Chronic myeloid leukemia (CML) with P190BCR-ABL - analysis of characteristics, outcomes and prognostic significance.

Dushyant Verma¹, Hagop M. Kantarjian¹, Dan Jones², Rajyalakshmi Luthra², Gautam Borthakur¹, Srdan Verstovsek¹, Mary Beth Rios¹, Jorge Cortes¹

¹ Department of Leukemia
² Department of Hematopathology
The University of Texas MD Anderson Cancer Center
Houston, TX 77030. USA.

Running Title: e1a2 fusion transcripts in CML

Address for correspondence:
Jorge Cortes, MD
Professor of Medicine
Department of Leukemia
The University of Texas MD Anderson Cancer Center
1515 Holcombe Blvd, Unit 428
Houston, TX 77030. USA
Tel: +1 713-794-5783
Fax: +1 713-794-4297
Email: jcortes@mdanderson.org

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Abstract

The most common BCR-ABL transcripts in CML are e13a2(b2a2) and e14a2(b3a2). Other transcripts like e1a2 are rare and their outcome with TKI therapy is undefined. We analyzed 1292 CML patients and identified 14 with only e1a2 transcripts, 9 in chronic (CP), 1 accelerated (AP), and 4 blast phase (BP). Of the CP, 4 achieved CHR, 2 CCyR, 2 PCyR, and 1 did not respond to imatinib. Five patients progressed to myeloid BP (3), lymphoid BP (1), or AP (1). The AP patient received various TKIs sequentially and achieved only CHR. BP patients received Hyper-CVAD+imatinib/dasatinib or idarubicin+Ara-C; 2 did not respond, 1 had CCyR, and 1 short-lasting CMR. Overall, cytogenetic responses lasted 3-18 months, only 2 achieved MMR on TKI. P190<sup>BCR-ABL</sup> CML is rare and is associated with an inferior outcome to therapy with TKI. These patients need to be identified as high-risk patients.
Introduction

The Philadelphia (Ph) chromosome, t(9;22) (q34;q11.2) in chronic myeloid leukemia (CML) is transcribed into a fusion gene, \textit{BCR-ABL}. The breakpoint in \textit{BCR} gene on chromosome 22 usually occurs in the major breakpoint cluster region (M-bcr) between exons e12-e16 (formerly named b1-b5), while breakpoints in \textit{ABL} gene on chromosome 9 happen in exon a2 resulting in fusion transcripts e13a2(b2a2) and e14a2(b3a2).\textsuperscript{1} Rarely, the minor breakpoint cluster region (m-bcr) may be involved with a resultant fusion transcript e1a2.\textsuperscript{2-5} Other transcripts such as e19a2,\textsuperscript{2,6-7} e2a2,\textsuperscript{8} e1a3, e6a2, e13a3(b2a3), e14a3(b3a3),\textsuperscript{9-10} occur less frequently. The e13a2(b2a2)/e14a2(b3a2) fusion transcripts encode for a 210-kd protein (P210 \textit{BCR-ABL}), while the e1a2 encodes for a 190-kd protein (P190 \textit{BCR-ABL}), and the e19a2 encodes for a 230-kd protein (P230\textit{BCR-ABL}).

In CML, the e1a2 transcripts may co-exist with e13a2(b2a2)/e14a2(b3a2),\textsuperscript{11} but CML expressing only e1a2 transcripts (from here on referred to as P190\textit{BCR-ABL} CML) is uncommon, and outcome of patients with this transcript alone in the era of tyrosine kinase inhibitors (TKI) is not well known. Although there are anecdotal reports of patients with P190\textit{BCR-ABL} CML treated with imatinib\textsuperscript{2} or other therapies\textsuperscript{3-5,11-14} to our knowledge, there are no published series of data on efficacy of imatinib or other TKI in CML with this transcript. We performed this study to investigate the frequency of P190\textit{BCR-ABL} CML, the clinical characteristics of patients with this entity, and their outcome after treatment with TKI.
Materials and methods

The records of all patients with CML treated with TKI at MD Anderson Cancer Center from January 2000 to November 2008 were reviewed to identify patients with only e1a2 BCR-ABL fusion transcripts consequent to breakpoints in minor bcr. Patients with e1a2 co-existing with e13a2(b2a2) and/or e14a2(b3a2) were excluded from this analysis. The criteria for chronic (CP), accelerated (AP), and blast phase (BP) were as previously described. All patients were enrolled in various studies approved by the institutional review board of MD Anderson Cancer Center and signed informed consents in accordance with the Declaration of Helsinki.

