Check for updates

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[1] 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 thrombocythemia and presented similarities with two other published cases of thrombocythemia associated with c3/a2 junction.[2,3]

A study of biological and clinical data collected in the seven cases of c3/a2 BCR/ABL junction reported so far in the literature[1-4] 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 refered to us on 1990 because of a high platelet count: thrombocytes were 1,370 $\times$ 10^9/L, white blood cell count 15 $\times$ 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 histologial examination, without fibrosis. Iron stores were normal. A diagnosis of essential thrombocytemia was considered and hydroxyurea treatment started with excellent response. A bone marrow cytogenetic study disclosed a t(9;22) in 50/50 mitosis, but repeated Southern blot analysis failed to detect any BCR/ABL fusion DNA. In 1991, she was given an interferon treatment (5 $\times$ 10^6 units/d) that was stopped after 7 months because of pronounced thrombocytopenia (38.10^6/L). This treatment obtained a major cytogenetic response: 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 RNA from blood cells was subjected to RT-PCR using primers described by Roth et al,[5] three amplification bands were observed and DNA sequencing demonstrated the existence of three types of junction, namely c1/a2, c2/a2, and c3/a2, respectively. Analysis of the three sequences indicated that only c3/a2 hybrid transcripts remained in frame after splicing. The two other transcripts resulted probably from alternative splicing realized in the same clone because they were associated with a frameshift at the junction and consequently with a stop codon at nucleotide 3579 for c1/a2 and 3696 for c2/a2 in BCR/ABL hybrid cDNA sequence. Because the SH3, SH2, and SH1 regions of the chimeric transcripts were not translated, they were not supposed to have expressed the abl oncogene activity. Moreover, their influence on the phenotypic expression of the c3/a2 chimeric transcript cannot be evaluated, but is likely to have been negligible.

In retrospect, metamyelocytes were occasionally found (1% to 2%) in initial blood smears but the diagnosis of atypical CML was not considered until the discovery of a Phi$^+$. The demonstration of an atypical BCR/ABL translocation (so-called c3/a2 or e19/a2) in this patient led to the discussion of the relationships between this rare type of BCR/ABL fusion and hematological presentation.

To our knowledge only seven cases of c3/a2 BCR/ABL translocation had been previously published (Table 1). Considering the related clinical and hematological data, these cases have atypical presentation when compared to usual cases of CML, with low incidence of immature granulocytes and moderate leukocytosis associated, in 4 of 8 cases, with elevated thrombocytosis.

Pane et al[1] and Melo[6] proposed to classify these diseases as ''neutrophilic chronic myeloid leukemia (N-CML).'' We tend to diseagree with their proposal. N-CML (also described as chronic neutrophilic leukemia) is a poorly defined disorder characterized by persistant unexplained neutrophilia, hepato-splenomegaly, and elevated neutrophil alkalin phosphatase. It is typically Phi-negative.[7] We believe that the data collected in the few cases presented on Table 1 are not fitting with this description: 4 of 8 of these cases presented in fact as so-called Phi$^+$ essential thrombocythemia (Phi$^+$ ET). Moreover, most of the patients described in the literature as Phi$^+$ ET could indeed be classified as N-CML, on Pane's criteria, except that all these patients, when studied with RT-PCR are characterized by a classical BCR/ABL, b2/a2, or b3/a2 junction.[8-10]

We think that it is premature to claim any conclusion about the c3/a2 genotype/phenotype relationship. This discussion deserves additional prospective exploration, namely a careful study by RT-PCR in the so-called ET Phi$^+$ and atypical cases of chronic myeloproliferative disorders.

Hervé Mittre
Pierre Leymarie
Laboratoire de Biochimie B
Margaret Macro
Michel Leporrier
Service d'Hématologie Clinique
Centre Hospitalier Universitaire
Caen, France

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

Reference	Age	Sex	Splenomegaly	WBC ($\times$10^9/L)	Immature Cells %	Basophils %	Hb (g/dL)	Platelets ($\times$10^9/L)
1	65	F	–	58	1	0	8.8	160
1	41	M	+	43	3	0	15.8	191
1	22	F	+	45	0	0	12.7	1,240
4	76	F	+	28	NA	NA	NA	1,020
4	62	F	+	16	NA	NA	NA	870
3	13	F	+	17	4	4	10.3	1,440
2	50	F	–	8	3	1	9.5	762
Our patient	46	F	–	15	2	2	12.5	1,370

Abbreviation: NA, not available.

