

Risk management of ESAs in cancer patients: a role for the hospital pharmacist

Erythropoiesis-stimulating agents (ESAs) have become the standard way of managing chemotherapy-induced anaemia in cancer patients. However, safety concerns have led the European Society for Medical Oncology to recommend guidelines for their use. When used responsibly, the benefits of ESAs outweigh the risks.

Introduction

Over the past decade, there have been remarkable advances in cancer treatment with the development of new therapies and the availability of novel medications. The field of oncology has taken on a multidisciplinary approach combining the latest diagnostic and treatment modalities to reduce the morbidity and mortality associated with cancer. However, the unfortunate side effects of many of these chemotherapeutic cancer regimes have a significant impact on the quality of life of patients and their ability to tolerate full cycles of therapy.

Anaemia, a common complication of many cancers and treatment regimes, causes fatigue, shortness of breath, tachycardia and headache. In addition to quality of life concerns, low haemoglobin concentration has been identified as a negative prognostic factor for overall survival in most types of cancers. While it is known that anaemia is a negative prognostic factor for survival, it is not known whether correcting this anaemia improves prognosis. Anaemia is estimated to be present in up to 40% of patients with non-myeloid malignancies and up to 80% of patients receiving chemotherapy. The incidence varies by cancer type and increases significantly with the amount of treatment cycles [1].

Historically, cancer-related anaemia has been treated with blood transfusions when haemoglobin concentrations dropped below 10 g/dL. This practice fell out of favour when the safety of the blood supply became an issue in the 1980s and most clinicians reserved transfusions for patients with more severe anaemia in the 7–8 g/dL range. With the successful introduction of erythropoiesis-stimulating agents (ESAs) in dialysis patients with

end-stage renal disease, this treatment replaced transfusions and was integrated into cancer treatment regimes. Since then, there has been an estimated 50% reduction in the need for transfusions in patients taking ESAs. Cancer patients have responded well to this therapy with increased haemoglobin levels and improved quality of life measures. ESAs have subsequently become standard treatment for cancer patients to manage the symptoms associated with cancer-related anaemia [2].

However, despite their initial success, evidence over the past five years has raised concerns regarding their safety. Meta-analyses have linked ESAs with an increased risk of venous thrombosis and decreased survival when patients are treated at Hb levels above the recommended guidelines. In addition, clinical studies have been published linking the use of ESAs to tumour progression and survival (for a detailed discussion see [3]). This has led experts to take a close look at their indications and recommend more stringent guidelines for their use.

Guidelines for the use of erythropoiesis-stimulating agents

Despite recent safety concerns, there remain clear indications for the continued use of ESAs in cancer patients. Many of the adverse events were associated with off-label dosing regimes that attempted to achieve haemoglobin levels greater than 12 g/dL or were used in patients with other co-morbid risk factors. Several recently published European and US guidelines support the use of ESAs in chemotherapy-induced anaemia. Differentiating themselves from European standards, some guidelines from the US go as far as to support the use of ESAs in

cancer-induced anaemia. What is clear is when used within label indications and in accordance with the updated guidelines, ESAs continue to have a favourable benefit to risk ratio and a role in the treatment of symptomatic chemotherapy-associated anaemia [4].

As more safety data became available, the guidelines for the use of ESAs have been adjusted to take into account this information. The American Society of Clinical Oncology and the American Society of Hematology have published updated guidelines in 2007 [4]. Treating physicians should be aware of the recent changes and hospital pharmacists can play an important role in the education process. To help guide physicians and pharmacists in Europe, the European Society for Medical Oncology (ESMO) has developed a set of recommendations for the appropriate use of ESAs. These guidelines emphasise the goal of treatment is to maintain a haemoglobin (Hb) level of 12 g/dL and that with proper use, adverse events such as venous thrombosis should rarely be a problem [1].

ESMO differentiates between the treatments of non-myeloid and myeloid malignancies taking into account the increased thrombotic risk of the latter. For any cancer patient with anaemia, it is essential to take a detailed medical history and perform a thorough workup to rule out other causes of anaemia such as occult blood loss, vitamin deficiency and renal insufficiency. If any exacerbating factors are identified, these should be corrected prior to treatment.

