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Haematologica 2016 [Epub ahead of print]

doi:10.3324/haematol.2015.139568

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Letter to the Editor

Imatinib-induced long-term remission in a relapsed RCSD1-ABL1-positive acute lymphoblastic leukemia

Thomas Perwein¹, Sabine Strehl², Margit König², Herwig Lackner¹, Renate Panzer-Grümmayr²,3, Georg Mann³, Andishe Attarbaschi³, Ernst-Christian Urban¹, and Oskar A. Haas²,3

¹ Division of Pediatric Hematology/Oncology, Medical University of Graz, Graz, Austria
²CCRI, Children’s Cancer Research Institute, St. Anna Kinderkrebsforschung, Vienna, Austria
³ St. Anna Children’s Hospital and Medical University of Vienna, Vienna, Austria

*TP and SS share first authorship

Imatinib-induced remission in RCSD1-ABL1+ ALL

Correspondence

Oskar A. Haas
CCRI, Children’s Cancer Research Institute
St. Anna Kinderkrebsforschung
Zimmermannplatz 10
1090 Vienna, Austria
Email: oskar.haas@ccri.at
The treatment of patients with *BCR-ABL1* positive chronic myeloid leukemia and acute lymphoblastic leukemia (ALL) with tyrosine kinase inhibitors (TKIs) has significantly improved their overall survival.\(^1\)\(^-\)\(^3\) Several reports confirm that this type of treatment may be similarly effective also in cases with other types of kinase or cytokine receptor signaling activating fusion genes, particularly those involving the *ABL1, ABL2, JAK2, PDGFRB, EPOR, CRLF2* and *CSF1R* genes.\(^1\)\(^-\)\(^7\) However, follow-up times are generally short, with treatment still ongoing at the time of publication and it therefore remains open, whether continuous long-term remissions can be achieved and sustained even after discontinuation of TKI treatment.\(^6\) Herein we present the case of a young adolescent with a relapsed B-cell precursor (BCP) ALL and a rare *RCSD1-ABL1* gene fusion, in whom transitory treatment with imatinib induced a continuing remission that to date lasts eleven years.

In April 2001, a 15-year-old boy was admitted to the Pediatric Hematology/Oncology Department of the Medical University in Graz because of increasing pallor and deteriorating physical performance. His white blood cell count (WBC) was 68.7 \(\times\) 10\(^9\)/L with 71% blasts, 93 \(\times\) 10\(^9\)/L platelets and 44 g/L hemoglobin. The 95% blasts in the bone marrow (BM) were CD10, CD19, cyCD22, CD79a, CD34, TdT and HLA-DR positive and negative for myeloid and T-cell markers. Cytogenetic analysis revealed an abnormal clone with a 46,XY,t(1;9)(q31?;q34), which was shown by fluorescence in situ hybridization (FISH) using a LSI *BCR/ABL1* dual color single fusion probe (Vysis) to disrupt the *ABL1* gene. The description of *RCSD1* as the *ABL1* fusion partner in an identical translocation in 2007 facilitated the subsequent identification of the respective *RCSD-ABL1* fusion gene by RT-PCR and sequencing also in our case (Figure 1).\(^8\)
The patient was stratified into the intermediate risk group of the AIEOP-BFM ALL 2000 study protocol and treated accordingly. The day 15 BM aspirate still contained 62% blasts. Morphological remission was achieved on day 33, although immunoglobulin gene rearrangement-based minimal residual disease (MRD) was still detectable on days 33 and 77 at levels of $10^{-3}$ and $10^{-4}$, respectively (Figure 2A). After 39 months the patient experienced a BM relapse with a WBC of 24,000 $10^9$/L and 64% blast cells in the peripheral blood. Therefore, further treatment was initiated according to the ALL-REZ BFM 2002 protocol. Due to therapy refractory disease, this regimen was complemented with daily oral doses of 400 mg imatinib on day 64 of relapse treatment. This decision was driven not only by the fact that the patient was resistant to conventional therapy but also by the presence of an ABL1 gene fusion, although at that time the partner gene had not yet been identified. Morphological remission was achieved on day 68, whereas MRD levels remained positive until day 79 but became negative by day 109 (Figure 2B). Imatinib was given during the entire course of relapse chemotherapy and was thereafter continued following the patient's explicit request and the treating physicians' discretion for another 69 months as mono-therapy, before it was discontinued based on a joint decision and with the patient's approval. He has now been without any treatment for more than 36 months and remains in remission almost 15 years after disease onset. Although this response pattern clearly indicates that conventional chemotherapy was adequate to reduce the disease burden, it must remain open whether it alone would also have been as sufficient to cure the patient.

