G-CSF and monosomy 7 in marrow failure patients

Kojima and colleagues (page 786) report a correlation between G-CSF treatment of children with aplastic anemia and evolution to cytogenetic abnormalities and myelodysplasia. How strong is this relationship and how generalizable the conclusions?

The Japanese investigators administered high G-CSF doses (close to the adult equivalent of 10 μg/kg/d, later thrice weekly) for very long periods (in all patients for at least 3 months and in nonresponders beyond, in some cases for years) and largely independent of blood count values. This is far from the usual practice. G-CSF is not recommended as first therapy in marrow failure; therapeutic trials aim at elevating the neutrophil counts; and in those few patients who respond, the dose is adjusted to maintain granulocytes above a safe level. The Japanese protocol likely was based on earlier favorable results from Europe, where G-CSF combined with immunosuppression in producing excellent survival in aplastic anemia patients, but neither later analysis of these data nor a formal randomized comparison could confirm the specific value of the cytokine, even in protecting patients from serious infection.

The results of Kojima et al must be balanced by other evidence. G-CSF has passed long-term testing in many animal species. Its standard use in cyclic neutropenia has been free of complications. In aplastic anemia, G-CSF in the European trials has been sparingly, are comparable to other evidence. G-CSF has passed long-term testing in many animal species. Its standard use in cyclic neutropenia has been free of complications. In aplastic anemia, G-CSF is used sparingly, are comparable to normal stem cells, while allowing PNH cells to prosper. Chronic G-CSF therapy also has been associated with monosomy 7 in children with Kostmann syndrome. In both constitutional neutropenia and aplastic anemia, improved survival secondary to better supportive care may allow manifestation of a latent malignant potential. That small numbers of abnormal cells may reside quietly, even innocuously, in failed bone marrows has become apparent only with the development of increasingly sensitive techniques, as flow cytometry for paroxysmal nocturnal hemoglobinuria and fluorescence in situ hybridization for aneuploidy. Whether and how G-CSF might promote expansion of stem cells lacking chromosome 7 is amenable to laboratory experimentation; clarification of this relationship will have serious clinical implications for marrow failure patients.

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PNH cells are hard to kill

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disorder and a most distressing one for the patients who suffer from it. The mechanism of the intravascular hemolysis that underlies hemoglobinuria is now understood, and we know that PNH is a clonal disorder due to a somatic mutation in the PIG-A gene. The most perplexing outstanding question is the mechanism whereby the PNH clone can expand, to the extent that it can take over the patient's hematopoiesis almost entirely. Nakakuma's group (page 1031) reports a pertinent finding. Nagakura and colleagues used mononuclear cells enriched in natural killer (NK) cells to carry out cytotoxicity assays, using as targets 3 human leukemia cell lines (one myeloid, one of B-cell lineage, and one of T-cell lineage). Then they compared mutant cell lines with PIG-A mutations, therefore having a PNH-like membrane phenotype, with the same cell lines in which the phenotype had been restored to normal by transfection with PIG-A cDNA. In all cases the rate of killing of the PNH-like cells was significantly less than that of the non–PNH-like cells. This difference is not due to a defect in perforin-mediated lysis; it is due, instead, to the fact that PNH-like cells were unable to activate NK cells to the extent that non–PNH-like cells did.

These results are in keeping with the notion, previously stated over a decade ago, that in the pathogenesis of PNH there is an obligatory cooperation of (1) an abnormality intrinsic to the mutant clone and (2) an abnormality in the marrow environment. A question that remains open is whether the difference in NK cell activation reported here, which is in contrast with some previously published data, applies to normal stem cells (as opposed to cell lines). Finally, one will need to find out what may cause, in PNH patients in vivo, an increased NK activity sufficient to cause the demise of normal stem cells, while allowing PNH stem cells to prosper.

