

## CORRESPONDENCE

### Might Essential Thrombocythemia Carry Ph Anomaly?

To the Editor:

We read with interest the paper of Blickstein et al<sup>1</sup> dealing with clinical presentation of 25 Ph<sup>-</sup> essential thrombocythemia (ET) patients, 48% of which showed positivity for BCR-ABL transcripts. On the basis of their findings, the investigators suggest the possibility of a new variant of ET. We would like to make some comments and report on our experience.

We investigated 20 patients (8 men and 12 women; median age, 54 years; range, 24 to 86 years) diagnosed as ET following the criteria of the Polycythemia Vera Study Group (PVSG)<sup>2</sup>; only patients with a platelet count greater than 1,000,000/ $\mu$ L were enrolled, considering a lower platelet count misleading for a correct diagnosis of ET.<sup>2</sup> In our group, the platelet count ranged from 1,120,000 to 2,700,000/ $\mu$ L. The white blood cell count showed a mean count of 8,900/ $\mu$ L, with less than 3% basophils and the absence of immature cells in the peripheral blood. The leukocyte alkaline phosphatase (LAP) score was normal in 5 patients and increased in 15. Splenomegaly (<3 cm palpable) was observed in 3 patients. For 6 newly diagnosed patients, the mean follow-up time was 7 months (range, 6 to 8 months), whereas for the remaining 14 patients, the mean follow-up time was 54.2 months (range, 13 to 144 months); 9 patients were observed for 71 months (range, 32 to 144 months). All patients were Ph<sup>-</sup> at cytogenetic level at diagnosis. The study for BCR-ABL transcripts by reverse transcriptase-polymerase chain reaction (RT-PCR; sensitivity 1:10<sup>5</sup>) showed the chimeric product (b3a2 type) only in 1 patient (5%). The clinical and hematologic features remained unchanged in all patients, with only 2 exceptions: 1 patient (BCR-ABL negative) showed a transformation to idiopathic myelofibrosis (IM) 6 years after diagnosis; the other patient (BCR-ABL positive) progressed to blastic crisis 12 years after diagnosis, via IM detected 6 years after diagnosis. We already reported on this patient,<sup>3</sup> who was first considered to have ET; the presence of BCR-ABL transcript was indeed detected on archival specimens only recently.

Based on our data, we cannot confirm such a high percentage of BCR-ABL-positive ET cases reported by Blickstein et al.<sup>1</sup> It is unlikely that technical reasons may account for the discrepancy between the two studies, given the comparable sensitivity of the PCR methods used. It should be taken in mind that Ph can be detected either cytogenetically or by molecular analysis for the BCR rearrangement.<sup>4</sup> It is now well accepted that the presence of BCR-ABL transcript is diagnostic of chronic myeloid leukemia (CML), even in those cases that are Ph<sup>-</sup> at cytogenetic level. Thus, we suggest that the so-called BCR-ABL-positive ET should be better considered clinical variants of CML, rather than of ET. On the other hand, Ph<sup>+</sup>, BCR-ABL-positive CML of ET onset is a well-recognized entity.<sup>5,6</sup> Furthermore, we would like to point out that the findings of Blickstein et al<sup>1</sup> of similar clinical and laboratory characteristics between their two groups of patients (BCR-ABL negative and positive) and the absence of progression of the disease in all cases is rather unexpected. The short follow-up (20 and 22.5 months)

and the inclusion in the study of patients with less than 1,000,000/ $\mu$ L platelets are probably misleading. CML with ET onset may develop the features of classical CML only several years after diagnosis.<sup>7,8</sup> We agree with the investigators that the BCR-ABL status should be examined in all ET patients, but our suggestion is that the CML variants, like the so-called BCR-ABL-positive ET, need a longer follow-up period to allow a better understanding of their clinical and biological events.

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### Response

We thank Marasca et al for their thoughtful comments. In their letter, Marasca et al describe a retrospectively recruited cohort of 20 patients with platelet counts greater than  $1,000 \times 10^9/L$ . This cohort represents a

selection bias in which only part of ET patients were enrolled in the study, whereas the lower limit of the PVSG criteria has been set at  $600 \times 10^9/L$ .<sup>1,2</sup> It is not known how many ET patients were excluded by this selection.

