Review

Science review: Recombinant human erythropoietin in critical illness: a role beyond anemia?

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Abstract

Erythropoiesis usually fails during severe illness because of a blunting of the kidney–erythropoietin (EPO)–bone marrow axis. In this setting, clinical studies have shown that recombinant human erythropoietin (rhEPO), administered in pharmacological amounts, significantly reduces the need for blood transfusions. In addition to the kidney, however, EPO is also produced locally by other tissues in a paracrine–autocrine manner. Here, similar to its role in the bone marrow, EPO rescues cells from apoptosis. Additionally, EPO reduces inflammatory responses, restores vascular autoregulation, and promotes healing. The results of many studies (including a phase II clinical trial in ischemic stroke) demonstrate that rhEPO protects the brain, spinal cord, retina, heart, and kidney from ischemic and other types of injury. Although rhEPO is efficacious in the treatment of EPO-deficient anemia during illness, inadequate effort has been devoted to determining whether direct tissue protection might also result from its administration. Here, we speculate on the potential utility of EPO as a protective cytokine in the context of acute critical illness and suggest key parameters required for a proof-of-concept clinical study.

Keywords apoptosis, clinical study, critical illness, cytokine, erythropoietin

Introduction

Erythropoietin (EPO), a member of the type I cytokine superfamily, was first identified as the hormone that stimulates erythroid progenitors within the bone marrow to mature into erythrocytes. In recent years, however, many other physiologic roles for EPO have been identified. EPO is now known to be a local product of diverse cells that specifically protect cells from potential cytotoxic events (for review, see Erbayraktar and coworkers [1]). In this capacity, EPO maintains and protects tissue function, especially during metabolic stress.

The behavior of the classical EPO–erythroid precursor system in serious illness is reasonably well understood. Typically, both the production of EPO and its action in the bone marrow are impaired by multiple factors (e.g. circulating EPO-suppressing proinflammatory cytokines [2]), resulting in anemia. An exception to this generalization is observed in acute renal failure, in which the systemic concentrations of EPO are transiently increased, presumably as a result of unregulated release of EPO from injured EPO-producing cells within the renal interstitium [3]. However, increases in circulating EPO following renal failure do not usually reach the minimum concentration required for effective paracrine–autocrine signaling in preclinical models (see below).

The results of multiple clinical studies have shown that pharmacologic doses of recombinant human erythropoietin (rhEPO) effectively reactivate the bone marrow in critical illness to produce erythrocytes. Although blood transfusions can be avoided in rhEPO-treated patients, clinical trials to date have shown no differences in patient survival or recovery (e.g. [4,5]). In one small study performed in a multidisciplinary intensive care unit [6], however, the length of stay was a third shorter for those patients who received rhEPO.

EPO = erythropoietin; EPOR = erythropoietin receptor; rhEPO = recombinant human erythropoietin.

Although EPO that is produced in an autocrine–paracrine manner has been implicated in tissue protective effects in the brain, spinal cord, retina, and heart, similar protective roles in severe illnesses have not been directly evaluated. Notably, published clinical trials have focused on erythrocyte production and thus were not designed to assess potential benefits of rhEPO on survival or recovery unrelated to treatment of anemia. A number of preclinical models that mimick aspects of multiple organ dysfunction syndrome (e.g. splanchnic artery occlusion induced shock [7], ischemic renal damage [8], and intestinal injury [9]) are ameliorated by rhEPO, suggesting other potential roles for rhEPO in critical illness. In this article, we review probable contributions of the nonclassical EPO system to physiologic conditions associated with severe illness. We conclude by outlining several essential parameters to be considered when designing clinical trials to evaluate potential tissue protection by EPO in critical illness.

What evidence exists for tissue protection conferred by erythropoietin?

