Asialoerythropoietin to Protect the Failing Heart

Is it Possible to Run With the Hare and Hunt With the Hounds?*

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Anemia is commonly observed in patients with renal failure and chronic heart failure (HF). Its presence is associated with a lower quality of life and an impaired survival (1). As a logical next step it was thought that correction of anemia would result in an improved outcome. Although erythropoietin (EPO) has been successfully used in clinical practice for more than 2 decades, the relationships among anemia, EPO treatment, and outcome seems to be more complex than first thought. A meta-analysis by Phrommintikul et al. (2) showed that EPO treatment in anemic patients with renal failure, which was targeted to achieve higher hemoglobin values, was associated with increased mortality and higher risk of hypertension and thrombosis. Recently published results of the TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) study only emphasized these concerns (3). In this phase III clinical trial, 4,038 patients with diabetes, chronic kidney disease, and anemia were randomly assigned to darbepoetin alfa (a long-acting erythropoietin analogue) to achieve a hemoglobin level of approximately 13 g/dl or placebo, with rescue darbepoetin alfa when the hemoglobin levels dropped below 9.0 g/dl. Darbepoetin alfa administration did not reduce the composite end point of death or a cardiovascular event. Moreover, it was associated with an increased risk of stroke (hazard ratio: 1.92, 95% confidence interval: 1.38 to 2.68, p < 0.001). It has been postulated that the increased viscosity or hypertension related to EPO use might be involved.

It has been shown that EPO also harbors, besides direct hematopoietic effects, pleiotropic effects beyond correcting anemia (4). The EPO receptor has been detected in several non-hematopoietic tissues, including brain and heart (5,6). Studies have shown that EPO treatment improves cardiac function in experimental heart failure. However, hemoglobin levels do increase and might in part offset the beneficial effects of EPO, related to increased viscosity and hypertension. One possibility to avoid hematopoiesis is to use a low dose of EPO. Previously, it has been shown that tissue protection in the heart is achieved even with a low dose of EPO without unwanted effects on the hematocrit (7). Conversely, this might limit the extent of tissue protection, and higher doses might be necessary to render optimal cardiac protection.

Therefore, a non-hematopoietic derivate of EPO (the so-called asialoerythropoietin [asialoEPO]) has been developed. AsialoEPO is produced by removing the sialic acid moieties from the EPO molecule, which are responsible for its delayed clearance in vivo (8). This modification renders asialoEPO a very short half-life, insufficient to significantly stimulate the hematopoiesis. However, only brief exposure to EPO is needed for tissue-protective effects (9). In a study performed by Erbayraktar et al. (10), asialoEPO exhibited neuroprotective effects in different experimental models of brain and spine injury, without an effect on hemoglobin levels. This concept was further validated in other tissues, including kidneys. Administration of asialoEPO protected against renal ischemia-reperfusion injury, possibly through mechanisms involving inhibition of apoptosis (11). In this issue of the Journal, Ogino et al. (12) demonstrate for the first time cardioprotective effects of asialoEPO as well. In their study, asialoEPO attenuated nephrectomy-induced left ventricular remodeling and dysfunction. This underscores that the improvement of cardiac function is not mediated through increased hemoglobin levels but through pleiotropic effects. In this light, the authors show that asialoEPO inhibited fibrosis, inflammatory changes, and oxidative damage. Furthermore, treatment with asialoEPO resulted in an improved capillary density, providing an attractive mechanism for cardioprotection in heart failure (13). Our group has previously shown that EPO-induced neovascularization is associated with improved cardiac performance in a post-myocardial infarction model (14). This effect is partly mediated through stimulation of endothelial progenitor cells from the bone marrow as well as induction of myocardial vascular endothelial growth factor expression (15). Interestingly, in an ischemic hind limb model, asialoEPO enhanced angiogenesis through a stimulating effect on bone marrow cells (16).

A different approach to avoid hematopoietic effects of EPO and preserve tissue protection is to use derivates with
different affinity to the EPO receptor. Carbamylated erythropoietin (CEPO) is an EPO derivate that does not bind to homodimeric EPO-receptor, mediating hematopoiesis. Instead, CEPO activates a heteroreceptor complex consisting of both the EPO receptor and beta-common receptor subunit, which is expressed in numerous organs, including heart and kidney (17). CEPO has proven its effects already in experimental myocardial injury. In rats subjected to ischemia-reperfusion injury CEPO treatment reduced myocardial cell loss and improved left ventricular function, without any effect on the hematocrit (18).

Thus, the idea of EPO-mediated cardioprotection without the undesirable increase in hemoglobin levels seems attractive for clinical use, and it might indeed be possible to run with the hare and hunt with the hounds. However, future clinical studies are needed to support this concept from "bench to bedside."

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