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Recurrent venous thromboembolism and pregnancy

Current guidelines with respect to antepartum anticoagulation for women who have had a previous episode of venous thromboembolism (VTE) are not well defined, in part because the degree of risk has not been established in large clinical studies. Anticoagulation is recommended during the postpartum period for this patient group, since thrombotic risk is considered to be substantially increased. Pabinger and colleagues (page 1060) have addressed the risk for recurrent VTE during the antepartum period in a retrospective study of 109 women with a history of an episode of VTE who were followed for a total of 1014 years, of which 73 observation years occurred during pregnancy. The postpartum...
period was excluded for analysis, since anti-coagulation during that time was recommended. In this study, 40% of the women tested positive for factor V Leiden and an additional 20% had another type of thrombophilia. In this group of 109 women, the recurrence rate of VTE in the antepartum period was 10.9 episodes per 100 patient years. Risk for recurrence was not necessarily based on the presence of thrombophilia.

Although not discussed in this paper, another reason to consider antepartum anti-coagulation in women with thrombophilia is to reduce the likelihood of other complications such as pre-eclampsia, abruptio placentae, and fetal loss. The impact of anticoagulation on these adverse outcomes is unknown other than for women with the antiphospholipid syndrome.

The authors mention low molecular weight heparins (LMWHs) for prophylaxis; these agents are commonly used in pregnancy although not officially approved by the Food and Drug Administration in this clinical setting. Pabinger et al’s study supports the need for a large, well-designed trial to define the risk-benefit ratio of antepartum anticoagulation, most likely with a LMWH, in women with and also without underlying thrombophilia who have had previous VTE.

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**Factor V Leiden and the genetics of myocardial infarction: we need to look elsewhere**

In the July 1, 2002, issue of *Blood*, Juul and colleagues (Blood. 2002;100:3-10) convincingly demonstrate Factor V Leiden (FVL) to be a risk factor neither for myocardial infarction (MI) nor for ischemic stroke or non–MI ischemic heart disease. FVL is a point mutation in the gene for factor V, which results in the replacement of single amino acid residue: Arg506 is changed to Gln. As a consequence, the FV molecule becomes less sensitive to cleavage and inhibition by the anticoagulant serine protease activated protein C (APC). The condition is also known as APC resistance. The hypercoagulable state being associated with FVL conveys a lifelong 5- to 10-fold increased risk factor for venous thrombosis, FVL being the most prevalent genetic risk factor for venous thrombosis yet described. It is present in 2%-15% of white populations, whereas it is absent in other populations, this difference contributing an explanation for the low incidence of venous thrombosis in nonwhite populations.

FVL is the result of a founder effect, the single mutational event being estimated to have occurred approximately 30,000 years ago. A reason for the high prevalence of FVL in certain populations is believed to be that the associated hypercoagulable state conveys a survival advantage to its carriers due to decreased risk of severe bleeds, for example, after delivery. The results of Juul et al highlight an interesting difference in the pathogenesis of arterial and venous thrombosis. None of the known genetic risk factors of venous thrombosis—that is, FVL, the 20210G>A mutation in the prothrombin gene, and deficiencies of protein C, protein S, and antithrombin—are risk factors for arterial thrombosis. Arterial thrombosis is developing in a high-flow, high-pressure system and is usually associated with atherosclerotic plaque ruptures resulting in the formation of a platelet plug and concomitant activation of blood coagulation through the exposure of plaque-associated tissue factor. In contrast, venous thrombosis develops at low flow rate in a low-pressure system, where the naturally occurring anticoagulant pathways apparently are crucial for inhibition of thrombosis. These anticoagulant pathways are insufficient in preventing thrombosis in the arterial circulation in the event of an atherosclerotic plaque rupture. The search for genetic risk factors of MI will continue and will hopefully provide insights into the pathogenetic mechanisms of arterial thrombosis. The results of Juul et al demonstrate that genetic investigation of the protein C system is less likely to provide the solution to the problem.

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