EPO is a tissue protective cytokine that mediates local (innate) stress responses [10–12]. The innate stress response system evolved to counteract invasion by infectious agents. In this biologic adaptation, a nidus of infection is rapidly populated by macrophages that secrete inflammatory cytokines, which in turn both trigger apoptosis and recruit additional macrophages. The net result of this apoptotic feedback loop is an amplification of injury involving 'innocent bystander' cells, sterilizing the region surrounding the pathogen. Although this approach is efficient for microbes, an identical response is activated by other insults (e.g. metabolic stress). In this case, the innate stress response is maladaptive because viable tissue is irreversibly injured.

Multiple organs and tissues express EPO and its receptor (EPOR), implicating both in the local stress response system [13–20]. The tissue response to stress is characterized by an increase in EPO and EPOR within the penumbra of injury (i.e. the region at risk for cell death). In cerebral ischemia, for example, a rapid and marked upregulation of EPOR occurs, followed only later by an increase in local EPO production [10–12]. These two processes prevent the spread of injury by neutralizing the apoptotic program initiated by exposure to proinflammatory cytokines such as tumor necrosis factor-α and interleukin-1, among others [21]. Therefore, when using exogenous EPO as a tissue protective cytokine, it is crucial to administer it early in order to activate existing EPORs expressed by viable cells within the penumbra, thus abrogating apoptosis.

Many preclinical data support the concept of early rhEPO administration for tissue protection. First, the powerful mechanism of ischemic preconditioning (increased tissue protection by a brief pre-exposure to nontoxic stressors) depends on EPO upregulation within the affected tissues [11,22–24]. Preconditioning occurs following exposure to a wide variety of stressors in addition to hypoxia and ischemia, including lipopolysaccharide, seizures, and exposure to excitotoxins. Second, many tissues injured by ischemia, mechanical trauma, excitotoxins, and other stressors are significantly improved by administration of rhEPO following injury (reviewed by Erbayraktar and coworkers [25] and by Beumi and coworkers [26]) in multiple species, including humans [27]. Third, rhEPO has been associated with improved residual tissue function (e.g. following myocardial infarction in rats [28]). Notably, a few clinical trials have been conducted using rhEPO in chronic or subacute conditions, and these demonstrated improved clinical status after rhEPO administration. For example, the effects of rhEPO administration to patients experiencing severe congestive heart failure include a significant improvement in exercise tolerance, as well as reduced need for hospitalization and diuretics [29–32]. However, these studies were not designed to assess the effects of rhEPO independent of increased hemoglobin concentrations. This distinction is important because preclinical studies conducted in experimental models [17,33–35] have shown direct (i.e. without increases in serum hemoblogin) beneficial effects of rhEPO on myocardium, including improved remodeling following ischemic injury.

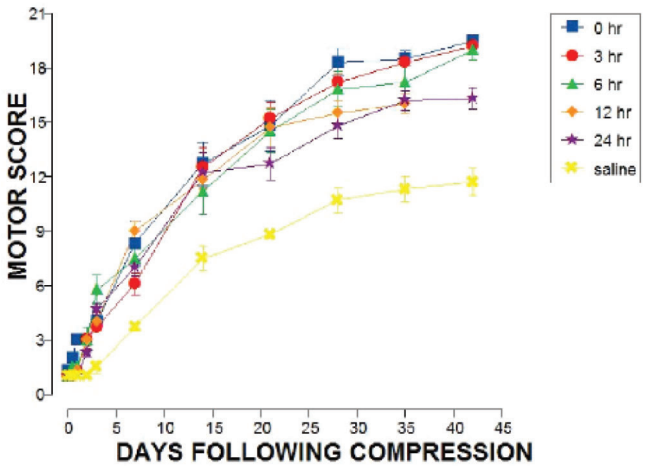
Relevance of a 'therapeutic window'

