Absence of bcr/ abl rearrangement in 41 patients with essential thrombocythemia

We report cytogenetic and fluorescence in situ hybridization (FISH) findings with the BCR/ABL probe in 41 consecutive newly diagnosed patients with essential thrombocythemia. All patients had a normal karyotype and none of them showed the BCR/ABL rearrangement as detectable by FISH.

Sir,

Essential thrombocythemia (ET) is a chronic myeloproliferative disorder (MPD) characterized by extreme thrombocytosis and megakaryocytic hyperplasia, for which no primary cause can be found.\(^1\,2\) Strict diagnostic criteria have been proposed by the Polycythemia Vera Study Group (PVSG).\(^1\) Karyotypic abnormalities are rare (occurring in approximately 5% of patients) and a specific chromosomal anomaly has not been established in this disorder.\(^3\,5\) We report cytogenetic and fluorescence in situ hybridization (FISH) findings using the BCR/ABL probe in a series of 41 patients newly diagnosed as having ET.

Bone marrow cells were obtained from a total of 41 patients who fulfilled the criteria of ET from the PVSG\(^1\) between 1985 and 1998. All patients were studied at diagnosis prior to any treatment. Chromosome analyses were carried out in all cases (Table 1) with a 24-hour culture method. FISH studies on cultured bone marrow cells were performed in all patients using a dual-color locus specific BCR/ABL probe (VYSIS, Inc., Downers Grove, USA) following the proceedings supplied by the manufacturer. A minimum of 200 nuclei per case were analyzed by two different observers. Cut-off levels for the BCR/ABL rearrangement were defined by adding three standard deviations to the mean of the frequency of blood cells with BCR/ABL rearrangement FISH signals in ten normal specimens. We considered there to be BCR/ABL rearrangement when the number of cells with a BCR/ABL signal was ≥12%.

Mitoses were obtained from 40 out of 41 patients, and three of them showed polyploid metaphases (Table 1). No BCR-ABL rearrangement was found in any patient by FISH. The percentage of rearranged cells ranged between 1 and 10.3% (Table 1).

Previous papers observed that some ET patients showed the BCR/ABL rearrangement.\(^6\,7\) In our series, this critical point was analyzed using the FISH technique with the BCR/ABL probe, and no patient was positive for the BCR/ABL rearrangement. The Philadelphia chromosome, as detected by conventional cytogenetics, was also missing. Blickstein et al.\(^8\) examined the BCR-ABL status by reverse transcriptase two-step nested polymerase chain reaction (PCR) in 25 Ph\(^-\) negative ET patients, and observed that 12 were BCR-ABL positive and 13 were negative. Based on their findings, the investigators suggested the possibility of a new variant of ET. As a consequence, Marasca et al.\(^9\) presented a series of 20 ET patients, but in only one patient was the BCR-ABL rearrangement detected by RT-PCR. This patient progressed to a blastic crisis 12 years after diagnosis. Recently, Hackwell et al.\(^10\) presented the RT-PCR study of 18 consecutive newly diagnosed ET patients. None showed the BCR-ABL rearrangement.

It is unlikely that technical reasons could account for the discrepancy among these studies; perhaps these differences could be explained by the inclusion of patients not fulfilling the strict criteria necessary for a diagnosis of ET. Based on our data, we can not confirm the presence of BCR-ABL-positive ET cases but we agree with Blickstein et al.\(^8\) that BCR-ABL status should be examined in all ET patients.

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Key words
Cytogenetics, in situ hybridization (ISH), essential thrombocythemia, Philadelphia chromosome.

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Cladribine as monotherapy or combined with dexamethasone and idarubicin or mitoxantrone in previously treated patients with low-grade lymphoid malignancies

We compared efficiency and toxicity of cladribine (2-CdA) in monotherapy and in combination with dexamethasone and mitoxantrone (CMD) or idarubicin (CID) in pretreated patients with low grade NHL. We have shown that 2-CdA has significant activity in this disease but the addition of dexamethasone and anthracyclines may not be of advantage compared to 2-CdA alone.

Sir,

The long-term prognosis for patients with advanced relapsed or refractory low grade non-Hodgkin’s lymphoma (LGNHL) remains poor. Therefore many new therapeutic approaches including new chemotherapy agents and new combinations regimens have been evaluated.

In this report we present our experience with the new purine analog 2-chlorodeoxyadenosine (2-CdA) used as monotherapy and combined with dexamethasone and mitoxantrone (CMD) or dexamethasone and idarubicin (CID) in patients with LGNHL.

This study was an open phase II single institution trial initiated in January 1996 and closed in April 1999. Criteria for entry into the study included a histologic diagnosis of LGNHL, and advanced stage of refractory or relapsed disease. All patients had received at least three prior regimens of chemotherapy in NHL.

2-CdA was given at a dose of 0.12 mg/kg in a 2-hour intravenous infusion, on days 1-5. In the CMD program mitoxantrone 10 mg/m² i.v., day 1 and dexamethasone 20 mg p.o., days 1-5, were added to 2-CdA. In the CID program idarubicin 12 mg/m² i.v., day 1 was given. The cycles were repeated at 4-week intervals in most cases.

Complete and partial responses (CR and PR) were defined as reported elsewhere. Toxic effects were monitored and assessed according to the WHO criteria.

Fifty-eight patients entered the study. Thirty-six of them were treated with 2-CdA alone, 17 received chemotherapy according to the CMD regimen and 5 according to the CID program. The characteristics of the patients are listed in Table 1.

Of the 36 patients treated with 2-CdA alone 13 (36.2%) responded. The median duration of CRs was 12 months (range from 7 to 48 months) and the median duration of PRs was 6 months. The CRs were observed after a median of 4 cycles and PRs after a median of 3 cycles of 2-CdA.

Of the 17 patients treated with CMD, 7 (41.2%) responded. The CRs were observed after 2 and 3 cycles of CMD and lasted 13 and 8+ months. PRs were observed after a median of 2 cycles of 2-CdA and their median duration was 7 months.

Among the 5 patients treated with CID we observed 1 CR and 1 PR which lasted, respectively, 6+ and 5 months. Both CR and PR were observed after 2 courses of CID. Table 2 summarizes the patients’ responses.

Both 2-CdA and CMD (or CID) programs were well tolerated. The major toxicity was myelosuppression. Grade 3 or 4 thrombocytopenia occurred in 36.5% of patients treated with 2-CdA and 34% treated with...