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No RIC in high-risk myeloma?

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of a 70-kDa N-terminal fragment of fibronectin or a bacterial peptide that inhibits fibronectin binding to fibroblasts. Furthermore, platelet activation with lysophosphatidic acid was necessary, and all of these effects were concentration dependent. Finally, there was a synergism of the 2 mechanisms of thrombus enhancement by fibronectin: cross-linking to fibrin and assembly by adherent and aggregating platelets (see figure).

It is not yet entirely clear which platelet receptors are responsible for these effects of fibronectin. It seems that binding of the type III modules 9 to 10 of fibronectin to $\beta 3$ integrins is responsible for enhancing platelet adherence to fibronectin-fibrin versus fibrin, and $\beta 3$ integrins likely mediate adhesive interactions of platelets to assembled fibronectin. However, the binding of the N-terminal 70-kDa region of fibronectin may be mediated by nonintegrin receptors.

These results can be put into the context of other adhesive proteins that play important roles in thrombogenesis. Evidence from a variety of sources now suggests that von Willebrand factor, fibrinogen, and fibronectin all have separate roles in thrombus formation. Von Willebrand factor is important in initiating and supporting platelet-vessel wall and platelet-platelet interactions at high shear rates. Fibrin(ogen) is present at high concentrations in plasma, and its high affinity for acti-

vated $\alpha \text{IIb}\beta 3$ means it will have a fundamental role in platelet aggregation under normal conditions. Because platelet adhesion to fibrin and platelet-platelet interactions are both affected by fibronectin, it seems that fibronectin is involved at all stages.

In conclusion, these results provide a potential explanation for the association of elevated levels of plasma fibronectin with coronary artery disease. The finding, reported in this paper, that thrombus formation in fibrin matrices is enhanced as fibronectin increases suggests that higher levels of plasma fibronectin may predispose subjects to larger and more stable arterial thrombi. Further research will be necessary to determine if fibronectin could be a potential risk factor and a target for reduction. ■

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CLINICAL OBSERVATIONS

Comment on Garban et al, page 3474

No RIC in high-risk myeloma?

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In a prospective IFM study in high-risk de novo myeloma, autologous cell transplantation followed by allogeneic transplantation with reduced-intensity conditioning was not superior to tandem autologous stem cell transplantation.

Allogeneic stem cell transplantation (allo-SCT) is probably the only curative option for patients with myeloma. The reduced relapse risk after allo-SCT and the induction of sustained molecular remissions in several patients are likely due to the efficacy of donor lymphocytes to eliminate recipient plasma cells.^{1,2} The existence of this graft-versus-myeloma (GVM) effect is best illustrated by the response to donor lymphocyte infusion (DLI) in 30% to 40% of patients with relapsed

myeloma.³ However, the potential benefit of GVM in myeloablative allo-SCT is probably completely offset by the high transplant-related mortality (TRM). The feasibility of initial studies of allo-SCT after conditioning with a reduced dose and minimal-intensity regimen has led to an enthusiastic revival of allo-SCT in myeloma.⁴ However, due to the heterogeneity of conditioning regimens and heterogeneity of patients reported, the place of reduced-intensity con-

ditioning (RIC) in myeloma treatment is not established.

The Intergroupe Francophone du Myelome (IFM) is the first group to evaluate in a prospective comparison a new promising treatment modality in myeloma. In this issue, Garban and colleagues report on the outcome of tandem autologous, allogeneic RIC in patients with an HLA-identical sibling donor versus tandem autologous transplantation in patients without a donor. Although the low TRM of 10% following RIC was a major achievement, progression-free survival (PFS) and overall survival (OS) in both arms were comparable.

What are the implications? Should we abandon RIC in (de novo high-risk) myeloma? A probable negative aspect for outcome of the RIC arm was the use of high-dose ATG in the conditioning regimen. The beneficial effect of in vivo T-cell depletion is the low incidence of acute and chronic graft-versus-host disease (GVHD); the detrimental effect is the elimination of the GVM effect. The importance of immune-competent donor T cells for GVM is best illustrated by the absolute correlation between response to DLI and the occurrence of acute and chronic GVHD.⁵ European study groups, including the Dutch Hemato-Oncology Association (HOVON), Spain's Programa para el estudio y tratamiento de las hemopatias malignas (PETHEMA), and the European Group for Blood and Marrow Transplantation (EBMT), are performing comparable prospective studies, but with a larger number of patients at all risk levels receiving a RIC regimen without T-cell depletion. In anticipation of the results of these studies, it is necessary to begin to explore new strategies. The IFM study shows that by using reduced-intensity conditioning, the first step (ie, the replacement of a deficient autologous immune system by an immune-competent donor system) may be achieved without fatal toxicity. The time has come to focus on strategies after allotransplantation, to redirect the donor T cells toward the residual myeloma cells without enhancing GVHD. The suggestion that the novel anti-myeloma agents such as bortezomib, thalidomide, and revlimid may preferentially stimulate the graft-versus-tumor effect and not GVHD is fascinating.⁵ One of these observations was a remarkably high response rate (15 of 18 patients, including 3 complete responses) to these agents in DLI refractory multiple myeloma (MM) patients.⁶ ■

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CLINICAL OBSERVATIONS

Comment on Popat et al, page 3486, and Passamonti et al, page 3676

Is bone marrow fibrosis the real problem?

