indicating a frequency of 4% (confidence intervals 0 – 14%; Dr. T. Ross, March 2002, personal communication). No cytogenetic information was available for this patient. Together, these results suggest that the frequency of PDGFRβ fusion proteins in CMML is low. However, other PDGFRβ fusion proteins involving the fusion partners Rab5, H4 and CEV14 have not yet been screened for in CMML patients and might occur at a higher frequency. Furthermore, it is likely that other uncharacterized PDGFRβ fusion proteins exist, which may also affect the total frequency of PDGFRβ fusion proteins in CMML. Nevertheless, to date the Rab5 fusion has only been detected in one CMML patient, the CEV14 fusion in one AML patient and the H4 fusion in one BCR/ABL negative CML patient, indicating a low frequency of these PDGFRβ fusions in general.

New treatment modalities are urgently needed for CMML, a disease that currently has no curative therapies other than allogeneic stem cell transplantation and is associated with a poor prognosis (median survival is approximately 14 months).
Although imatinib has recently been demonstrated to be an effective treatment for patients possessing PDGFRβ fusion protein positive myeloproliferative disorders, the apparent low incidence of these fusion proteins in clinically diagnosed CMML patients suggests that its use may be limited and should be reserved to those patients with PDGFRβ abnormalities. A more detailed analysis of PDGFRβ translocations is required in order to determine definitively the proportion of CMML patients that potentially could respond to imatinib treatment. The development of fluorescence in situ hybridization probes specific for PDGFRβ will certainly assist in achieving this aim. Patients with PDGFRβ fusions have recently been described to have similar clinical phenotypes32 (myeloproliferative disorder with eosinophilia, splenomegaly, monocytosis and an extreme male bias); this fact could help in identifying patients with PDGFRβ fusions. For CMML cases that do not involve PDGFRβ translocations, further characterization of the etiology of CMML is required in order to develop alternative, rationally designed therapies.

References


Pre-Publication Report & Outcomes of Peer Review

Contributions
CG-P was responsible for the conception and design of the study. RG and CG-P were responsible for interpretation of the data and writing the manuscript. RG and PLC performed the in vitro studies on the effect of imatinib and are responsible for Figures 2 and 3, respectively. GC and ET performed the RT-PCR analysis and are responsible for Figure 4. EP, GS and AB were responsible for selecting the patients, cytogenetic analysis, providing clinical data and for Table 1. All authors contributed to and approved the final version of the manuscript. RG and CG-P have primary responsibility for the paper. The authors would like to thank Dr. V. Liso (Istituto di Medicina Clinica, Policlinico, Bari, Italy) and Dr. A. Rambaldi (Ospedali Riuniti di Bergamo, Bergamo, Italy) for providing samples from patient and for the morphologic revision of all samples; Dr. Stephen W. Morris (St. Jude Children’s Hospital, Memphis, Tennessee, USA) and Dr. Martin Carroll (University of Pennsylvania, Philadelphia, PA, USA) for providing cell lines; Edoardo Marchesi (Istituto Nazionale Tumori, Milan, Italy) for technical assistance; Dr. Theodore Ross (University of Michigan Comprehensive Cancer Center, MI, USA) for providing data on the Hip1/PDGFRβ fusion protein and for critical comments.

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Disclosures
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This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Professor Cazzola and the Editors. Manuscript received November 21, 2002; accepted February 25, 2002.

In the following paragraphs, the Editor-in-Chief summarizes the peer-review process and its outcomes.

What is already known on this topic
Imatinib mesylate has been found to be very effective not only in chronic myeloid leukemia but also in other disorders such as gastrointestinal stromal tumors, chronic myeloproliferative diseases with rearrangements of the platelet-derived growth factor receptor β, and hypereosinophilic syndrome. Chronic myelomonocytic leukemia is an atypical disorder with both myelodysplastic and myeloproliferative features that might theoretically be associated with abnormal platelet-derived growth factor receptor β signaling.

What this study adds
Abnormal platelet-derived growth factor receptor β signaling, namely the TEL/PDGFRβ protein, is found only in occasional patients with chronic myelomonocytic leukemia.