Patients had complete blood counts and blood chemistry prior to the start of therapy and every month for the first 3 months, then every 3 months for 9 months, and then every 6 months. Cytogenetic response was assessed by G-banding assessed in the bone marrow with at least 20 metaphases counted. The BCR-ABL fusion transcripts were analyzed using reverse transcription quantitative polymerase chain reaction (RQ-PCR) assay that detects e1a2, e13a2(b2a2) and e14a2(b3a2) transcripts in a single tube and is normalized to ABL1, with BCR-ABL transcript type determined by subsequent capillary electrophoretic separation of the fluorochrome-labeled products. Both cytogenetic and molecular response assessments were performed at baseline, every 3 months for the first 12 months, and then every 6 months. Response and relapse criteria were as previously reported.

Event-free survival (EFS) was measured from the start of each therapy until loss of complete hematologic response (CHR) or major cytogenetic response (MCyR), progression to the AP or BP, or death from any cause during treatment. Overall survival (OS) was defined from date of CML diagnosis to date of death or last follow-up.
Results and Discussion

Fourteen (1%) of the 1292 CML patients treated with TKI, during the study period had P190\textsuperscript{BCR-ABL} CML. At the time of diagnosis, 9 patients were in CP, 4 in BP (1 myeloid – MyBP, 3 lymphoid – LyBP), and 1 in AP [based on clonal evolution – double Philadelphia and t(9;17)(q32;q12),+8,+10,+19,+21]. Patient characteristics are shown in Table 1. The median age at the time of diagnosis was 60 years (range 28-86). The median follow-up since the diagnosis of CML is 40 months (range 2-109).

Ten patients (6 CP, 1 AP, 3 BP) received TKI (alone or in combination) as their initial therapy (9 imatinib, 1 nilotinib) (Table 2). Among patients in CP, 5 received imatinib as frontline therapy and 3 after IFN failure, and after a median follow-up of 37 months (range, 12 to 72), one patient (frontline) had no response to imatinib, and the best response for the others was CHR in 4, complete cytogenetic response (CCyR) in 1, and partial cytogenetic response (PCyR) in 2. Notably, only 1 of 5 patients receiving imatinib as frontline therapy achieved CCyR. The patient treated with nilotinib frontline has achieved CCyR after 3 months. None of these patients achieved a major molecular response (MMR) except one who received Hyper-CVAD (hyperfractionated cyclophosphamide vincristine adriamycin dexamethasone) with dasatinib after progression to LyBP, achieved CCyR, underwent allogeneic stem cell transplant (SCT) and has been in complete molecular response (CMR) for 9 months on dasatinib post-transplant. Cytogenetic responses were short-lived, lasting a median of 5 months (range, 3-18 months). Five of the 9 (56%) patients in CP (3 receiving frontline TKI therapy) progressed to AP (n=1) or BP (myeloid n=3, lymphoid n=1) after a median of 48 months (range 4-92 months) and only 1 is alive (after SCT).
The sole patient in AP at diagnosis received imatinib, dasatinib and bosutinib sequentially, achieving only CHR with each of them. Of the 4 patients with BP at diagnosis, 3 had transient CCyR with HCVAD + TKI or with clofarabine, but eventually all relapsed and died.

Overall, 6 patients (5 CP, 1 AP) were alive at a median 39 (range 2-85) months after diagnosis: 3 with CHR (2 on imatinib, 1 bosutinib), 1 with PCyR on imatinib, 1 with CCyR on nilotinib, and 1 with CMR after allogeneic SCT. Median survival was 56 months for patients in CP at the start of therapy, and 13 months for those in BP; the patient in AP has been alive for 55 months.

The e1a2 transcripts may co-exist with e13a2(b2a2)/e14a2(b3a2), but their expression as the only transcript in CML is rare. P190BCR-ABL is present in 60-75% of patients with Ph+ acute lymphoblastic leukemia, and it can induce rapid transformation of lymphoid progenitor cells. P190BCR-ABL CML has been reported to have increased monocytosis, with a peripheral blood morphology resembling chronic myelomonocytic leukemia. In our study, 4 patients (2 CP, 1 AP, 1 BP) had splenomegaly and 5 (3 CP, 2 BP) had monocytosis. The 3 with CP and monocytosis at presentation continue to be in CP with imatinib treatment, while the 2 in BP did not respond to treatment.