In addition to BCR, eight other ABL1 fusion partners are currently known in B-cell precursor ALL, namely ETV6, ZMIZ1, NUP214, FOXP1, SNX2, RANBP2, SFPQ and RCSD1 and four, NUP214, INPP5D (SHIP1), EML1 and SEPT9 in T-cell precursor
ALL.²,⁴,⁶,⁸-¹⁴ TKI treatment has shown very promising results already in a considerable number of patients with such kinase-activating gene fusions,¹,²,⁴,⁷,⁹,¹⁰ although they may become refractory to this therapy in a similar fashion as BCR-ABL1-positive CML and ALL due to various molecular mechanisms, such as ABL1 kinase domain mutations, additional genetic lesions as well as signaling pathway alterations.¹-⁴,¹²-¹⁴ Resistance can, at least in part, be overcome with second and third generation TKIs, such as dasatinib, nilotinib, bosutinib, and ponatinib, which do not only affect different conformational states of the respective fusion proteins but also a broader spectrum of tyrosine kinases.¹-⁴,⁶,¹⁴

Including the patient described herein, ten cases with B-cell precursor ALL and a molecular genetically verified RCSD1-ABL1 fusion gene have been reported so far (Table 1).⁴-⁶,⁸,¹⁰-¹⁴ An identical translocation was also found in an ABL1-positive biphenotypic ALL case in which, however, the partner gene has not been ascertained.¹⁵ Four of these patients were treated with TKIs and all of them achieved at least a partial remission (Table 1).⁶,¹⁰,¹³,¹⁴ To the best of our knowledge, time-wise and formally, however, our patient is not only the first RCSD1-ABL1-positive case, but also the overall first one with a variant ABL1 fusion, who was rescued with imatinib treatment and cured despite cessation of therapy.

Our instructive case underscores the importance of identifying these particular genetic lesions, as they may become highly relevant for appropriate treatment decisions. The choice of TKI is generally based on the specific gene rearrangement and the associated constitutively activated kinase. As exemplified in our ABL1-positive case, even the knowledge of the particular kinase alone may already suffice the selection of the most appropriate first-line TKI, in this instance imatinib, because
this drug is not only effective in BCR-ABL1-positive cases but may perhaps be also in a similar fashion in those with other ABL1 kinase-activating gene fusions. The treatment with second and third generation TKIs may thus be restricted only to cases that are either primarily refractory, become resistant or relapse. Owing to the low number and the consequential general lack of experience with cases that harbor such rarer types of tyrosine-kinase activating fusion genes, the pros and cons when and if at all an apparently successful TKI treatment should be stopped must still be carefully weighed up against each other and the final decision can therefore only be made on an individual basis.
References


11. Zamecnikova A. Chromosomal translocation t(1;9)(q24;q34) in acute lymphoblastic leukemia patient involving the ABL1 gene. Leuk Res. 2011;35(9):e149-150.


TABLES

Table 1. Clinical and hematological characteristics of reported patients with RCSD1-ABL1+ ALL.

(A) RCSD1-ABL1 not assessed; (1) BMT at 31 m; (2) refractory disease after induction, + dasatinib: CR after 1 m, continued until HSCT at 4 m / R at 16 m, chemotherapy + dasatinib: CR, then dasatinib monotherapy, switched to imatinib due to immunological side effects; (3) partial response to chemotherapy and DXM + imatinib/dasatinib / PD after 3 m: partial response to chemotherapy and DXM + dasatinib / PD at 6 m: no response, death; (4) no further data reported; (5) R 3, 33 and 75 m after diagnosis, BMT at 4, 35 and 84 m; (6) no further data reported; (7) no treatment compliance; (8) poor response to induction, imatinib: residual disease 2% after 1 m; (9) chemotherapy + dasatinib: 0.2% residual disease, continued until HSCT at 5 m / R1 at 15 m: CR1 under chemotherapy / R2 at 19 m: CR under ponatinib monotherapy, continued until HSCT2 at 22 m / R3 at 24 m: ponatinib monotherapy: response, severe GvHD and death due to septic shock; (10) chemotherapy + imatinib 2 m after relapse: sustained CR after 1 m.

