

* CHAPTER 9

Treatment with erythropoiesis stimulating agents

Nicole Casadevall

1. Introduction

The glycoprotein hormone erythropoietin (Epo) is the major regulator of erythropoiesis. The kidneys are the main sites for the production of Epo in adults humans and Epo is produced with an inverse relation to oxygen availability (1). The hormonal regulation of erythropoiesis has been recognised for several decades (2). However the modern era of Epo began in 1977 with the successful purification of small amounts of human Epo from the urine of patients with aplastic anaemia (3). Based on limited peptide sequence information of this purified material, the gene for human Epo was cloned in 1983 (4, 5).

Subsequently the use of genetic engineering technology allowed the large-scale production of recombinant human Epo (rHuEpo) in mammalian cells (Chinese Hamster Ovary cell line (CHO)). The first clinical indication for this product was the treatment of the anaemia of chronic kidney disease (6, 7). The clinical success of this product is obvious and rHuEpo is now used in millions of patients worldwide both with renal but also non-renal anaemia.

Because of the short half-life of plasma rHuEpo, patients require two or three injections a week. Thus there was a clinical need for longer acting erythropoiesis stimulating agents (ESAs). Moreover, patents are expiring, knowledge about the cellular action of Epo is increasing and huge progress in drug development has prompted several new approaches for the development of new ESAs.

2. Types of erythropoiesis stimulating agents

2.1 Protein based ESA therapy

2.1.1 Epoetin

The original rHuEpos (epoetin alfa and epoetin beta) have now been used for about 20 years. The two products are synthesised in CHO cells transfected with the human *EPO* gene. The amino-acid sequence of both proteins is identical; the major difference between these two products is their glycosylation pattern. Other epoetins with the same amino-acid sequence have been developed: epoetin omega, epoetin delta and other biosimilars of epoetin alfa (8). The first biosimilar of epoetin alfa received marketing authorisation in 2007 from the European Commission after positive advice by the European Medicines Agency (EMA). This first biosimilar is marketed by three different companies under 3 different names but it is in fact the same product from the same manufacturer. Epoetin zeta, which is another biosimilar of epoetin alfa, was registered in Europe in 2008.

Epoetin delta (9) is a new recombinant Epo synthesised in a human fibrosarcoma

cell line in which the native human *EPO* gene is activated by Cytomegalovirus promoter. This product was approved by EMEA in 2002, and was launched in Germany and Europe in 2007, but recently the company announced that for economic reasons it would no longer be marketing the drug.

2.1.2 Long-lasting ESAs

The development of long lasting ESAs responded to a clinical need for a product with the same biological properties as epoetins but requiring less frequent dosing. The observation that a high number of sialic acid residues resulted in a longer circulating half life (10) led to the development by AMGEN laboratories of darbepoetin alfa: using site- directed mutagenesis five amino-acid substitutions were implemented, allowing darbepoetin alfa to carry a maximum of 22 sialic acid residues compared with a maximum of 14 with epoetins. These modifications confer a greater stability *in vivo* and the half-life in man after a single intravenous injection of darbepoetin alfa is about three-fold longer (25.2 h) compared with epoetin alfa (8.5 h) (11). This characteristic allows less frequent dosing with most patients receiving injections once weekly or once every other week, with the possibility in some patients of once monthly dosing.

Another strategy was used by ROCHE Laboratories to create CERA (Continuous Erythropoietin Receptor Activator): a 30 kDa polymer chain of methoxy-polyethyleneglycol was integrated into the Epo molecule. The half-life is considerably increased to about 130 hours in human (12). CERA can be administered every 3/4 weeks, which is very convenient for patients with chronic kidney disease not yet in dialysis and also for patients with cancer receiving chemotherapy. This product recently received a license in both US and Europe, but is not marketed in the US. As with darbepoetin alfa, the binding affinity for the Epo receptor is less than for rHuEpo, but the benefits of the greater half-life *in vivo* outweigh this biological disadvantage.

2.1.3 Other Epo derivatives

Several other Epo derivatives have been designed and are in preclinical or clinical trials (13). These include SEP, for Synthetic Erythropoiesis Protein, a 51 kDa polymer of Epo which has a longer half-life than rHuEpo. Another large Epo fusion protein of 76 kDa has also been designed from cDNA encoding two human Epo molecules linked by small flexible polypeptides.