Anecdotal reports suggest a poor outcome of patients with P190BCR-ABL CML treated with imatinib or other therapies. Our analysis demonstrates the poor outcome of these patients despite therapy with TKI. Of the 6 CP patients treated with TKI as initial therapy, 3 transformed to AP or BP and two of them died shortly thereafter while the one patient treated with nilotinib as initial therapy has achieved CCyR after 3 months of therapy. In addition, none of the 14 patients reported on our analysis achieved MMR with TKI therapy.
We conclude that although P190^{BCR-ABL} CML represents only 1% of patients with CML, it is associated with an inferior outcome to therapy with TKI, with few, usually short-lived responses. These patients need to be identified as high-risk patients, monitored closely for efficacy during therapy with TKI, and offered SCT early if eligible for this procedure.
**Acknowledgments:**

DV wrote the manuscript, analyzed data and approved it. JC designed the study, managed the patients, analyzed data and reviewed and approved the manuscript. HK, DJ, RL, GB, SV, MR approved the manuscript and managed the patients.

**Conflict of Interest Disclosure:**

HK and JC have research grants from Novartis and BMS.
References


Table 1. Patient characteristics and overall responses to treatment at CML diagnosis with e1a2 BCR-ABL fusion transcripts  CP: chronic phase, AP: accelerated phase, CE: clonal evolution, BP: blast phase, MyBP: myeloid blast phase, LyBP: lymphoid blast phase, PB: peripheral blood, BM: bone marrow, IFN: interferon, TKI: tyrosine kinase inhibitor, KD: kinase domain, F/up: follow-up, Dx: diagnosis, mo: months, number (%), median [range].

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>CP (n=9)</th>
<th>AP (CP+CE) (n=1)</th>
<th>BP (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>9</td>
<td>1</td>
<td>1:MyBP, 3:LyBP</td>
</tr>
<tr>
<td>Age at CML diagnosis, years</td>
<td>60 [28-86]</td>
<td>46</td>
<td>60.5 [47-66]</td>
</tr>
<tr>
<td>F/up after CML diagnosis, mo</td>
<td>57 [2-109]</td>
<td>55</td>
<td>12.5 [8-40]</td>
</tr>
<tr>
<td>Time from CML Dx to treatment, mo</td>
<td>0.5 [0-2]</td>
<td>1</td>
<td>0.25[0-0.5]</td>
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<td>IFN therapy prior to TKI</td>
<td>3 (33)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TKI as first line (alone or in combination)</td>
<td>6 (67)</td>
<td>1 (100)</td>
<td>3 (75), all LBP</td>
</tr>
<tr>
<td>Evolution into AP</td>
<td>1 (11)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Evolution into BP</td>
<td>4 (44)</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>Overall survival, mo</td>
<td>56 [3+ to 109]</td>
<td>55+</td>
<td>13 [8-40]</td>
</tr>
<tr>
<td>Number surviving</td>
<td>5 (56)</td>
<td>1 (100)</td>
<td>0</td>
</tr>
<tr>
<td>BCR-ABL/KD mutations at relapse</td>
<td>2* of 7 (29)</td>
<td>NA</td>
<td>2 of 2* (100)</td>
</tr>
</tbody>
</table>

* (Mutations: E459K in CP patients; V299L and T315I in BP patients)