Abbreviations: y, years; WBC, white blood cells; PB, peripheral blood; BM, bone marrow; TKI, tyrosine kinase inhibitor; m, month(s); M, male; F, female; NA, no data available; †, death; R, relapse; CR, complete remission; BMT, bone marrow transplantation; HSCT, hematopoietic stem cell transplantation; DXM, dexamethasone; PD, progressive disease.
Table 1. Clinical and hematological characteristics of reported patients with \textit{RCSD1-ABL1+ ALL}.

<table>
<thead>
<tr>
<th>Case</th>
<th>Phenotype</th>
<th>Year of diagnosis/report</th>
<th>Sex</th>
<th>Age (y)</th>
<th>WBC $10^9$/L</th>
<th>PB blasts (%)</th>
<th>BM blasts (%)</th>
<th>Treatment</th>
<th>Relapse (m)</th>
<th>Survival (m)</th>
<th>Cytogenetics</th>
<th>Ref.</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>biphenotypic leukemia</td>
<td>2004</td>
<td>M</td>
<td>15</td>
<td>122 $^{23R}$</td>
<td>95 $^{R}$</td>
<td>NA $^{R}$</td>
<td>chemotherapy</td>
<td>10</td>
<td>10 $^{T}$</td>
<td>$t(1;9)(q23.3~q25;q34)$</td>
<td>13,15</td>
</tr>
<tr>
<td>1</td>
<td>BCP-ALL</td>
<td>2003</td>
<td>M</td>
<td>11</td>
<td>6 $^{R}$</td>
<td>47 $^{R}$</td>
<td>92 $^{R}$</td>
<td>chemotherapy + HSCT</td>
<td>11</td>
<td>97</td>
<td>$t(1;9)(q24;q34)$</td>
<td>4,8,12,13</td>
</tr>
<tr>
<td>2</td>
<td>BCP-ALL</td>
<td>2009</td>
<td>M</td>
<td>40</td>
<td>24</td>
<td>34</td>
<td>80</td>
<td>chemotherapy + dasatinib + HSCT; chemotherapy + dasatinib/imatinib/$^{R}$</td>
<td>16</td>
<td>66</td>
<td>$t(1;9)(q24;q34)$</td>
<td>4,10,12,13</td>
</tr>
<tr>
<td>3</td>
<td>BCP-ALL</td>
<td>2010</td>
<td>M</td>
<td>31</td>
<td>146</td>
<td>90</td>
<td>NA</td>
<td>chemotherapy + imatinib/dasatinib</td>
<td>no CR</td>
<td>6.5 $^{T}$</td>
<td>$t(1;9)(q23;q34)$</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>BCP-ALL</td>
<td>2010</td>
<td>F</td>
<td>18</td>
<td>110</td>
<td>87</td>
<td>92</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA $^{T}$</td>
<td>t(1;9)(q24;q34)</td>
</tr>
<tr>
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<td>BCP-ALL</td>
<td>2011</td>
<td>F</td>
<td>15</td>
<td>348</td>
<td>NA</td>
<td>NA</td>
<td>chemotherapy + HSCT</td>
<td>3/33/75</td>
<td>84 $^{T}$</td>
<td>$t(1;9)(q24;q34)$</td>
<td>4,12</td>
</tr>
<tr>
<td>6</td>
<td>BCP-ALL</td>
<td>2012</td>
<td>M</td>
<td>15</td>
<td>48</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>5</td>
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<tr>
<td>7</td>
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<td>M</td>
<td>18</td>
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<td>52</td>
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<td>no treatment compliance</td>
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<td>12</td>
<td>$t(1;9)(q24;q34)$</td>
<td>12</td>
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<tr>
<td>8</td>
<td>BCP-ALL</td>
<td>2014</td>
<td>M</td>
<td>6</td>
<td>108</td>
<td>NA</td>
<td>NA</td>
<td>chemotherapy + imatinib</td>
<td>-</td>
<td>1</td>
<td>$t(1;9)(q24;q34)$</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>BCP-ALL</td>
<td>2012</td>
<td>F</td>
<td>26</td>
<td>26</td>
<td>84</td>
<td>86</td>
<td>chemotherapy + dasatinib + HSCT; chemotherapy$_R^{R_1}$; ponatinib + HSCT$_R^{R_2}$; ponatinib$_H$</td>
<td>15/19/24</td>
<td>25 $^{T}$</td>
<td>$t(1;9)(q24;q34)$</td>
<td>14</td>
</tr>
<tr>
<td>10</td>
<td>BCP-ALL</td>
<td>2001</td>
<td>M</td>
<td>15</td>
<td>18 $^{R}$</td>
<td>69 $^{R}$</td>
<td>71 $^{R}$</td>
<td>chemotherapy; chemotherapy + CNS irradiation + imatinib$_H$</td>
<td>39</td>
<td>163</td>
<td>$t(1;9)(q31;q34)$</td>
<td>present work</td>
</tr>
</tbody>
</table>

