Correspondence

To the editor:

Imatinib mesylate in polycythemia vera

In the September 15, 2003, issue of Blood, Oehler et al describe imatinib mesylate inhibition of the autonomous in vitro proliferation of peripheral blood– and bone-marrow–derived polycythemia vera (PV) erythroid burst-forming units (BFU-Es). While their results superficially correlate with the previously published in vivo clinical observations of Silver, the conclusions of Oehler et al are at variance with their own data and the known pathophysiology of PV. First, contrary to the authors’ supposition, autonomous in vitro erythroid colony formation does not define the limits of the malignant clone in PV. Indeed, PV erythropoietin-independent BFU-Es could give rise to erythropoietin-dependent BFU-Es. Second, with respect to the actual suppression of autonomous PV BFU-Es by imatinib mesylate, in 7 of the 13 patients studied, in vitro colony formation was not sufficiently robust for meaningful interpretation of the data, and for the rest, inhibition was not always complete and the dose of imatinib mesylate required was similar to that previously observed to suppress normal marrow BFU-E proliferation. Third, and most important, imatinib mesylate failed to significantly inhibit PV BFU-E proliferation in the presence of hematopoietic growth factors. The authors consider this to be due to the proliferation of coexistent normal erythroid progenitor cells without providing actual proof from clonality assays. However, since most, if not all, circulating PV erythroid progenitor cells derive from the malignant clone, it is unlikely that normal erythroid progenitor proliferation could account for the growth factor–associated resistance to imatinib mesylate, nor were these cells less sensitive to imatinib mesylate in vitro. Rather, it is more likely that it was the PV erythroid progenitor cells that were resistant. In this regard, it is also important to note that Oehler et al used unfractionated peripheral blood mononuclear cells rather than purified erythroid progenitor cells in their experiments. Since imatinib mesylate inhibits in vitro monocyte proliferation and differentiation, given the conditions of their experimental protocol, it is impossible for Oehler et al to determine if the results they observed were a consequence of imatinib mesylate’s effects on monocytes as opposed to erythroid progenitor cells. The hematopoietic growth factor–associated resistance of the erythroid progenitor cells to imatinib mesylate suggests that the drug was indeed acting on the monocytes in the cultured mononuclear cell population.

Finally, it is worth emphasizing that PV is a disorder arising in a multipotent hematopoietic progenitor cell, not a committed erythroid progenitor cell. Indeed, the authors appear to have overlooked the observation that c-kit expression in PV is increased in these cells, which may account for the observed clinical effects of imatinib mesylate in this disorder. Chemotherapy directed at committed erythroid progenitor cells, even if effective, would be unlikely to have more impact on the natural history of PV than phlebotomy.

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Response:

Imatinib mesylate inhibits autonomous BFU-E growth in polycythemia vera

Spivak and Silver raise several questions concerning the in vitro effects of imatinib mesylate in polycythemia vera (PV). We agree with their statement that autonomous erythroid burst-forming unit (BFU-E) formation does not define the limits of the malignant clone in PV. Unfortunately, however, there is no method available thus far to separate normal erythropoietic progenitor cells from clonal cells, which would allow in vitro testing of new drugs on normal and clonal hematopoiesis in PV separately. Therefore, spontaneous BFU-E formation is still the most adequate in vitro system that can be used for this purpose. Moreover, we never assumed that autonomous BFU-E growth defines the limits of the malignant clone, but, instead, clearly stated that an unknown mechanism causes growth alterations of a single pluripotent hematopoietic progenitor cell in PV. It is well known that the
magnitude of autonomous BFU-E growth greatly varies between individual patients. This is not unexpected and is in line with a large number of in vitro studies using primary cells from patients with other hematologic diseases.\(^2,3\) However, we completely disagree with Spivak and Silver that a lower BFU-E growth in some experiments prevents a meaningful interpretation of the results. Imatinib mesylate completely suppressed autonomous erythroid colony growth in the majority of our patients at a concentration of 10 \(\mu M\), a dose that did not block colony formation in our 5 healthy controls. Furthermore, imatinib mesylate inhibited BFU-E growth by more than 70\% at 1 \(\mu M\), a concentration of imatinib mesylate that is also achieved in patients.

