A New Case of Chronic Myeloid Leukemia With c3/a2 BCR/ABL Junction. Is It Really a Distinct Disease?

To the Editor:

In a recent issue of Blood, Pane et al. reported on five cases of mild Phi+ myeloproliferative disorders characterized by a c3/a2 junction in the BCR/ABL hybrid gene transcript and suggested to use the term “neutrophilic chronic myeloid leukemia (N-CML)" to distinguish a “distinct disease" with c3/a2 BCR/ABL junction as a “specific molecular marker.”

We report here a case of BCR/ABL recombination with c3/a2 junction whose phenotype was originally classified as essential thrombocytopenia and presented similarities with two other published cases of thrombocytopenia associated with c3/a2 junction.

A study of biological and clinical data collected in the seven cases of c3/a2 BCR/ABL junction reported so far in the literature led us to question the opportunity of creating, as proposed by Pane, a new nosologic classification only based on the genotypic criterium of a c3/a2 type of recombination in the BCR/ABL hybrid gene.

Our patient, a 45-year-old woman, was referred to us on 1990 because of a high platelet count: thrombocytes were 1,370×10^9/L, white blood cell count 15×10^9/L (72% neutrophils, 20% lymphocytes, 2% monocytes), hemoglobin 12.9 g/dL, mean corpuscular volume 94 Fl. There was no splenomegaly. Bone marrow was hyperplastic on histologic examination, without fibrosis. Iron stores were normal. A diagnosis of essential thrombocytopenia was considered and hydroxyurea treatment started with excellent response. A bone marrow cytogenetic study disclosed a t(9; 22) in 50/50 mitosis, but the literature as Phi-negative mitosis were 18 of 18 in 1994 and 13 of 18 in 1995. Reverse transcriptase-polymerase chain reaction (RT-PCR) was performed at that time. The result was atypical: when in the so-called ET Phi-positive leukocytes, 2% monocytes), hemoglobin 12.9 g/dL, mean corpuscular volume 94 Fl. There was no splenomegaly. Bone marrow was hyperplastic on histologic examination, without fibrosis. Iron stores were normal. A diagnosis of essential thrombocytopenia was considered and hydroxyurea treatment started with excellent response. A bone marrow cytogenetic study disclosed a t(9; 22) in 50/50 mitosis, but the literature as Phi-negative mitosis were 18 of 18 in 1994 and 13 of 18 in 1995. Reverse transcriptase-polymerase chain reaction (RT-PCR) was performed at that time. The result was atypical: when in the so-called ET Phi-negative mitosis were 18 of 18 in 1994 and 13 of 18 in 1995. Reverse transcriptase-polymerase chain reaction (RT-PCR) was performed at that time. The result was atypical: when in the so-called ET Phi-negative mitosis were 18 of 18 in 1994 and 13 of 18 in 1995. Reverse transcriptase-polymerase chain reaction (RT-PCR) was performed at that time. The result was atypical: when

Table 1. Characteristics of the Patients With c3/a2 BCR/ABL Junctions Reported in the Literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Sex</th>
<th>Splenomegaly</th>
<th>WBC (×10^9/L)</th>
<th>Immature Cells %</th>
<th>Basophils %</th>
<th>Hb (g/dL)</th>
<th>Platelets (×10^9/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>F</td>
<td>–</td>
<td>58</td>
<td>1</td>
<td>0</td>
<td>8.8</td>
<td>160</td>
</tr>
<tr>
<td>1</td>
<td>41</td>
<td>M</td>
<td>+</td>
<td>43</td>
<td>3</td>
<td>0</td>
<td>15.8</td>
<td>191</td>
</tr>
<tr>
<td>1</td>
<td>22</td>
<td>F</td>
<td>+</td>
<td>45</td>
<td>0</td>
<td>0</td>
<td>12.7</td>
<td>1,240</td>
</tr>
<tr>
<td>4</td>
<td>76</td>
<td>F</td>
<td>+</td>
<td>28</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>62</td>
<td>F</td>
<td>+</td>
<td>16</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1,020</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>F</td>
<td>+</td>
<td>17</td>
<td>4</td>
<td>4</td>
<td>10.3</td>
<td>1,440</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>F</td>
<td>–</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>9.5</td>
<td>762</td>
</tr>
<tr>
<td>Our patient</td>
<td>46</td>
<td>F</td>
<td>–</td>
<td>15</td>
<td>2</td>
<td>2</td>
<td>12.5</td>
<td>1,370</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not available.
REFERENCES


Response

We thank our French colleagues for adding another patient to the small series of c3a2-associated myeloproliferative disorder and for reporting additional findings, such as the occurrence in their patient (as in that reported by Wada1) of alternative splicing giving rise to multiple types of transcripts within what we call μ-BCR,2 and the observation of a complete karyotypic response after interferon treatment.

The letter by Mittre et al brings up three issues on the condition we have called CML-N, which bear on: (1) the spectrum of clinical presentation, (2) nosography, and (3) nomenclature. We welcome this opportunity to comment briefly on each of these points.