\(A\) \textit{RCSD1-ABL1} not assessed; \(1\) BMT at 31 m; \(2\) refractory disease after induction, + dasatinib: CR after 1 m, continued until HSCT at 4 m / R at 16 m, chemotherapy + dasatinib: CR, then dasatinib monotherapy, switched to imatinib due to immunological side effects; \(3\) partial response to chemotherapy and DXM + imatinib/dasatinib / PD after 3 m: partial response to chemotherapy and DXM + dasatinib / PD at 6 m: no response, death; \(4\) no further data reported; \(5\) R 3, 33 and 75 m after diagnosis, BMT at 4, 35 and 84 m; \(6\) no further data reported; \(7\) no treatment compliance; \(8\) poor response to induction, imatinib: residual disease 2% after 1 m; \(9\) chemotherapy + dasatinib: 0.2% residual disease, continued until HSCT at 5 m / R1 at 15 m: CR1 under chemotherapy / R2 at 19 m:
CR under ponatinib monotherapy, continued until HSCT2 at 22 m / R3 at 24 m: ponatinib monotherapy: response, severe GvHD and death due to septic shock; (10) chemotherapy + imatinib 2 m after relapse: sustained CR after 1 m.
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FIGURES LEGENDS

Figure 1. Detection of the RCSD1-ABL1 rearrangement.

(A) Fluorescence in situ hybridization (FISH) of a metaphase obtained from the bone marrow at relapse using the BCR/ABL Dual Color, Dual Fusion Translocation Probe (Oncor) showing two signals for BCR (red signals) and three signals for ABL1 (green signals). The black arrow indicates the ABL1 signal on the normal chromosome 9, the green and the red arrows the ABL1 signals on the der(9) and der(1) chromosomes, respectively.

(B) RT-PCR of RCSD1-ABL1 fusion transcripts using primers RCSD1ex1_2-F1 (5'-CCTGAAGGACATGGAGGAAAGACC-3') spanning exons 1 and 2 of RCSD1 and ABL1ex4-R1 (5'-CTGGATAATGGAGCGTGGTGATG-3') located in exon 4 of ABL1 showing two distinct amplification products.

(C-D) Sequence chromatograms corresponding to the two fusion transcript variants detected by RT-PCR. In-frame fusions of (C) RCSD1 exon 3 to ABL1 exon 4 and (D) alternatively spliced RCSD1-ABL1 lacking RCSD1 exon 3.

Abbreviations: M, molecular weight marker; Ctrl, control, normal cDNA; NTC, non-template control.

Figure 2. Course of initial disease and relapse.

(A) Initial disease: course of leukemic blasts detected in bone marrow (percent) and minimal residual disease (MRD) load (immunoglobulin heavy chain locus; QR: 1E-04) under treatment according to the ALL-BFM-2000 study protocol (Prot. IA-P+, Prot. IB [I]; Prot. M [M]; Prot. II [II]; maintenance therapy); maintenance therapy was continued until April 2003 (BM: CR)

(B) Relapse: course of leukemic blasts detected in bone marrow (percent) and minimal residual disease (MRD) load (immunoglobulin heavy chain locus; QR: 1E-
04) under treatment according to the ALL-REZ-BFM-2002 study protocol – S2A (Prot. F1 and F2 [F]; Prot. II-IDA [II-IDA]; Prot. R1 and R2 [R]; CNS irradiation [↓]; maintenance therapy [D24/V]); maintenance therapy was continued until March 2007; imatinib treatment was continued until November 2012; further assessments: BM: CR in April 2006, 2007 and 2008, MRD: ND in April 2008.

Abbreviations: ND, not detectable; BM, bone marrow; CR, complete remission