All these products stimulate erythropoiesis through activation of the Epo receptor and, like darbepoetin or CERA, they are given by the intravenous (IV) or subcutaneous (SC) route.

Interestingly, an Fc-Epo fusion protein has been successfully administered in a Phase I trial as an aerosol with an increase in serum Epo levels, associated with an increase

in reticulocyte counts. Other delivery systems have been investigated including ultrasound mediated transdermal uptake, liposomes given orally (tested in rats and dogs), or mucoadhesive tablets containing Epo.

It is still too early to say whether these strategies could have any clinical relevance in the treatment of anaemia in man.

2.1.4 Small molecule ESAs

Twelve years ago, small peptides of around 20 amino acids, unrelated in sequence to Epo, were identified by random phage display technology (14). These small peptides are able to bind to the Epo receptor and to induce JAK2/STAT5 signaling. The potency of these peptides has been greatly enhanced by dimerisation with a PEG linker. This led to the development of Hematide by Affymax. A phase I study (15) showed that IV or SC injections of this product induced a dose dependent increase in reticulocytes. Phase II studies demonstrated that Hematide can correct the anaemia of CKD patients. Interestingly antibodies against erythropoietin do not cross-react with Hematide, so patients with antibody-mediated pure red cell aplasia should be able to respond to Hematide. A clinical trial examining this issue is currently in progress.

Protein-based therapies have some disadvantages, notably immunogenicity. This has been illustrated by a recent upsurge of cases of pure red cell aplasia in patients who developed neutralising antibodies against rHuEpo which are cross-reactive with native erythropoietin (16). All these protein-based products require accurate storage and handling conditions particularly because of putative loss of stability and aggregation. All currently licensed products are parenteral, being administered by intravenous or subcutaneous route, and the development of orally active ESAs should be a great improvement in the treatment of anaemia. Various strategies are currently developed to circumvent the disadvantages of the available products.

2.2 Other strategies for stimulating erythropoiesis

All the currently available ESAs act after binding to the Epo receptor. A new approach to the treatment of anaemia has been opened up by the development of stimulators of endogenous Epo production. Epo expression is under the control of several transcription factors: the Epo enhancer is activated by Hypoxia Inducible Factor 2 (HIF-2) and the Epo promoter is suppressed by GATA-2 and NF- κ B.

The dimeric transcription factor HIF-2 is inactive in normoxia because of prolyl and asparaginyl hydroxylation and subsequent degradation in the proteasome. The HIF hydroxylases require different cofactors, including 2-oxoglutarate. Analogues of 2-oxoglutarate named "HIF stabilisers" prevent the degradation of HIF and consequently

stimulate Epo production (13). One product FG-22-16 (Fibrogen) has already been administered in healthy volunteers and to anaemic patients. A great advantage is that this agent is orally active. However one has to be aware that HIF stabilisers induce the expression of a great number of other genes such as, for example, vascular endothelial growth factor (VEGF), which may cause unwanted effects.

During one phase II trial a female patient developed fatal hepatic necrosis and all the clinical trial with HIF stabilisers have currently been suspended during investigations regarding causality.

Several GATA inhibitors are under investigation including a second-generation compound, K-11706. They are non peptidic compounds, and they are administered orally. They enhance Epo production both *in vitro* and *in vivo* in a mouse model, but clinical trials have not yet been started.

3. Clinical applications

ESAs are certainly among the most successful therapeutic agents developed through molecular genetic technology.

Their first indication was the treatment of patients with the anaemia of chronic kidney disease (CKD), which is mainly due to inappropriately low erythropoietin production. ESAs have also proven to be effective in other types of anaemias with more complex pathophysiology, particularly the anaemia of cancer. Other recognised or putative indications for ESAs are listed in [Table 1](#), some of them being registered by pharmaceutical agencies.