As stated above, the principle mechanism whereby EPO confers tissue protection involves the modulation of cellular apoptosis within the penumbra (region at risk). Because apoptosis is an active genetic expression program, a significant time window exists within which it can be terminated. Briefly, agents that can prevent apoptosis can be effective long after the injury has occurred. This phenomenon was corroborated by EPO tissue protective studies. One impressive example is the spinal cord, in which waves of apoptosis occur for days after a mechanical injury has been sustained [36]. Notably, rhEPO administered even 24 hours after injury is very effective in ameliorating injury (Fig. 1). In contrast, ischemic experimental brain injury is condensed in its response, and so the window of opportunity is only about 3–4 hours [37]. In addition to modulating apoptosis, EPO maintains the integrity of capillary function (e.g. the blood–brain barrier [38]). Therefore, the potential contributions of the size of the therapeutic window must be considered based on available preclinical data.

Rational design of clinical trials of recombinant human erythropoietin in critical illness

The presence of a therapeutic window dictates specific time constraints for efficacious administration of exogenous EPO as a tissue protectant. It is noteworthy that, in the larger clinical studies of critical illness conducted to date, administration of rhEPO was not initiated until 3 days after admission to the intensive care unit [4,5]. This delay in rhEPO

Figure 1



Protection by recombinant human erythropoietin (rhEPO) of compressive spinal cord injury in the rat. rhEPO ameliorates spinal cord injury with a wide therapeutic window. Spinal cord injury was initiated in rats (six per group) by application of an aneurysm clip for 1 min, as previously described [25]. Saline or rhEPO was administered once at the indicated times (1000 U/kg body weight intravenously) following injury. Animals were serially evaluated for motor function; a score of 0 is paraplegic and 21 is normal.

administration, which is even longer considering the time of onset of illness, cannot reasonably be expected to provide elevated rhEPO levels within the therapeutic window specific to an organ or tissue.

Because critical illness is so heterogeneous, selection of patients and illness is of utmost importance. As summarized above, rhEPO has been shown to be particularly effective in conditions in which apoptosis plays a major etiologic role. Ischemic injury to nervous tissue, the heart, and the kidney is attenuated following administration of rhEPO within hours, but not days, of the insult. For example, available preclinical data of experimental stroke suggest that EPO is much less effective if it is administered later than 6 hours after the insult [37]. Therefore, studies concerning rhEPO administration in the setting of critical illness should begin before or immediately after admission to the intensive care unit, with an enrolment cutoff time of perhaps 5 hours.

Importance of peak serum levels

The serum concentrations of EPO required for tissue protection are higher than those required for erythropoiesis. One reason for this is that the receptor for tissue protection exhibits a lower affinity (approximately 1000-fold) as compared with erythroid progenitors [39]. Another reason may be the presence of blood–tissue barriers such as for the brain and spinal cord. Preclinical data suggest that the minimum therapeutic level needed for protection against tissue injury appears to be in the order of 300–500 mIU/kg body weight (intravenously or intraperitoneally) for the organs that have thus far been adequately investigated [37,40]. The successful phase II clinical trial in stroke [27] employed a dose within this range. This requirement means that, from a practical perspective, only intravenous dosing routes should be contemplated for clinical studies.

Potential hazards of high dose recombinant human erythropoietin administration?

A number of documented and theoretical problems have been associated with administration of high dose rhEPO. Most notably, rhEPO interacts with thrombocyte production and activates endothelial cells to augment platelet aggregation, increasing the likelihood of microinfarctions and macro-infarctions [41,42]. In confirmation of this, several recent clinical trials in which rhEPO was administered to cancer patients were terminated following increased symptomatic or fatal thrombosis in patients receiving the drug [43–46]. Additionally, cancer patients who receive chemotherapy administered via catheters may have an especially markedly increased risk for thrombosis [47]. The relevance of this phenomenon to critically ill patients who may receive limited dosing has not been determined, but it may be important for certain high risk patients. However, limited available data suggest that dosing in acute settings is not likely to be detrimental [27].

