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The absence of any favorable effects of early high-dose recombinant human erythropoietin (rEpo) in acute ischemic stroke reported by the EPO Stroke Trial Group is highly remarkable.1 The findings that rEpo was associated with an overall increased risk of death and of further serious complications (intracerebral hemorrhage, brain edema, thromboembolic events) when combined with recombinant tissue plasminogen activator need to be critically considered in the context of 2 other recent clinical studies on the use of rEpo or darbepoetin-α (a higher glycosylated Epo derivative) aimed at brain or cardiovascular protection. In adults with diabetes, chronic kidney disease, and moderate anemia, darbepoetin-α did not reduce the risk of death or cardiovascular events and was even associated with a higher rate of stroke.2 In very immature preterm infants with a gestational age <26 weeks that received early high-dose rEpo, the rates of severe intraventricular hemorrhage were rather increased, although not statistically significant.3

In these studies, which were conducted with different specific aims, complications emerged that can be attributed to disturbed endothelial functions of immature, vulnerable, or damaged vessels. This notion is supported by experimental data. Analysis of developing mice provide evidence for Epo action on endothelial cells, because ablation of the genes coding for Epo or its receptor results in severe angiogenic defects.4 rEpo protects endothelial cells against apoptosis and stabilizes vascular integrity.5 However, rEpo enhances the expression of tissue factor in the extracellular matrix of endothelial cells, resulting in an increased platelet adherence to injured endothelium.6 Moreover, rEpo leads to excessive neointima formation in injured carotid arteries, likely to increase the risk of vascular stenosis.7 Genetic variations in the Epo gene may additionally predispose to increased severity of diabetic retinopathy.8

Thus, the Epo/Epo receptor biology on endothelial cells needs to be further elucidated not only with regard to tissue protection. Patients with cancer, in whom rEpo may promote tumor growth, angiogenesis, and modulate sensitivity of chemotherapeutic drugs,9 will also benefit from this research.

disclosures

None.

References

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