of stem cells, will require prolonged observation and serial transplantation procedures. Introduction of FcεRI-specific regulatory elements is likely needed to maintain a physiological response to signals that govern bone resorption. Moreover, the large number of stem cells that are injected to correct oc/oc mice, the need for myeloablation, and the timing (day + 1 of life) required for the procedure to be effective are formidable obstacles that need to be addressed in humans.

TCIRG1 defects only account for about half of the cases of AR osteopetrosis in humans. Other forms (such as those due to OSTM1 and CLCN7 gene defects) carry the burden of intrinsic retinal and neuronal degeneration, which are not corrected by HSCT. This indicates that molecular diagnosis and careful discussion of the potential benefits and limits of neonatal HSCT and/or gene therapy should all take place soon after birth to make the remarkable achievements of Johansson and colleagues applicable in the human situation.

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**What if conventional-dose imatinib fails?**

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The management of patients with chronic-phase CML refractory to standard doses of imatinib mesylate includes dose escalation, allogeneic transplantation, or a switch to a new BCR/ABL inhibitor. In this issue of *Blood*, Kantarjian and colleagues present the results of a multicenter trial demonstrating that, for highly refractory patients, treatment with dasatinib is superior to dose escalation of imatinib mesylate.

In the short period of time since the initial trials in the late 1990s, imatinib mesylate (Gleevec; Novartis, Basel, Switzerland) has revolutionized the treatment of chronic myelogenous leukemia (CML) and created a model for the development of other so-called targeted therapies. In contrast to the mixed results with putatively targeted treatments in more genetically complex malignancies, imatinib mesylate has been so effective because the single mutation producing the chimeric BCR/ABL protein is sufficient to produce the clinical features of CML.

The starting dose of imatinib mesylate in chronic phase is 400 mg per day with no adjustments for patient weight. With 5 years of follow-up, 87% of the 553 patients who received imatinib mesylate as initial treatment on the International Randomized Study of Interferon and STI571 trial achieved complete cytogenetic remission (CCyR) at some time, with progression-free survival of 83% and overall survival of 89%; 69% remain on imatinib mesylate. The depth of response improves over time, with decreases in BCR/ABL transcript number as assessed by serial quantitative polymerase chain reaction (PCR). Studies are in progress to assess whether higher doses of imatinib or the newer, more potent tyrosine kinase inhibitors, nilotinib (Tasigna; Novartis) and dasatinib (Spryce; Bristol-Meyers-Squibb, New York, NY), could improve upon these results, possibly permitting discontinuation of therapy in patients who become consistently PCR negative.

In the interim, there remain some patients who require changes after initial imatinib mesylate treatment. In this issue, Kantarjian and colleagues describe a phase 2 study in which chronic-phase patients refractory to 400 g or 600 g imatinib mesylate were randomized to receive dasatinib or a dose increase of imatinib mesylate to 400 mg twice a day. There is actually little information, from either the IRIS trial or elsewhere, on the results of dose increase from 400 mg to 800 mg, although some retrospective studies have suggested that responses are suboptimal.

Randomized phase 2 trials are generally underpowered and not intended to be definitive tests of hypotheses, although there is a recent tendency to use this design as a poor man’s phase 3 trial, hoping for substantive differences, as was noted in this study. The overall response rate and time to treatment failure (see figure) were strikingly superior in the dasatinib recipients, although the duration of benefit is not known because of the brief follow-up period. Certainly, it is not surprising that dasatinib treatment was better than an imatinib dose escalation of only 200 mg, particularly since the patients in this study had long-standing, rather resistant CML characterized by hematologic or cytogenetic relapses, with only 28% having ever achieved a major cytogenetic remission. Of note, however, is the fact that the superiority of dasatinib was less apparent in patients who had previously received only 400 mg imatinib mesylate.

