malignancy at 5 years was 0.43 (95% CI 0.16-1.15) and was unchanged at 10 years.

Our data allow some interesting considerations. The probability of developing an acute leukemia in patients who received chemotherapy or radiotherapy for a previous malignancy (PM), including acute leukemia, is a well-known occurrence: secondary forms constitute approximately 8% to 10% of all acute leukemias and are usually myeloid.6

The main reason for this event is that several drugs employed in the treatment of the PM, particularly topoisomerase II inhibitors (epipodophyllotoxins and anthracyclines), and combined chemotherapy including alkylating agents, are considered potentially mutagenic. As suggested by Latagliata et al,1 the use of intensive chemotherapy to cure APL, with the inclusion of topoisomerase II inhibitors, has a potential role in inducing a tMDS-AML.7 In our cohort of patients, the number of secondary malignancies is lower than expected in the normal population. The estimated cumulative incidence at 5 and 10 years is also lower than that expected. Furthermore, the brief latency between the onset of the 2 malignancies leads to the hypothesis that the second malignancy is probably not related to the carcinogenic action of the drugs employed for the treatment of APL, but perhaps to a chance association only.

These considerations suggest that APL treatment is not relevant in inducing the onset of secondary nonhematological malignancies. On the contrary, the action of topoisomerase II inhibitors, which represent one of the main anticancer drugs used in APL, could favor the development of a tMDS-AML with a leukemogenic action on blood stem cells.

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References

To the editor:

Oxidation of glutathione peroxidase–deficient red cells by organic peroxides

Red cells from mice with a disrupted glutathione peroxidase-1 (GSHPx-1) gene have no GSHPx activity, since GSHPx-1 is the only isoform of GSHPx found in the erythrocyte. In a recent article in Blood,1 we reported that these enzyme-deficient red cells are not oxidized by exogenous hydrogen peroxide any faster than wild-type cells. This strongly supports the view that catalase is the preeminent enzyme protecting red cells from attack by exogenous hydrogen peroxide. However, this conclusion also raises a question about the role of GSHPx in the red cell. In this regard, we noted that while catalase is completely specific for H2O2, GSHPx is able to reduce organic peroxides as well, suggesting that the distinctive role of GSHPx might be to detoxify organic peroxides. To test this, wild-type and GSHPx-deficient red cells2 were exposed to a range of compounds known to hemolysis red cells (cumene peroxide, t-butyl peroxide, primaquine, paraquat). Oxidation of hemoglobin (Hb) was used as an endpoint for oxidative damage. Preliminary studies also assayed K efflux, which is increased by organic peroxides.3,4 However, the alteration in K efflux was found to follow temporally the oxidation of Hb, indicating that Hb oxidation was an earlier indicator of oxidative damage. Of these compounds, the GSHPx-deficient red cells showed differential sensitivity only to organic peroxides. Figure 1 shows a distinct and reproducible difference between wild-type and GSHPx-deficient cells in their sensitivity to organic peroxides.

What might be the evolutionary benefits of an erythrocyte mechanism for detoxifying organic peroxides? Are there circumstances when organic peroxides might arise in animal issues?

Figure 1. Oxidation of hemoglobin in intact erythrocytes by organic peroxides. ● indicate wild-type red cells; ○, GSHPx-deficient red cells.
unsaturated compounds in the cellular environment would be expected to generate toxic organic peroxides, providing a rationale for the reduced virulence phenotype of strains deficient in organic peroxidase reductase. It would be important for the host organism that its cells are also able to detoxify such organic peroxides. Thus, we suggest that protection against organic peroxides produced during phagocyte killing is a physiological role for GSHPx in red cells.

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To the editor:

Long-term treatment with oral sildenafil in a thalassemic patient with pulmonary hypertension

Pulmonary hypertension (PHT), defined as Doppler peak systolic tricuspid gradient (TG) higher than 30 mmHg, develops in a high percentage of patients with β-thalassemia (10% in thalassemia major and greater than 50% in thalassemia intermedia [TI]). Recent studies correlate PHT with age and high cardiac output. In patients with TI, whether or not transfusion dependent, PHT is the main cause for congestive heart failure.1 We report the case of a thalassemic patient with secondary PHT who has been successfully treated with sildenafil, a selective and potent inhibitor of cGMP-specific phosphodiesterase (PDE5) that promotes smooth muscle relaxation in lung vasculature.2

A 34-year-old male with β-thalassemia intermedia, splenectomized at the age of 18, started regular transfusion and iron chelation therapy in our center at the age of 32. Echocardiography showed a steady increase of pulmonary artery pressure (PAP) with right ventricular enlargement and moderate tricuspid valve regurgitation (TG systolic 56 mmHg, mean 42 mmHg). Left ventricular systolic function was preserved. Patient symptoms included reduced tolerance to exercise, dyspnea during light physical exertion, and thoracic constriction. There were no signs of iron overload. Pulmonary scintigraphy with 99mTc demonstrated numerous defects in perfusion capacity of the right lung. Spirometry revealed medium-grade ventilation impairment with a restrictive pattern (Inspiratory Vital Capacity [IVC] = 2.66 L, 57% of the normal value, Forced Expiratory Volume L/s [FEV1] = 1.96 L, 52% of the normal value). Treatment was started with calcium antagonists but had to be quickly interrupted due to severe side effects. Based on the potential role suggested for sildenafil in the management of PHT,3 sildenafil, 25 mg 2 times per day, was administered for 1 month and progressively increased to 50 mg 2 times per day. After 15 months of therapy, right ventricular dimension and mean TG were back to normal (TG systolic 40 ± 3 mmHg, mean 25 mmHg; P < .03). Respiratory function tests showed only a mildly restrictive ventilation pattern (IVC = 3.54 L, 76% of the normal value, FEV1 = 3.03 L, 81% of the normal value). Systemic artery pressure was normal, and the patient’s conditions had improved. The drug was well tolerated except for transient episodes of nasal mucosa congestion. Different to what has previously been described in a patient with sickle cell trait treated with sildenafil, no priapism or erectile dysfunction was observed in our patient.4

The etiology of PHT in thalassemic patients remains unclear.5 Obstruction of pulmonary arteries by thrombotic events has been observed in autopsies of patients with β-thalassemia/HbE disease.6 In fact, perfusion pulmonary scintigraphy with Tc99m of our patient shows multiple areas of perfusion impairment in pulmonary microcirculation (data not shown). Recent studies have demonstrated the importance of the procagulant activity exerted by erythroblasts and damaged erythrocytes that have lost normal asymmetric distribution of membrane phospholipids.5,7 A higher risk has been attributed to splenectomized TI patients, especially those who are not transfusion-dependent. The low hemoglobin levels in untransfused patients leads to compensatory erythroblast hyperplasia and elevated levels of erythroblasts in circulation.7 This suggests that therapeutic strategies directed toward reduction of the raised pulmonary pressure should be combined with adequate transfusional support and iron chelation therapy8 in order to reduce hypoxic stimuli on the pulmonary vessels.

In vitro study has shown that the activation of soluble guanylate cyclase-cGMP–dependent protein kinase pathway is associated with the induction of γ-globin gene expression.9 This suggests that sildenafil is also capable of improving erythropoiesis in thalassemia patients. Since our patient is transfusion-dependent, it was not possible to correlate any improvement in erythropoiesis to treatment with sildenafil.

Previous experience has shown that calcium antagonists are effective in only 30% of patients with PHT10 and that prostacyclin analogs are expensive and difficult to manage. The selective antihypertensive effect, the minimal risk of side effects, and the
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