presence of FcγRIIb. Moreover, we found that B-CLL cells displayed comparable or even higher levels of FcγRII expression than B lymphocytes from healthy volunteers (Figure 1). No significant differences in FcγRII expression were observed between CD5+ and CD5− B lymphocytes from control donors (not shown). Discrepancy between Damle et al.’s findings and ours could not be attributed to antigen loss due to cryopreservation, as we obtained comparable results with fresh and thawed B-CLL cells.

In conclusion, our findings show that B-CLL cells from patients in early or advanced stage disease express comparable or even higher levels of FcγRII than normal peripheral B lymphocytes, suggesting that FcγRII expression is not a useful parameter to define antigen experience of B-CLL cells. However, given that FcγRII is far from being just a cell marker, we believe that the receptors’ role in B-CLL deserves further analysis. The main isoform expressed by B cells, FcγRIIb, functions as an inhibitory receptor. Its aggregation with B-cell receptors (BCRs) dampens B-cell activation by recruitment of a limited number of Src homology 2 domain (SH2)−containing phosphatases, predominantly SHIP (SH2-containing inositol phosphatase), which causes a dramatic and immediate hydrolysis of PIP3 (phosphatidylinositol 3,4,5-trisphosphate).3 FcγRIIb and SHIP are able to inhibit not only BCR-mediated signals but also signals induced by other cell surface receptors that require PIP3 generation.5 On the other hand, FcγRIIb can also signal independently of BCR clligation to directly mediate an apoptotic response.7 Whether or not this receptor is functional in B-CLL cells remains to be solved.

To the editor:

Imatinib mesylate elicits positive clinical response in atypical chronic myeloid leukemia involving the platelet-derived growth factor receptor beta

Atypical chronic myeloid leukemia (aCML) is a chronic myeloproliferative disorder with a clinical and hematologic picture similar to chronic myelocytic leukemia (CML) but lacking Philadelphia chromosome and BCR-ABL rearrangement. Cytogenetic studies have shown either a normal karyotype or numeric chromosomal changes.2 Recently the molecular cloning of t(5;10)(q33;q22) has been reported in 2 patients with aCML.3 This translocation creates a H4(D10S170)/platelet-derived growth factor receptor beta (PDGFβR) fusion transcript and suggests an association between deregulated tyrosine kinases and aCML. We report on a patient with an aCML and a t(5;10) who achieved a clinical and cytogenetic response after imatinib mesylate therapy.

The patient, a 44-year-old man, presented with leukocytosis and splenomegaly. The white blood cell count was 158 × 10^9/L (3% myelocytes; 6% metamyelocytes; 4% bands; 68% neutrophils; 8% eosinophils; 10% lymphocytes; 1% monocytes), hemoglobin level was 91 g/L, and platelet count was 352 × 10^9/L. Analysis of peripheral blood smear revealed a remarkable dysplasia in myeloid cells. Cytogenetic analysis showed the following: 46,XY,t(5;10)(q33;q22)[24]/46,XY[1] after G-banding and fluorescence in situ hybridization (FISH) studies (Figure 1A). Both FISH and polymerase chain reaction (PCR) studies failed to demonstrate the presence of BCR-ABL fusion. Therefore, nested reverse transcriptase (RT)−PCR analysis using specific primers flanking the predicted breakpoints was performed. Using 2 different sets of primers the region implicated in the translocation was amplified (Figure 1B). These results demonstrated that t(5;10)(q33;q22) involved the genes H4 and PDGFβR. Sequencing of the amplified bands confirmed that there was a fusion H4-PDGFβR occurring at exactly the same breakpoint as found in the previous t(5;10) reports.3 Based on the presence of PDGFβR rearrangement, the patient began treatment with imatinib, at a daily dose of 400 mg. The therapy was well tolerated, without obvious side effects. Clinical and cytogenetic complete response to imatinib was

References


Imatinib mesylate has been shown to be a highly effective therapy for Philadelphia chromosome-positive CML. It has also been reported to be effective in the treatment of aCML.2,7 However, the mechanisms of action of imatinib in aCML have not been fully elucidated.

Imatinib is a selective inhibitor of the tyrosine kinase activity of BCR-ABL, PDGFR, KIT, and platelet-derived growth factor receptor β (PDGFβR). It is thought to work by preventing the dimerization of receptor kinases and the activation of downstream signaling pathways.

In conclusion, our findings show that B-CLL cells from patients in early or advanced stage disease express comparable or even higher levels of FcγRII than normal peripheral B lymphocytes, suggesting that FcγRII expression is not a useful parameter to define antigen experience of B-CLL cells. However, given that FcγRII is far from being just a cell marker, we believe that the receptors’ role in B-CLL deserves further analysis. The main isoform expressed by B cells, FcγRIIb, functions as an inhibitory receptor.2,3 Its aggregation with B-cell receptors (BCRs) dampens B-cell activation by recruitment of a limited number of Src homology 2 domain (SH2)−containing phosphatases, predominantly SHIP (SH2-containing inositol phosphatase), which causes a dramatic and immediate hydrolysis of PIP3 (phosphatidylinositol 3,4,5-trisphosphate).3 FcγRIIb and SHIP are able to inhibit not only BCR-mediated signals but also signals induced by other cell surface receptors that require PIP3 generation.5 On the other hand, FcγRIIb can also signal independently of BCR clligation to directly mediate an apoptotic response.7 Whether or not this receptor is functional in B-CLL cells remains to be solved.

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achieved after 3 weeks of therapy. At 8 weeks after initiation of imatinib therapy, semiquantitative RT-PCR analysis showed a 99% reduction in H4/PDGFβR expression in peripheral blood compared with blood samples taken prior to treatment (Figure 1D). The patient remains in complete response after one year of therapy.

Imatinib mesylate has been shown to efficiently inhibit the activity of certain tyrosine kinases, including BCR-ABL, c-Kit, PDGFβR, PDGFRα, and ARG kinase.⁵⁶ Thus to further investigate the role of chimeric protein H4/PDGFβR, imatinib mesylate was tested in bone marrow primary cultures. Interestingly, bone marrow primary cultures from the t(5;10) patient displayed marked reduction in H4/PDGFβR activity when treated with imatinib (Figure 1C). Hence, the observed positive response strongly suggests that inhibition of PDGFβR activity may also be effective in other myeloproliferative diseases involving this tyrosine kinase receptor.

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To the editor:

Chromosomal abnormalities in Ph⁻ cells of patients on imatinib

The introduction of imatinib has been a major advance in the treatment of chronic myeloid leukemia (CML). Based on the results of the recently published IRIS study, imatinib has now been approved by the Food and Drug Administration as treatment for newly diagnosed CML patients.¹ However, despite its remarkable short-term efficacy and toxicity profile, little is known about the potential for long-term toxicity. This may be an important issue, as increasingly patients are declining stem cell transplantation (SCT) in favor of imatinib.

References