Table 1: Therapeutic indications for ESA

Chronic kidney disease*
Cancer*
Myelodysplastic syndrome
Autologous blood donation*
Surgery*
Prematurity*
Chronic inflammatory disease
Intensive care
Haematopoietic stem cell transplantation

* registered indications in Europe

3.1 Anaemia of CKD

The anaemia of CKD is the pure example of an Epo deficient state. More than 95% of CKD patients will respond to ESA therapy. ESA therapy increases haemoglobin level,

decreases transfusion needs and improves quality of life. All types of ESAs are beneficial in CKD patients, but the long lasting ESA have the advantage of requiring less frequent administration. In CKD patients, cardiovascular disease risk is increased. Observational studies suggest that ESA treatment decreases cardiovascular risks, however this has never been proven by interventional clinical studies.

The target haemoglobin has been a matter of debate since the first use of ESAs in this indication. The target haemoglobin concentrations have been set at 11-12 g/dL by the European and US recommendations. Two recent clinical trials (17, 18) support this recommendation showing that raising haemoglobin levels to 13.5 g/dL increased severe cardiovascular events (17) or was associated with an increase in arterial blood pressure and a trend toward more cardiovascular events (18).

Five to 10% of CKD patients are resistant or hypo-responsive to ESA treatment. Multiple causes of hypo-responsiveness have been identified, but the most important ones are iron deficiency, infection and inflammation.

Iron deficiency is one of the major factors affecting response to Epo therapy. It can be absolute iron deficiency or "functional iron deficiency" where iron-deficient erythropoiesis may occur even if iron stores are normal or elevated. It is the consequence of an imbalance between iron needs, increased by ESA stimulated erythropoiesis, and iron supply by macrophages that are not able to mobilise iron sufficiently rapidly.

The experience in CKD patients has clearly indicated that oral iron supplementation is not effective and that IV iron improves response to ESAs.

ESAs are well tolerated in CKD patients with rarely a transient increase in blood pressure which is usually responsive to antihypertensive medication. Thrombotic events are not significantly different from the expected incidence in dialysis patients not receiving ESAs.

In 1999–2000 an upsurge of pure red cell aplasia associated with neutralising anti-erythropoietin antibodies was described (16). This complication was mainly associated with the subcutaneous use of one product (epoetin alfa distributed outside the US). This problem seems likely to have been caused by a change in formulation of the product. In 1998 a new buffer (polysorbate 80) replaced human serum albumin and induced the release of organic compounds from the rubber stoppers of prefilled syringes. This complication has now been resolved. There are still very rare cases of anti-erythropoietin antibodies observed only after subcutaneous injections. The incidence is very low, estimated to be around 0.1/10,000 patient/year.

Anti-Epo antibodies have been described only in CKD patients. Interestingly antibody formation has not been described in cancer patients, perhaps because this population is immunosuppressed by chemotherapy or because the duration of treatment with ESA is usually shorter in this indication.

3.2 Cancer-associated anaemia

The anaemia associated with cancer is multifactorial and may be due to cytotoxic chemotherapy, blood loss and iron deficiency, inflammation, and marrow infiltration. More than 80% of cancer patients undergoing chemotherapy develop anaemia. As in inflammatory diseases, the serum Epo concentration is inadequate for the severity of anaemia and there is a diminished response of marrow erythroid progenitors to endogenous Epo. Many randomised studies have shown that ESA therapy can ameliorate the anaemia associated with cancer and chemotherapy and reduce the need for transfusions independently of tumour response. Approximately 60–70% of patients respond to ESA treatment by increasing their haemoglobin level by a defined amount or raising their haemoglobin to 12 g/dL (the haemoglobin level should not exceed 12 g). In addition, ESA treatment improves quality of life in these patients (19).

However approximately 30 to 40% of cancer patients with chemotherapy-related anaemia do not achieve a meaningful response to ESA. Predictive algorithms of response could help to select patients and avoid prolonged ineffective use of this expensive medication. Algorithms combining endogenous Epo production together with early indicators of erythropoietic marrow response have been proposed (20). However most predictive algorithms have not yet been validated in large trials. Recently reports of clinical trials demonstrating that IV iron supplementation increased response to ESAs in patients with evidence of functional iron deficiency, whereas oral iron was not effective (21), were published. These studies confirm the utility of IV iron in oncology and support the notion that IV iron supplementation should be considered as a component of the management of the anaemia of cancer. Moreover the weekly ESA dose requirement was decreased, leading to a reduction in the cost of treatment. A safety concern, often raised when cancer patients are administered parenteral iron, is the possible risk of infections or progression of cancer as a consequence. Such complications have not been reported in the published trials. Larger controlled trials are warranted to confirm these findings.