Downloaded from http://ashpublications.net/blood/article-pdf/89/11/4239/1409218/4239.pdf by guest on 05 June 2024

REFERENCES

1. Pane F, Frigeri F, Sindona M, Luciano L, Ferrara F, Cimino R, Meloni G, Saglio G, Salvatore F, Rotoli B: Neutrophilic-chronic leukemia: A distinct disease with a specific molecular marker (BCR/ABL with C3/A2 junction). Blood 88:2410, 1996

2. Wada H, Mizutani S, Nishimura J, Usuki Y, Kohsaki M, Komai M, Kaneko H, Sakamoto S, Delia D, Kanamaru A, Kakishita E: Establishment and molecular characterization of a novel leukemia cell line with Philadelphia chromosome expressing p230 BCR/ABL fusion protein. Cancer Res 55:3192, 1995

3. Yamagata T, Mitani K, Kanda Y, Yazaki Y, Hirai H: Elevated platelet count features the variant type of BCR/ABL junction in chronic myelogenous leukemia. Br J Haematol 94:370, 1996

4. Saglio G, Guerrasio A, Rosso C, Zaccaria A, Tassinari A, Serra A, Rege-Cambrin G, Mazza U, Gavosto F: New type of bcr/abl junction in Philadelphia chromosome-positive chronic myelogenous leukemia. Blood 76:1819, 1990

5. Roth MS, Antin JH, Bingham EL, Ginsburg D: Detection of Philadelphia chromosome-positive cells by the polymerase chain reaction following bone marrow transplant for chronic myelogenous leukemia. Blood 74:882, 1989

6. Melo JV: The diversity of BCR-ABL fusion proteins and their relationship to leukemia phenotype. Blood 88:2375, 1996

7. Shepherd PCA, Ganesan TS, Galton DAG: Hematological classification of the chronic myeloid leukemias. Bailliere's Clin Hematol 1:887, 1987

8. Martiat P, Ifrah N, Rassool F, Morgan G, Giles F, Gow J, Goldman JM: Molecular analysis of Philadelphia positive essential thrombocythemia. Leukemia 3:563, 1989

9. Cervantes F, Urbano Ispizua A, Villamor N, Feliu E, Milla F, Lopez Guillermo A, Ribera JM, Granada J, Vives Corrons JL, Monserrat E, Rozman C: Ph-positive chronic myeloid leukemia mimicking essential thrombocythemia and terminating into megakarioblastic blast crisis. Leukemia 7:327, 1993

10. Morris CM, Heisterkamp N, Groffen J, Fitzgerald PH: Entire ABL gene joined with 5′-BCR in some patients with Philadelphia-positive leukemia. Blood 78:1078, 1991

Response

We thank our French collegues 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 Wada[1]) 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 reported by Wada et al[1]); however, at diagnosis this patient carried an additional chromosomal abnormality (iso 17) that may have affected the clinical course.

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 report[2] 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.[3] 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/RARα in AML-M3,[4] AML1/ETO in AML-M2,[5] and BCL6 in non-Hodgkin's lymphoma associated with the 3q27 breakpoint[6] are just some examples.