Although the maximal follow-up period reported by the Modena group was 144 months, 6 of their 20 patients were observed for 6 to 8 months only. This period is admittedly too short to observe ET patients. By contrast, our BCR-ABL-positive group has been observed for a minimum of 17 months, including 7 patients for 17 to 24 months and 5 for as long as 34 to 64 months. Thus, all of our patients were observed for a longer period than one third of those of the Modena group.

The unreferenced statement of Marasca et al about the diagnostic value of BCR-ABL transcript in Ph<sup>-</sup> patients implies that all our patients that lack any other clinical and laboratory evidence of CML as well as the normal subjects of Birneaux et al<sup>3</sup> were in fact CML patients. Thus, one criterion of CML does not establish the diagnosis. Furthermore, there is no evidence that BCR-ABL-positive Ph<sup>-</sup> ET patients will transform to CML. Otherwise, as the statement of Marasca et al may imply, all of these subjects should receive interferon therapy.

The fact that both groups of our study had similar clinical and laboratory characteristics should not surprise the Modena group. Even now, 18 months after the first stage of the study has been summarized in our report, none of our patients transformed to acute leukemia or CML. Moreover, all the patients reported in our study are still alive (except for an 86-year-old patient who died of an intercurrent infection).

Finally, Marasca et al cite Cervantes et al<sup>4</sup> and their unpublished material to support their concept. However, Cervantes et al describe patients with chronic-phase Ph<sup>+</sup> CML, whereas our patients had neither Ph chromosome nor CML.

Taken together, our results strongly disagree with the suggestion of Marasca et al that BCR-ABL-positive Ph<sup>-</sup> ET patients are CML variants. However, we concur with their opinion that a longer

follow-up period is needed to better understand the natural history of this entity.

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## Splenectomy in Gaucher Disease: New Management Dilemmas

To the Editor:

Gaucher disease, the inherited deficiency of lysosomal glucocerebrosidase, is currently managed with enzyme replacement therapy using a mannose-terminated form of human glucocerebrosidase.<sup>1</sup> This therapy,

costing \$100,000 to \$400,000 per adult per year, effectively improves the biochemical and hematologic manifestations of the disorder and reverses hepatosplenomegaly in most patients.<sup>1-4</sup> We describe an Ashkenazi patient with type 1 Gaucher disease demonstrating massive hepatosplenomegaly, anemia, and thrombocytopenia, who, despite 2

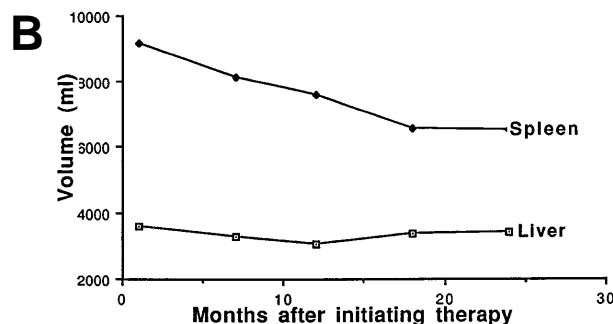
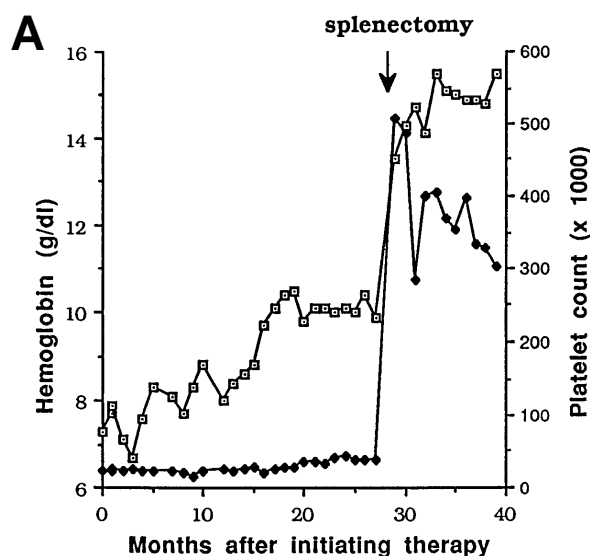


Fig 1. Response to therapy over time. (A) Response of (□) hemoglobin (in grams per deciliter) and (◆) platelets after initiation of therapy. (B) (□) Hepatic and (◆) splenic volumes.