We agree that additional experiments with purified erythroid progenitor cells are of interest in order to determine a potential involvement of accessory cells in imatinib mesylate–induced suppression of autonomous BFU-E formation. Since spontaneous BFU-E formation can also be observed when using purified progenitor cells from patients with PV,\(^4,5\) we cannot share in speculations that imatinib mesylate–induced inhibition of spontaneous BFU-E growth is solely mediated by a suppression of monocyte accessory cell function. Even if the effect of imatinib mesylate on spontaneous BFU-E growth is partly mediated by modulating accessory cell function, this may be clinically relevant since monocytes are also present in the in vivo situation. Moreover, we do not think that the reappearance of erythroid colonies in the presence of exogenous erythropoietin questions the potential usefulness of this drug in PV. The only conclusion that can be drawn from this observation is that the signal transduction pathways, which are activated by erythropoietin and by the unknown target that is blocked by imatinib mesylate, are either completely or at least partly different. C-kit may be one of such targets, but present data are insufficient to consider c-kit hyperexpression as the main pathophysiologic abnormality in PV. If imatinib mesylate blocks the mechanism that renders PV progenitors constitutively activated, exogenous growth factors may still stimulate PV progenitors similar to normal hematopoiesis. PV progenitor cells might thus lose their growth advantage over normal hematopoietic stem cells, which, in turn, may reconstitute normal hematopoiesis upon prolonged treatment.

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References


To the editor:

The GATA1 mutation in an adult patient with acute megakaryoblastic leukemia not accompanying Down syndrome

Mutations of the GATA1 gene, which is located on chromosome X, have been found in almost all cases of transient myeloproliferative disorder (TMD) and acute megakaryoblastic leukemia (AMKL) accompanying Down syndrome (DS).\(^1,5\) No GATA1 mutations have been detected in patients with AMKL who did not have DS, except in AMKL with acquired trisomy 21.\(^1,4,6\) However, because only 10 cases with AMKL in non-DS have been analyzed for mutations of the GATA1 gene, it remains unknown whether the GATA1 mutation is exclusively involved in the development of AMKL with DS. Here, we report for the first time a GATA1 mutation in AMKL cells from a patient who did not have DS or acquired trisomy 21.

In October 2002, a 48-year-old woman was admitted to Furukawa City Hospital with complaints of shortness of breath and a bleeding tendency. Peripheral blood analysis showed severe anemia, thrombocytopenia, and mild leukocytosis with the appearance of immature cells: red blood cell count, \(87 \times 10^{12}/L\); hemoglobin, 27 g/L (2.7 g/dL); platelet count, \(6 \times 10^{11}/L\); and white blood cell count, \(10.8 \times 10^{9}/L\) (neutrophils, 29\%; basophils, 1\%; lymphocytes, 46\%; blasts, 16\%; metamyelocytes, 2\%; myelocytes, 3\%; and promyelocytes, 3\%). Pathologic examination of her bone marrow showed a mixture of dominantly proliferated small lymphocytic cells, which were positive for leukocyte common antigen (LCA) and CD79a, and scattered blast cells, which were negative for myeloperoxidase. Chromosomal analysis revealed 47XX, add(17)(p11), +add(17), add(20)(q13). The patient was diagnosed with acute lymphoblastic leukemia, chemotherapy was given, and complete remission was achieved. In February 2003, the disease relapsed and became refractory to chemotherapy. The morphology of leukemic cells at the relapse resembled that of small megakaryocytes, and they were negative for myeloperoxidase and positive for acid phosphatase. Immunohistochemical examination revealed that the leukemic cells were positive for CD33, factor VIII, and CD41a, and dull-positive for CD4 and CD45. In addition, flow cytometric analysis using an anti–GATA-1 antibody revealed that the leukemic cells were positive for GATA-1.\(^7\) The same chromosomal anomaly as that detected at onset was detected by chromosomal analysis. Based on these results, she was finally diagnosed as having AMKL.

We analyzed the GATA1 mutation in her bone marrow samples. Written informed consent was obtained from the patient. Genomic
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