With respect to (3), we agree first of all that c3/a2 should be renamed e19/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. Luciano
Divisione di Ematologia
Università di Napoli Federico II
Napoli, Italy
F. Pane
F. Salvatore
CEINGE-Biotecnologie Avanzate
Dipartmento 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

Downloaded from http://ashpublications.net/blood/article-pdf/89/11/4239/1409218/4239.pdf by guest on 05 June 2024

REFERENCES

1. Wada H, Mizutani S, Nishimura J, Usuki Y, Kohsaki M, Komai M, Kaneko H, Sakamoto S, Delia D, Kanamaru A, Kakishita E: Establishment and molecular characterization of a novel leukemic cell line with Philadelphia chromosome expressing p230 BCR/ABL fusion protein. Cancer Res 55:3192, 1995

2. Pane F, Frigeri F, Sindona M, Luciano L, Ferrara F, Cimino R, Meloni G, Saglio G, Salvatore F, Rotoli B: Neutrophilic-chronic myeloid leukemia: A distinct disease with a specific molecular marker (BCR/ABL with c3a2 junction). Blood 88:2410, 1996

3. Melo JV: The diversity of BCR/ABL fusion proteins and their relationship to leukemia phenotype. Blood 88:2375, 1996

4. Grignani Fr, Fagioli M, Alcalay L, Longo L, Pandolfi PP, Donti E, Biondi F, Lo Coco F, Grignani F, Pelicci PG: Acute promyelocytic leukemia: From genetics to treatment. Blood 83:10, 1994

5. Nucifora G, Rowley JD: The AML1 and ETO genes in acute myeloid leukemia with a t(8;21). Leuk Lymphoma 14:353, 1994

6. Offit K, Lo Coco F, Louie DC, Parsa NZ, Leung D, Portlock C, Ye BH, Lista F, Filippa DA, Rosenbaum A, Ladanyi M, Jhanwar S, Dalla-Favera R, Chaganti RSK: Rearrangement of the bcl-6 gene as a prognosic marker in diffuse large-cell lymphoma. N Engl J Med 331:74, 1994

7. Cervantes F, Urbano Ispizua A, Villamor N, Feliu E, Milla F, Lopez Guillermo A, Ribera JM, Granada J, Vives Corrons JL, Monserrat E, Rozman C: Ph-positive chronic myeloid leukemia mimicking essential thrombocythemia and terminating into megakaryoblastic blastic crisis. Leukemia 7:327, 1993

Prognostic Impact of the Serum Levels of Soluble CD23 in B-Cell Chronic Lymphocytic Leukemia

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, ie, 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 $\leq$ 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.

Wolfgang U Knauf
Bärbel Ehlers
Birgitt Mohr
Eckhard Thiel
Medizinische Klinik III
(Hämatologie, Onkologie & Transfusionsmedizin),
Klinikum Benjamin Franklin
Freie Universität
Berlin, Germany
Irmgard Langenmayer
Michael Hallek
Berthold Emmerich
Medizinische Klinik
Klinikum Innenstadt
Ludwig-Maximilian-Universität
München, Germany
Dagmar Adorf
Christoph Nerl
Abteilung Hämatologie & Onkologie
Städtisches Krankenhaus Schwabing
München, Germany
Theodor Zwingers
Estimate Statistics Inc
Augsburg, Germany

REFERENCES

1. Sarfati M, Chevret S, Chastang C, Biron G, Stryckmans P, Delespesse G, Binet J-L, Merle-Beral H, Bron D: Prognostic importance of serum soluble CD23 level in chronic lymphocytic leukemia. Blood 88:4259, 1996

2. Knauf WU, Langenmayer I, Ehlers B, Mohr B, Adorf D, Nerl Ch, Hallek M, Zwingers Th, Emmerich B, Thiel E: Serum levels of soluble CD23, but not soluble CD25, predict disease progression in early stage B-cell chronic lymphocytic leukemia. Leuk Lymphoma 1997 (in press)

3. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternak BS: Clinical staging of chronic lymphocytic leukemia. Blood 46:219, 1975

4. Binet JL, Auquier A, Dighiero G, Chastang C, Piguet H, Goasguen J, Vaugier G, Potron G, Colona P, Oberlin F, Thomas M, Tchernia G, Jacquillt C, Boivin P, Lesty C, Dulaut MT, Monconduit M, Belabbes S, Gremy F: A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer 48:198, 1981

5. International Workshop on Chronic Lymphocytic Leukemia (IWCLL): Chronic lymphocytic leukemia: Recommendations for di-

Downloaded from http://ashpublications.net/blood/article-pdf/89/11/4239/1409218/4239.pdf by guest on 05 June 2024