This study does not address patients with more subtle suggestions of treatment failure to 400 mg imatinib mesylate. Of concern is the temptation to switch therapy for patients in CCyR who have had less than what has been received imatinib mesylate. Of concern is the temptation to switch therapy for patients in CCyR who have had less than what has been...
termed a major molecular response\(^1\) or who have had raised BCR/ABL transcript levels with serial monitoring. The cytogenetic relapse rate remains extremely low in patients in CCyR, and we are only beginning to learn how to react to these more sensitive measurements of residual disease.\(^2\) Before succumbing to the new disorder of “PCRitis,” it is important to remember that the treatment of chronic phase is a marathon, not a sprint. Currently, there is inadequate standardization of results of PCR assays among different laboratories in the United States, and fluctuation in values is common. If increasing transcript values are confirmed repeatedly in patients still in CCyR, an initial trial with a dose increase to 800 mg imatinib mesylate is reasonable, switching to dasatinib if no response is noted. If BCR/ABL mutations known to be resistant to the available tyrosine kinase inhibitors are detected, allogeneic transplantation should also be considered if there is cytogenetic relapse.

**Conflict-of-interest disclosure:** The author has received grant support for clinical trials and has served on advisory boards for Novartis and Bristol, Myers, Squibb.

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**HEMOSTASIS**

Comment on Panes et al, page 5242

**Platelet tissue factor comes of age**

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The origin of blood–borne tissue factor (TF) is a highly debated topic that is filled with controversy. In this issue of *Blood*, Panes and colleagues report that activated human platelets synthesize functional TF.

Expression of TF around blood vessels is thought to initiate clotting after vessel injury. However, in 1999, Giesen et al\(^1\) demonstrated that TF was present in blood, and that this so called blood–borne TF contributed to thrombus formation ex vivo. TF was found on microparticles (MPs), which are small membrane fragments derived from activated or apoptotic cells. Positive staining was also observed on platelets and was presumably due to the adsorption of TF–positive MPs. This bred a popular concept that TF present in blood was derived from MPs. Indeed, P-selectin glycoprotein-1 expressed by leukocyte-derived MPs can dock to P-selectin present on the surface of activated platelets.\(^2\)

Whether or not platelets intrinsically express TF has been controversial. In 2001, Zillman et al\(^3\) identified TF on the surface of platelets in collagen-stimulated whole blood. This observation was generally confirmed by others, and in a subsequent study, TF protein was localized to platelet α-granules. This suggested that platelets store TF, but did not distinguish between TF that was preformed in megakaryocytes and packaged into platelets versus the endocytosis of TF–positive MPs. These studies also did not take into account de novo protein synthesis, a mechanism of control used by platelets to generate new proteins.\(^4\)

The studies by Panes and coworkers provide further insight into these issues and demonstrate that activated human platelets synthesize TF. They show that unstimulated platelets express low levels of TF protein, which is enhanced in response to cellular activation. TF mRNA, the template for protein synthesis, is absent or expressed at low levels in unstimulated platelets. In response to activation, however, platelets from every subject express TF mRNA. The differential expression of TF mRNA in anucleate platelets can be explained by studies from our group demonstrating that resting platelets contain TF pre-mRNA that is spliced into mature mRNA upon platelet activation.\(^5\)

One limitation of the study by Panes and colleagues is that it is unclear if resting platelets express low basal levels of TF in vivo, or if these levels are due to postisolation activation of the platelets. This is a critical question to resolve, because constitutive versus inducible expression of platelet TF may have distinct functions in the initiation, propagation, and stabilization of a thrombus. It also raises the possibility that TF protein expression patterns in platelets may vary in human disease.

The fact that activated platelets express TF may have important implications for the therapeutic use of recombinant factor VIIa (NovoSeven, Clayton, NC) in the treatment of patients with bleeding disorders. High-dose recombinant factor VIIa has been proposed to restore hemostasis by binding to activated platelets in a TF–independent manner. However, low levels of TF generated by platelets may play a role in the hemostatic effects of recombinant factor VIIa.
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