Additionally, many tumors express EPOR [48,49], and several large clinical trials have clearly shown adverse outcomes following administration of EPO to cancer patients [44,46]. The potential hazard of acute dosing of EPO to critically ill patients not known to have a tumor burden is probably exceedingly minor, considering the potential benefits of treating a life-threatening disease.

Conclusion

Preclinical experience strongly suggests that rhEPO will confer significant tissue protection in the setting of critical illness. Appropriate clinical trials will require administration of these agents within a reasonable period of time, coincident with the therapeutic window that is characteristic of each organ and tissue considered in the study, and at doses high enough to engage the paracrine–autocrine receptors. The biologic substrate on which EPO acts is a conserved evolutionary adaptation designed to preserve the organism at the expense of the local tissue beds, which EPO antagonizes. It is important to realize that the vast therapeutic armamentarium available to modern medicine reduces significantly the protective role of the innate stress response. In this setting, salvage of tissue that is otherwise normal but has been injured by the host specific innate stress response can probably be achieved by administering tissue protective cytokines such as rhEPO. Only properly structured clinical trials can answer these questions. However, based on much preclinical data and limited human studies, it is clear that tissue protective cytokines are highly promising agents that may provide new therapeutic options in many forms of tissue injury.

Competing interests

The authors declare that they have no competing interests.