The use of ESA therapy in non-anaemic patients or off the label is not recommended and may even be deleterious. In 2003, two trials investigating the effects of ESA treatment to raise haemoglobin level above 12 g/dL in cancer patients undergoing radiotherapy (22) or chemotherapy (23) described higher mortality rates and tumour progression in patients receiving ESAs. The results of such studies prompted the US Food and Drug Administration (FDA) to convene an advisory committee to assess the safety of ESAs in patients with cancer. The committee agreed on the need for additional large and randomised trials in patients with several types of tumours. Four other recent studies showed evidence of harm associated with the use of ESAs

in patients with cancer (24). It is important to note that this was mainly in non-approved indications, including in patients who were not anaemic or who were not undergoing chemotherapy. In addition in several of these studies the treatment strategy was to achieve a target haemoglobin higher than the recommended level of 12 g/dL.

In the mean time two meta-analyses showed an increased risk of thromboembolic events (19, 25) and an increased in mortality risk in cancer patients receiving ESAs (25). In March 2007 the FDA mandated the addition of a “black box” warning about the potential risks of ESA treatment.

The American Society of Clinical Oncology/American Society of Haematology have published recommendations on the use of ESAs in cancer patients (26) (Table 2). In Europe the EMEA made key changes in the labelling of ESAs (Table 3). However the EMEA’s Committee for Medicinal products for Human Use (CHMP) and its Pharmaco-vigilance working party (PhVWP) concluded that the “benefits of these products continue to outweigh their risks in the approved indications”.

In November 2008 FDA added warnings for the use of ESAs and recommended using the lowest dose needed to avoid red blood cell transfusions, to use ESAs only for treatment of anaemia due to concomitant myelosuppressive chemotherapy, and they stated that ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.

The mechanisms underlying the increased mortality in some cancer patients remains uncertain. It is possible that certain tumour cells express Epo receptors that stimulate tumour growth when they are activated by ESAs. Some tumours have been reported

Table 2: International Evidence-based Guidelines for the use of ESAs in cancer patients

Recommendation	ASCO/ASH [1]	EORTC [2]
Indication	Symptomatic anaemia with chemotherapy	Symptomatic anaemia with chemotherapy
Initiate ESA therapy	Hb ≤ 10 g/dL (Clinical decision if Hb > 10 to ≤ 12 g/dL)	Hb 9-11 g/dL (Clinical decision if Hb ≤ 11.9 g/dL)
Goal of treatment	Maintain Hb at or near 12 g/dL	Target Hb should be 11-13 g/dL

1. Rizzo JD, et al. *J Clin Oncol* 2008; 26: 132-149.

2. EORTC Guidelines. *Erythropoiesis-stimulating agents – ESAs: The 2007 position of the EORTC Working Party*. Brussels: EORTC, 2007.

(http://www.cancerworld.org/CancerWorld/eventDetail.aspx?id_sito=1&id_stato=1&id=1975).

Table 3: EU Label Update: Key Changes

	Before February 2008	From February 2008
Therapeutic indication	Treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy	
Start Hb	< 11 g/dL	< 10 g/dL
Target range	Not specified	10-12 g/dL
Do not exceed	13 g/dL	12 g/dL
Dose withholding	Withhold dose if Hb > 13 g/dL	Withhold dose if Hb > 13 g/dL
Dose adjustment *	Dose reduce to maintain Hb	* Dose reduce to ensure that the lowest approved dose is used to maintain Hb at a level that controls the symptoms of anaemia

* Reduce dose Hb \geq 12 g/dL, Withhold dose Hb \geq 13 g/dL, Reinitiate at reduced dose Hb \leq 12 g/dL.

to express Epo receptors, but the role, if any, of such receptors in tumour growth is unclear and is a controversially debated issue (27). The quality of the reagents used to detect Epo receptors must be considered in interpreting these data (28). Ongoing studies will help to clarify the role of Epo receptors in the cancer setting and the use of more specific tools, particularly true anti-receptor antibodies will be crucial.