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Popat and colleagues and Passamonti and colleagues provide additional evidence that the constitutive mobilization of CD34⁺ cells into the peripheral blood (PB) of patients with chronic myeloproliferative disorders (MPDs) is not merely due to the physical disruption of the bone marrow (BM) microenvironment by fibrosis, but rather is a consequence of the continuous biologic processes provided by the cellular progeny of the malignant clone.

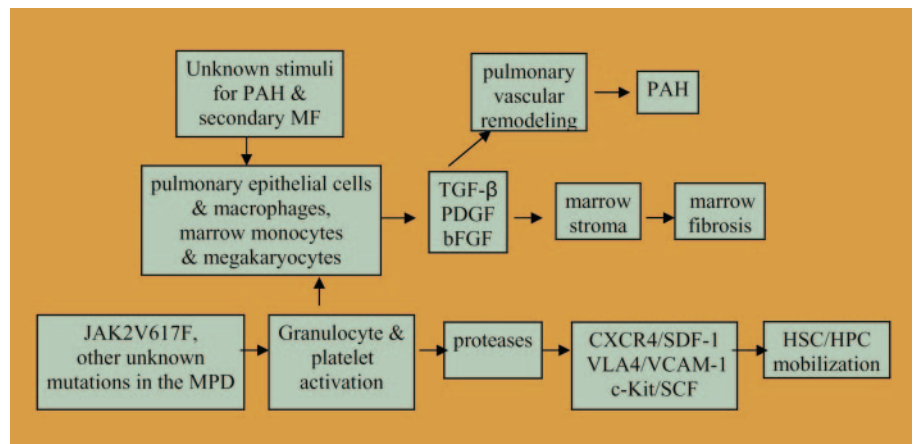
Both chronic idiopathic myelofibrosis (CIMF) and myelofibrosis (MF) that occurs during the terminal phases of polycythemia vera (post-PV MF) are accompanied by constitutive mobilization of CD34⁺ hematopoietic stem cells (HSCs) and hematopoietic progenitor cells (HPCs) into the peripheral blood (PB).¹ This mobilization of CD34⁺ cells and the resultant extramedullary hematopoiesis have previously been thought to be a consequence of a fibrous distortion of the BM microenvironment, leading to the forced egress of CD34⁺ cells from the BM. Recently, this dogma has been challenged by data that suggest that the abnormal trafficking of CD34⁺ cells in CIMF is due to the release of proteases by the cellular progeny of HSCs/HPCs. These proteases have been shown to lead to the disruption of adhesive interactions that normally result in the retention of HSCs/HPCs within the BM.¹ Popat and colleagues show that patients with pulmonary arterial hypertension (PAH) and secondary BM fibrosis equivalent to a control population with CIMF do not have high levels of CD34⁺ cells in their PB. The authors conclude that BM fibrosis alone cannot account for the abnormal

HSC/HPC trafficking observed in CIMF and post-PV MF.

Chronic myeloproliferative disorders (MPDs) have previously been reported to be associated with an unusually high incidence of PAH.² TGF- β , PDGF, and basic FGF have all been implicated in the development of not only PAH but also primary and secondary forms of MF.^{2,3} PAH occurring in patients

with MPDs has been reported to improve with treatment of underlying chronic MPDs.² Schermuly et al³ have recently reported that the PDGF receptor antagonist imatinib mesylate, which is routinely used effectively to treat chronic MPDs, reverses pulmonary vascular remodeling in 2 different animal models of PAH. A pilot trial evaluating the safety and efficacy of imatinib in patients with PAH is currently in progress.³ The clinical observations of the PAH's association with secondary BM fibrosis and with chronic MPDs suggest that there are common mediators of disease in these 2 diverse settings (see figure).

Passamonti and colleagues provide additional insight into the origins of abnormal CD34⁺ cell trafficking in chronic MPDs. They studied the relationship between the JAK2 (V617F) mutational status of patients with PV and the degree of CD34⁺ cell mobilization into the PB. The authors demonstrated that PV patients with fibrotic BMs and abnormal CD34⁺ cell trafficking had a higher percentage of mutant alleles than PV patients without BM fibrosis. Several groups (Popat et al, Passamonti et al, and Tefferi et al⁴) have now shown that most patients with post-PV MF are homozygous for the JAK2 (V617F) mutation, while the mutant allele percentage is less than 50% in many PV patients without BM fibrosis. Two of those groups, who studied PV patients sequentially during their clinical course, were able to show that patients had an increase in the mutant allele percentage over time (Passamonti et al and Tefferi et al⁴). Passamonti et al conclude that the significant mobilization of CD34⁺ cells into the PB of PV



A proposed schema of common pathobiological events leading to bone marrow fibrosis and pulmonary vascular remodeling in such diseases as pulmonary arterial hypertension, secondary myelofibrosis, and chronic myeloproliferative disorders.