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References

1. Erbayraktar S, Yilmaz O, Gokmen N, Brines M: **Erythropoietin is a multifunctional tissue-protective cytokine.** *Curr Hematol Rep* 2003, **2:**465-470.
2. Hobisch-Hagen P, Wiedermann F, Mayr A, Fries D, Jelkmann W, Fuchs D, Hasibeder W, Mutz N, Klingler A, Schobersberger W: **Blunted erythropoietic response to anemia in multiply traumatized patients.** *Crit Care Med* 2001, **29:**743-747.
3. Elliot JM, Virankabutra T, Jones S, Tanudsintum S, Lipkin G, Todd S, Bion J: **Erythropoietin mimics the acute phase response in critical illness.** *Crit Care* 2003, **7:**R35-R40.
4. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Shapiro MJ, Corwin MJ, Colton T: **Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial.** *JAMA* 2002, **288:**2827-2835.
5. Corwin HL, Gettinger A, Rodriguez RM, Pearl RG, Gubler KD, Enny C, Colton T, Corwin MJ: **Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized, double-blind, placebo-controlled trial.** *Crit Care Med* 1999, **27:** 2346-2350.
6. van Iperen CE, Gaillard CA, Kraaijenhagen RJ, Braam BG, Marx JJ, van de Wiel A: **Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in intensive care unit patients.** *Crit Care Med* 2000, **28:**2773-2778.
7. Squadrito F, Altavilla D, Squadrito G, Campo GM, Arlotta M, Quartarone C, Saitta A, Caputi AP: **Recombinant human erythropoietin inhibits iNOS activity and reverts vascular dysfunction in splanchnic artery occlusion shock.** *Br J Pharmacol* 1999, **127:**482-488.
8. Yang CW, Li C, Jung JY, Shin SJ, Choi BS, Lim SW, Sun BK, Kim YS, Kim J, Chang YS, Bang BK: **Preconditioning with erythropoietin protects against subsequent ischemia-reperfusion injury in rat kidney.** *FASEB J* 2003, **17:**1754-1755.
9. Kumral A, Baskin H, Duman N, Yilmaz O, Tatli M, Ozer E, Gokmen N, Genc S, Ozkan H: **Erythropoietin protects against necrotizing enterocolitis of newborn rats by the inhibiting nitric oxide formation.** *Biol Neonate* 2003, **84:**325-329.
10. Bernaudin M, Marti HH, Roussel S, Divoux D, Nouvelot A, MacKenzie ET, Petit E: **A potential role for erythropoietin in focal permanent cerebral ischemia in mice.** *J Cereb Blood Flow Metab* 1999, **19:**643-651.
11. Bernaudin M, Nedelec AS, Divoux D, MacKenzie ET, Petit E, Schumann-Bard P: **Normobaric hypoxia induces tolerance to focal permanent cerebral ischemia in association with an increased expression of hypoxia- inducible factor-1 and its target genes, erythropoietin and VEGF, in the adult mouse brain.** *J Cereb Blood Flow Metab* 2002, **22:**393-403.
12. Siren AL, Knerlich F, Poser W, Gleiter CH, Bruck W, Ehrenreich H: **Erythropoietin and erythropoietin receptor in human ischemic/hypoxic brain.** *Acta Neuropathol (Berl)* 2001, **101:** 271-276.
13. Anagnostou A, Liu Z, Steiner M, Chin K, Lee ES, Kessimian N, Noguchi CT: **Erythropoietin receptor mRNA expression in human endothelial cells.** *Proc Natl Acad Sci USA* 1994, **91:** 3974-3978.
14. Foresta C, Mioni R, Bordon P, Miotto D, Montini G, Varotto A: **Erythropoietin stimulates testosterone production in man.** *J Clin Endocrinol Metab* 1994, **78:**753-756.
15. Morishita E, Masuda S, Nagao M, Yasuda Y, Sasaki R: **Erythropoietin receptor is expressed in rat hippocampal and cerebral cortical neurons, and erythropoietin prevents in vitro glutamate-induced neuronal death.** *Neuroscience* 1997, **76**:105-116.
16. Nagai A, Nakagawa E, Choi HB, Hatori K, Kobayashi S, Kim SU: **Erythropoietin and erythropoietin receptors in human CNS neurons, astrocytes, microglia, and oligodendrocytes grown in culture.** *J Neuropathol Exp Neurol* 2001, **60:**386-392.
17. Tramontano AF, Muniyappa R, Black AD, Blendea MC, Cohen I, Deng L, Sowers JR, Cutaia MV, El-Sherif N: **Erythropoietin protects cardiac myocytes from hypoxia-induced apoptosis through an Akt-dependent pathway.** *Biochem Biophys Res Commun* 2003, **308:**990-994.
18. Wald MR, Borda ES, Sterin-Borda L: **Mitogenic effect of erythropoietin on neonatal rat cardiomyocytes: signal transduction pathways.** *J Cell Physiol* 1996, **167:**461-468.