3.3 Anaemia in MDS

There is evidence that supports the use of ESAs in patients with anaemia associated with low and intermediate-1 risk myelodysplasia (MDS) (see Chapter 4 for definition of risk groups). These patients may be treated with ESAs alone or in combination with low dose G-CSF. When G-CSF is added to ESA, response rates of around 40–60% can be achieved (29).

A predictive model of response based on serum Epo levels and transfusion requirements has been proposed.

Amelioration of anaemia in patients with MDS may improve quality of life in responding patients and can obviate the need for transfusions. Perhaps of greater importance, emerging evidence indicates that sustained amelioration of anaemia may have an impact on the natural history of the disease; interestingly the French group for MDS (GFM) in a recent publication (30) reported a better survival in MDS patients responding to ESA treatment. It is however unclear if these effects relate to a direct effect of ESA treatment on the natural history of MDS or if non-responding patients possess a more aggressive disease biology.

3.4 Other clinical effects of Epo

Besides its erythropoietic effects, there is accumulating evidence that Epo possesses a large range of non-erythropoietic, pleiotropic cytoprotective effects. There are examples of tissue protection in the nervous system, the kidney, and the myocardium. These pleiotropic effects open a large area of research and must encourage physicians to investigate new potential indications for ESA treatment.

References

1. Jelkmann W. Erythropoietin: Structure, control of production, and function. *Physiol Rev* 1992; 72: 449-489.
2. Carnot P, Deflandre C. Sur l'activité hémopoïétique du sérum au cours de la régénération du sang. *CR Acad Sci Paris* 1906; 143: 384-386.
3. Miyake T, Kung CK, Goldwasser E. Purification of human erythropoietin. *J Biol Chem* 1977; 252: 5558-5564.
4. Jacobs K, Shoemaker C, Rudersdorf R, et al. Isolation and characterization of genomic and cDNA clones of human erythropoietin. *Nature* 1985; 313: 806-810.
5. Lin FK, Suggs S, Lin CH, et al. Cloning and expression of the human erythropoietin gene. *Proc Natl Acad Sci USA* 1985; 82: 7580-7584.
6. Winearls CG, Oliver DO, Pippard MJ, et al. Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. *Lancet* 1986; ii: 1175-1178.
7. Eschbach JW, Egrie JC, Downing MR, et al. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N Engl J Med* 1987; 316: 73-78.
8. Schellekens H. The first biosimilar epoetin: But how similar is it? *Clin J Am Soc Nephrol* 2008; 3: 174-178.
9. Martin KJ; Epoetin Delta 3001 Study Group. Epoetin delta in the management of renal anaemia: Results of a 6-month study. *Nephrol Dial Transplant* 2007; 22: 3052-3054.
10. Egrie JC, Browne JK. Development and characterization of novel erythropoiesis stimulating protein (NESP). *Br J Cancer* 2001; 84 Suppl 1: 3-10.
11. Macdougall IC, Gray SJ, Elston O, et al. Pharmacokinetics of novel erythropoiesis stimulating protein compared with epoetin alfa in dialysis patients. *J Am Soc Nephrol* 1999; 10: 2392-2395.
12. Haselbeck A, Bailon P, Pahlke W et al. The discovery and characterization of CERA, an innovative agent for the treatment of anemia. *Blood* 2002; 100: 227A (abstr 857).
13. Macdougall IC. Novel erythropoiesis-stimulating agents: A new era in anemia management. *Clin J Am Soc Nephrol* 2008; 3: 200-207.
14. Wrighton NC, Farrell FX, Chang R, et al. Small peptides as potent mimetics of the protein hormone erythropoietin. *Science* 1996; 273: 458-464.
15. Stead RB, Lambert J, Wessels D, et al. Evaluation of the safety and pharmacodynamics of Hematide, a novel erythropoietic agent, in a phase 1, double-blind, placebo-controlled, dose-escalation study in healthy volunteers. *Blood* 2006; 108: 1830-1834.