<table>
<thead>
<tr>
<th>Pt No</th>
<th>Age, sex</th>
<th>CML f/up (mo)</th>
<th>Frontline</th>
<th>1st salvage</th>
<th>2nd salvage</th>
<th>3rd salvage</th>
<th>4th salvage</th>
<th>Time to progress (mo)</th>
<th>CML Status</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>28F</td>
<td>108</td>
<td>IFN CP</td>
<td>NR 0</td>
<td>IFN +AraC  CP CHR 8</td>
<td>Allo CP CCyR 6</td>
<td>IM CP, CHR 40</td>
<td>Allo CP NR 0 89</td>
<td>Died in MyBP</td>
</tr>
<tr>
<td>2</td>
<td>64F</td>
<td>109</td>
<td>IFN CP</td>
<td>NR 0</td>
<td>HHT +AraC CP CHR 9</td>
<td>IM CP PCyR 6</td>
<td>Nilot AP(CE) PCyR 5</td>
<td>Dasat MyBP NR 0 92</td>
<td>Died in MyBP</td>
</tr>
<tr>
<td>3</td>
<td>55F</td>
<td>85</td>
<td>IFN CP</td>
<td>NR 0</td>
<td>IFN +AraC CP NR 0</td>
<td>IM CP CHR 65+</td>
<td>- - - - - -</td>
<td>- - - - - -</td>
<td>CHR</td>
</tr>
<tr>
<td>4</td>
<td>79F</td>
<td>73</td>
<td>IM CP</td>
<td>CHR 73+</td>
<td>- - - - - - - - -</td>
<td>- - - - - -</td>
<td>- - - - - -</td>
<td>- - - - - -</td>
<td>CHR</td>
</tr>
<tr>
<td>5</td>
<td>35M</td>
<td>57</td>
<td>IM CP</td>
<td>CCyR 9</td>
<td>Dasat AP(CE) CCyR 3</td>
<td>I+A AP NR 0</td>
<td>2-CdA AP NR 0</td>
<td>Ara-C+Mitox AP NR 0 48</td>
<td>Died in AP</td>
</tr>
<tr>
<td>6</td>
<td>61F</td>
<td>13</td>
<td>IM CP</td>
<td>CHR 4</td>
<td>None MyBP - - - - -</td>
<td>- - - - - -</td>
<td>- - - - - -</td>
<td>- - - - - -</td>
<td>10 Died in MyBP</td>
</tr>
<tr>
<td>7</td>
<td>38F</td>
<td>39</td>
<td>IM CP</td>
<td>NR 0</td>
<td>HCVAD + IM LyBP NR 0</td>
<td>MTX +AraC LyBP NR 0</td>
<td>HCVAD+Dasat LyBP CCyR 4</td>
<td>Allo CP (CCyR) CMR 4 4</td>
<td>CMR</td>
</tr>
<tr>
<td>8</td>
<td>60M</td>
<td>20</td>
<td>IM CP</td>
<td>PCyR 18+</td>
<td>- - - - - - - - -</td>
<td>- - - - - -</td>
<td>- - - - - -</td>
<td>- - - - - -</td>
<td>CHR, PCyR</td>
</tr>
<tr>
<td>9</td>
<td>86F</td>
<td>3</td>
<td>Nilot CP</td>
<td>CCyR 3+</td>
<td>- - - - - - - - -</td>
<td>- - - - - -</td>
<td>- - - - - -</td>
<td>- - - - - -</td>
<td>CCyR</td>
</tr>
<tr>
<td>10</td>
<td>46M</td>
<td>55</td>
<td>IM AP(CE) CHR, no CE 12</td>
<td>Dasat CP (CHR) CHR 27</td>
<td>Bosu CP (CHR) CHR 12+</td>
<td>- - - - - -</td>
<td>- - - - - -</td>
<td>- - - - - -</td>
<td>CHR, CE gone</td>
</tr>
<tr>
<td>11</td>
<td>59M</td>
<td>8</td>
<td>I+A MyBP</td>
<td>NR 0</td>
<td>HD AraC MyBP NR 0</td>
<td>IM MyBP CHR 0.75</td>
<td>- - - - - -</td>
<td>- - - - - -</td>
<td>Died in MyBP w/ Breast Ca mets</td>
</tr>
<tr>
<td>12</td>
<td>66M</td>
<td>11</td>
<td>HCVAD + IM LyBP NR 0</td>
<td>IM LyBP CHR 0.25</td>
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<td>- - - - - -</td>
<td>- - - - - -</td>
<td>Died in LyBP</td>
</tr>
<tr>
<td>13</td>
<td>47F</td>
<td>40</td>
<td>HCVAD + IM LyBP CCyR 12</td>
<td>Dasat LyBP CCyR 1 HCVAD</td>
<td>LyBP NR 0</td>
<td>Auto LyBP CCyR 3</td>
<td>- - - - - -</td>
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</tr>
<tr>
<td>14</td>
<td>62M</td>
<td>14</td>
<td>IM LyBP</td>
<td>NR 0</td>
<td>HCVAD + Dasat LyBP MMR 2</td>
<td>Allo CP, MMR CMR 2</td>
<td>KW-2449 LyBP NR 0</td>
<td>- - - - - -</td>
<td>Died in LyBP</td>
</tr>
</tbody>
</table>

Patient number 1 received 5th salvage with Nilotinib in AP and achieved CHR for 12 months, then received 6th salvage with dasatinib in MyBP and had no response.
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