19. Okada A, Kinoshita Y, Maekawa T, Hassan MS, Kawanami C, Asahara M, Matsushima Y, Kishi K, Nakata H, Naribayashi Y, Chiba T: **Erythropoietin stimulates proliferation of rat-cultured gastric mucosal cells.** *Digestion* 1996, **57:**328-332.
20. Yasuda Y, Masuda S, Chikuma M, Inoue K, Nagao M, Sasaki R: **Estrogen-dependent production of erythropoietin in uterus and its implication in uterine angiogenesis.** *J Biol Chem* 1998, **273:**25381-25387.
21. Villa P, Bigini P, Mennini T, Agnello D, Laragione T, Cagnotto A, Viviani B, Marinovich M, Cerami A, Coleman TR, Brines M, Ghezzi P: **Erythropoietin selectively attenuates cytokine production and inflammation in cerebral ischemia by targeting neuronal apoptosis.** *J Exp Med* 2003, **198:**971-975.
22. Ruscher K, Freyer D, Karsch M, Isaev N, Megow D, Sawitzki B, Priller J, Dirnagl U, Meisel A: **Erythropoietin is a paracrine mediator of ischemic tolerance in the brain: evidence from an in vitro model.** *J Neurosci* 2002, **22:**10291-10301.
23. Grimm C, Wenzel A, Groszer M, Mayser H, Seeliger M, Samardzija M, Bauer C, Gassmann M, Reme CE: **HIF-1-induced erythropoietin in the hypoxic retina protects against light-induced retinal degeneration.** *Nat Med* 2002, **8:**718-724.
24. Prass K, Scharff A, Ruscher K, Lowl D, Muselmann C, Victorov I, Kapinya K, Dirnagl U, Meisel A: **Hypoxia-induced stroke tolerance in the mouse is mediated by erythropoietin.** *Stroke* 2003, **34:**1981-1986.
25. Erbayraktar S, Grasso G, Sfacteria A, Xie QW, Coleman T, Kreilgaard M, Torup L, Sager T, Erbayraktar Z, Gokmen N, Yilmaz O, Ghezzi P, Villa P, Fratelli M, Casagrande S, Leist M, Helboe L, Gerwein J, Christensen S, Geist MA, Pedersen LO, Cerami-Hand C, Wuerth JP, Cerami A, Brines M: **Asialoerythropoietin is a nonerythropoietic cytokine with broad neuroprotective activity in vivo.** *Proc Natl Acad Sci USA* 2003, **100:**6741-6746.
26. Buemi M, Vaccaro M, Sturiale A, Galeano MR, Sansotta C, Cavallari V, Floccari F, D'Amico D, Torre V, Calapai G, Frisina N, Guarneri F, Vermiglio G: **Recombinant human erythropoietin influences revascularization and healing in a rat model of random ischaemic flaps.** *Acta Derm Venereol* 2002, **82**:411-417.
27. Ehrenreich H, Hasselblatt M, Dembowski C, Cepek L, Lewczuk P, Stiefel M, Rustenbeck HH, Breiter N, Jacob S, Knerlich F, Bohn M, Poser W, Ruther E, Kochen M, Gefeller O, Gleiter C, Wessel TC, De Ryck M, Itri L, Prange H, Cerami A, Brines M, Siren AL: **Erythropoietin therapy for acute stroke is both safe and beneficial.** *Mol Med* 2002, **8:**494-505.
28. Calvillo L, Latini R, Kajstura J, Leri A, Anversa P, Ghezzi P, Salio M, Cerami A, Brines M: **Recombinant human erythropoietin protects the myocardium from ischemia-reperfusion injury and promotes beneficial remodeling.** *Proc Natl Acad Sci USA* 2003, **100:**4802-4806.
29. Silverberg DS, Wexler D, Blum M, Schwartz D, Keren G, Sheps D, Iaina A: **Effect of correction of anemia with erythropoietin and intravenous iron in resistant heart failure in octogenarians.** *Isr Med Assoc J* 2003, **5:**337-339.
30. Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS: **Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure.** *Circulation* 2003, **107:**294-299.
31. Silverberg DS, Wexler D, Iaina A: **The importance of anemia and its correction in the management of severe congestive heart failure.** *Eur J Heart Fail* 2002, **4:**681-686.
32. Silverberg DS, Wexler D, Blum M, Tchebiner J, Sheps D, Keren G, Schwartz D, Baruch R, Yachnin T, Shaked M, Zubkov A, Steinbruch S, Iaina A: **The correction of anemia in severe resistant heart failure with erythropoietin and intravenous iron prevents the progression of both the heart and the renal failure and markedly reduces hospitalization.** *Clin Nephrol* 2002, **Suppl 1:** S37-S45.
33. Cai Z, Manalo DJ, Wei G, Rodriguez ER, Fox-Talbot K, Lu H, Zweier JL, Semenza GL: **Hearts from rodents exposed to inter-**