With respect to (1), of course we agree that this will need to be defined more precisely as more patients are appropriately tested. We also agree that a high platelet count is emerging as a prominent, although not obligatory, component of the presentation of CML-N. In fact, it appears from the available universe of eight patients (see Table 1 in Dr Mittre’s letter) that some have pronounced neutrophil leukocytosis, some have pronounced thrombocytosis, and at least one has both. We do not know why one lineage appears to be more affected than the other in each particular case, and this deserves further investigation. However, we believe that the clinically most important and distinctive feature of this group of patients is their prolonged benign course. Of the eight patients reported so far, only one died from a blastic crisis (no. 7 in Dr Mittre’s table, who was blastic phase.7)

With respect to (2), we think that Mittre et al agree that the classification of patients with ‘chronic neutrophilic leukemia’ is less than satisfactory. It is true that some textbooks have included a Ph-negative status in the definition, probably because it was believed that any Ph-positive patient must be regarded as having a potentially aggressive clinical course and should therefore not be designated by any term other than CML. On the other hand, and perhaps not consistent with this notion, it has been accepted that patients with essential thrombocythemia (ET) may be Ph-positive. The point of our report7 is that we provide an explanation of why a small subset of Ph-positive patients have a benign clinical course—a view shared by Melo.4 Indeed, these patients can be regarded as having a ‘variant’ of CML, because their leukemic cells carry a hybrid gene in which the same genes as in CML, ie, BCR and ABL, are involved. However, the junction joining the two is different and produces a different chimeric protein leading to a different clinical course. It is hardly necessary these days to recall the many situations in which molecular analysis has helped to classify patients in categories that are useful from the point of view of prognosis and therapeutic decisions: PML/RARA in AML-M3,4 AML1/ETO in AML-M2,5 and BCL6 in non-Hodgkin’s lymphoma associated with the 3q27 breakpoint6 are just some examples.

With respect to (3), we agree first of all that c3/a2 should be renamed c19/a2. Patients with this type of junction may well present with clinical and hematologic features similar to those of patients labeled thus far as ‘chronic neutrophilic leukemia’ or ET, but we believe they deserve a more precise label because they have a precise lesion. Indeed, the patient reported in Dr Mittre’s letter was first diagnosed as having essential thrombocythemia and then as atypical CML, while she had a typical c3a2-associated myeloproliferative disorder. We prefer the term CML-N because this reflects the finding that the cytogenetically visible abnormality is the same as in CML, but the molecular lesion is different and, it is reasonable to presume, responsible for their more benign clinical course. On the other hand, patients with a myeloproliferative disorder carrying a Ph chromosome with the classical junction b2a2 or b3a2 should be considered as having a true clinical variant of CML; they have often a more aggressive disease and are at a high risk of a terminal blastic phase.7

B. Rotoli
L. Lucia
Divisione di Ematologia
Università di Napoli Federico II
Napoli, Italy
F. Pane
F. Salvatore
CEINGE-Biotecnologie Avanzate
Dipartimento di Biochimica e Biotecnologie Mediche
Università di Napoli Federico II
Napoli, Italy
G. Saglio
Istituto di Clinica Medica Generale
Facoltà di Medicina e Chirurgia di Novara
Università di Torino
Torino, Italy
To the Editor:

With great interest we read the article of Sarfati et al 1 dealing with the prognostic impact of the serum levels of soluble CD23 (sCD23) in B-cell chronic lymphocytic leukemia (B-CLL). The results of their study show that, as expected, the stage of disease at initial presentation of the patient predicts survival, and that the serum levels of sCD23 correlate with the total tumor burden, i.e., the involvement of lymph nodes and the involvement of liver and spleen, and with the rate of progression into higher stages of the disease. Interestingly, the authors describe a threshold level of sCD23 of 574 U/mL above that the probability of survival of the patients is adversely affected. The conclusion is drawn that the serum level of sCD23 at first diagnosis is a major risk factor for disease progression and has an impact on overall survival. These results are in accordance with data of our own trial that will be published elsewhere.2 However, the design of the study of Sarfati et al provokes some critical comments.

Survival data from patients diagnosed in 1983 as well as from patients first presented in 1994 were summarized and plotted together. In the meantime, however, the probability of survival within a given risk group has changed, probably due to advances in supportive care. While in 1975 Rai et al 3 reported a median survival time of 19 months for patients with stages III and IV disease—corresponding to the 20 months median survival time for patients with stage C disease as published by Binet et al 4 in 1981—the median survival was recorded to be 30 months for the same risk group of patients in 1989.5 In addition, at least since 1990, a proportion of patients may have received treatment with nucleoside analogues which could have influenced the overall outcome.6 Therefore, and because no analysis of the causes of death is given, the survival curves presented by Sarfati et al may be biased essentially and cannot confirm definitely the prognostic importance of sCD23. Also, unfortunately, Sarfati et al were not able to examine any correlation of sCD23 levels with other already known risk factors including the pattern of bone marrow (BM) infiltration,7 the lymphocyte doubling time (LDT),8 and levels of the serum thymidine kinase (sTK).9 In our own trial on newly diagnosed patients with Binet stage A B-CLL a strong correlation between high levels of sCD23 and a diffuse BM infiltration, an LDT ≤ 12 months and an sTK > 5 U/mL was established. Multivariate analysis showed that sCD23 and the LDT were superior over the BM infiltration pattern and sTK levels in predicting progressive disease.2 Thus, we are convinced that the serum level of sCD23 at initial presentation of a patient with early stage B-CLL has a great prognostic impact. However, the study of Sarfati et al contributes only partially to the establishment of sCD23 as a recognized risk factor in B-CLL.

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Margaret Macro, Michel Leporrier, Hervé Mittre and Pierre Leymarie

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