16. Casadevall N, Nataf J, Viron B, et al. Pure Red-Cell Aplasia and Antierythropoietin Antibodies in Patients Treated with Recombinant Erythropoietin. *N Engl J Med* 2002; 346: 469-475.
17. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; 355: 2085-2098.
18. Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, Burger HU, Scherhag A; CREATE Investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006; 355: 2071-2084.
19. Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: Updated meta-analysis of 57 studies including 9353 patients. *J Natl Cancer Inst* 2006; 98: 708-714.
20. Ludwig H, Fritz E, Leitgeb C, et al. Prediction of response to erythropoietin treatment in chronic anemia of cancer. *Blood* 1994; 84: 1056-1063.
21. Auerbach M. Should intravenous iron be the standard of care in oncology? *J Clin Oncol* 2008; 26: 1579-1581.
22. Henke M, Laszig R, Rube C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: Randomised, double-blind, placebo-controlled trial. *Lancet* 2003; 362: 1255-1260.
23. Leyland-Jones B; BEST Investigators and Study Group. Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet Oncol* 2003; 4: 459-60.
24. Khuri FR. Weighing the hazards of erythropoiesis stimulation in patients with cancer. *N Engl J Med* 2007; 356: 2445-2448.
25. Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *JAMA* 2008; 299: 914-924.
26. Rizzo JD, Somerfield MR, Hagerty KL, Seidenfeld J, Bohlius J, Bennett CL, Cella DF, Djulbegovic B, Goode MJ, Jakubowski AA, Rarick MU, Regan DH, Lichtin AE; American Society of Clinical Oncology; American Society of Hematology. Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update. *J Clin Oncol* 2008; 26: 132-149. Erratum in: *J Clin Oncol* 2008; 26: 1192.
27. Osterborg A, Aapro M, Cornes P, et al. Preclinical studies of erythropoietin receptor expression in tumour cells: Impact on clinical use of erythropoietic proteins to correct cancer-related anaemia. *Eur J Cancer* 2007; 43: 510-519.
28. Sinclair AM, Rogers N, Busse L, et al. Erythropoietin receptor transcription is neither elevated nor predictive of surface expression in human tumour cells. *Br J Cancer* 2008; 98: 1059-1067.
29. Casadevall N, Durieux P, Dubois S, et al. Health, economic, and quality-of-life effects of erythropoietin and granulocyte colony-stimulating factor for the treatment of myelodysplastic syndromes: A randomised, controlled trial. *Blood* 2004; 104: 321-327.
30. Park S, Grabar S, Kelaidi C, Beyne-Rauzy O, Picard F, Bardet V, Coiteux V, Leroux G, Lepelley

P, Daniel MT, Cheze S, Mahé B, Ferrant A, Ravoet C, Escoffre-Barbe M, Adès L, Vey N, Aljasseem L, Stamatoullas A, Mannone L, Dombret H, Bourgeois K, Greenberg P, Fenaux P, Dreyfus F; GFM group (Groupe Francophone des Myélodysplasies). Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: The GFM experience. *Blood* 2008; 111: 574-582.

Multiple Choice Questionnaire

To find the correct answer, go to <http://www.esh.org/iron-handbook2009answers.htm>

1. In adults the main site of production of erythropoietin is:

- a) The liver
- b) The brain
- c) The kidney
- d) The suprarenal gland

2. *In utero* the main site of production of erythropoietin is:

- a) The liver
- b) The brain
- c) The kidney
- d) The suprarenal gland

3. In the treatment of anaemia of CKD by ESAs, the most frequent cause of resistance is:

- a) Infection
- b) Insufficient dialysis intensity
- c) Iron deficiency
- d) Anti-erythropoietin antibodies

4. In the treatment of anaemia of cancer patients by ESAs the average response rate is:

- a) Less than 30%
- b) 30-40%
- c) 40-50%
- d) 50-60%

5. In MDS patients treated with ESAs, the probability of response is greater in which one of the following situations?

- a) High grade MDS
- b) When endogenous Epo level is < 500 U/mL
- c) When transfusion needs are high
- d) When there is multilineage dysplasia

NOTES