mittent hypoxia or erythropoietin are protected against ischemia-reperfusion injury. *Circulation* 2003, **108:**79-85.
34. Moon C, Krawczyk M, Ahn D, Ahmet I, Paik D, Lakatta EG, Talan MI: **Erythropoietin reduces myocardial infarction and left ventricular functional decline after coronary artery ligation in rats.** *Proc Natl Acad Sci USA* 2003, **100:**11612-11617.
35. Parsa CJ, Matsumoto A, Kim J, Riel RU, Pascal LS, Walton GB, Thompson RB, Petrofski JA, Annex BH, Stamler JS, Koch WJ: **A novel protective effect of erythropoietin in the infarcted heart.** *J Clin Invest* 2003, **112:**999-1007.
36. Liu XZ, Xu XM, Hu R, Du C, Zhang SX, McDonald JW, Dong HX, Wu YJ, Fan GS, Jacquin MF, Hsu CY, Choi DW: **Neuronal and glial apoptosis after traumatic spinal cord injury.** *J Neurosci* 1997, **17:**5395-5406.
37. Brines ML, Ghezzi P, Keenan S, Agnello D, de Lanerolle NC, Cerami C, Itri LM, Cerami A: **Erythropoietin crosses the blood-brain barrier to protect against experimental brain injury.** *Proc Natl Acad Sci USA* 2000, **97:**10526-10531.
38. Martinez-Estrada OM, Rodriguez-Millan E, Gonzalez-De Vicente E, Reina M, Vilaro S, Fabre M: **Erythropoietin protects the in vitro blood-brain barrier against VEGF-induced permeability.** *Eur J Neurosci* 2003, **18:**2538-2544.
39. Masuda S, Nagao M, Takahata K, Konishi Y, Gallyas F, Jr., Tabira T, Sasaki R: **Functional erythropoietin receptor of the cells with neural characteristics. Comparison with receptor properties of erythroid cells.** *J Biol Chem* 1993, **268:**11208-11216.
40. Agnello D, Bigini P, Villa P, Mennini T, Cerami A, Brines M, Ghezzi P: **Erythropoietin exerts an anti-inflammatory effect on the CNS in a model of experimental autoimmune encephalomyelitis.** *Brain Res* 2002, **952:**128.
41. Aguilera A, Selgas R, Ruiz-Caravaca ML, Bajo MA, Cuesta MV, Plaza MA, Hernanz A: **Effects of recombinant human erythropoietin on functional and injury endothelial markers in peritoneal dialysis patients.** *Perit Dial Int* 1999, **Suppl 2:** S161-S166.
42. Wolf RF, Gilmore LS, Friese P, Downs T, Burstein SA, Dale GL: **Erythropoietin potentiates thrombus development in a canine arterio-venous shunt model.** *Thromb Haemost* 1997, **77:**1020-1024.
43. Wun T, Law L, Harvey D, Sieracki B, Scudder SA, Ryu JK: **Increased incidence of symptomatic venous thrombosis in patients with cervical carcinoma treated with concurrent chemotherapy, radiation, and erythropoietin.** *Cancer* 2003, **98:** 1514-1520.
44. Leyland-Jones B: **Breast cancer trial with erythropoietin terminated unexpectedly.** *Lancet Oncol* 2003, **4:**459-460.
45. Brower V: **Erythropoietin may impair, not improve, cancer survival.** *Nat Med* 2003, **9:**1439.
46. Henke M, Laszig R, Rube C, Schafer U, Haase KD, Schilcher B, Mose S, Beer KT, Burger U, Dougherty C, Frommhold H: **Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial.** *Lancet* 2003, **362:**1255-1260.
47. Steurer M, Sudmeier I, Stauder R, Gastl G: **Thromboembolic events in patients with myelodysplastic syndrome receiving thalidomide in combination with darbepoietin-alpha.** *Br J Haematol* 2003, **121:**101-103.
48. Batra S, Perelman N, Luck LR, Shimada H, Malik P: **Pediatric tumor cells express erythropoietin and a functional erythropoietin receptor that promotes angiogenesis and tumor cell survival.** *Lab Invest* 2003, **83:**1477-1487.
49. Acs G, Acs P, Beckwith SM, Pitts RL, Clements E, Wong K, Verma A: **Erythropoietin and erythropoietin receptor expression in human cancer.** *Cancer Res* 2001, **61:**3561-3565.