According to ESMO, the main goal of treatment is to reduce transfusion requirements and avoid complications such as

The guidelines ratings in brackets are based on the levels of evidence (I–IV) and grades of recommendation (A–D) used by the ESMO as described below [7]

Level	Type of Evidence
I	Evidence is obtained from meta-analysis of multiple, well-designed, controlled studies. Randomised trials with low false-positive and low false-negative errors (high power).
II	Evidence is obtained from at least one well-designed experimental study. Randomised trials with high false-positive and/or negative errors (low power).
III	Evidence is obtained from well-designed, quasi-experimental studies such as non-randomised, controlled single-group, pre-post, cohort, time, or matched case-control series.
IV	Evidence is from well-designed, non-experimental studies such as comparative and correlational descriptive and case studies
V	Evidence from case reports and clinical examples
Grade	Grading of Recommendation
A	There is evidence of type I or consistent findings from multiple studies of types II, III, or IV
B	There is evidence of types II, III, or IV and findings are generally consistent
C	There is evidence of types II, III, or IV but findings are inconsistent
D	There is little or no systematic empirical evidence

iron overload, transfusion-associated infection and immunosuppression related to repeated transfusions. The other major objective is to improve the quality of life of cancer patients by avoiding the common side effects associated with anaemia. Overall, the treatment with ESAs in patients with chemotherapy-induced anaemia increased Hb levels on average 1.63 g/dL compared with controls. ESAs also significantly reduced the relative risk of receiving red blood cell transfusions by 36%, saving blood and reducing associated risks [5].

Since 1996, the UK Serious Hazards of Transfusion (SHOT) scheme has been providing annual reports on transfusion-related adverse events and serves as a model for the haemovigilance schemes that are now being initiated in Europe. The UK SHOT report demonstrates that serious hazards continue to occur despite advances in blood transfusion screening and technology. The most common complications include incorrect or inappropriate blood component transfusion, transfusion-related acute lung injury, transfusion-transmitted infections, acute or haemolytic transfusion reactions and transfusion of anti-D immunoglobulins. From 1996 to 2007, SHOT received more than 4,000

reports of transfusion problems which resulted in 491 cases of death or significant morbidity [6].

ESMO guidelines for symptomatic anaemic patients with non-myeloid malignancies (see box for explanation of rating level and type of evidence) [1]:

- In patients treated with chemotherapy and an Hb concentration of ≤ 10 g/dL, treatment with ESAs might be considered to increase Hb to < 12 g/dL or to prevent a further decline in Hb (I, A).
- In patients treated with chemotherapy and an Hb concentration of 10–12 g/dL, treatment with ESAs could be considered in the case of symptoms or to prevent a further decline in Hb (I, A). However, this is an off-label indication.
- In patients not treated with chemotherapy, there is no indication for the use of ESAs since there might be an increased risk of death when ESAs are administered to a target Hb of 12 g/dL (I, A).
- In patients treated with curative intent, ESAs should be used with caution (D).
- If the Hb increase is at least 1 g/dL above baseline after four weeks of treatment, the dose may remain the same or may be decreased by 25–50%.
- If the Hb increase is < 1 g/dL above base-

line, the dose of selected ESA should be increased (see Table 1). If after an additional four weeks of therapy, the Hb has increased 1 g/dL the dose may remain the same or may be decreased by 25–50%.

- In the case of response, treatment with ESAs should be discontinued four weeks after the end of chemotherapy.
- If the Hb increase is < 1 g/dL above baseline after 8–9 weeks of therapy, response to ESAs therapy is unlikely and treatment should be discontinued.
- If the Hb rises by > 2 g/dL per four weeks or if the Hb exceeds 12 g/dL, the dose should be reduced by 25–50%.
- If the Hb exceeds 12 g/dL, therapy should be discontinued until Hb falls below 12 g/dL and then reinstated at a dose 25% below the previous dose.
- Patients with solid tumours and patients who are on platinum-based chemotherapy seem to benefit more than patients with other tumour types and receiving other tumour therapies (I).
- Continuing ESA treatment beyond 6–8 weeks in the absence of response defined as a rise in Hb concentration of < 1 –2 g/dL or no diminution of transfusion requirement is not beneficial (I, A).
- The Hb concentration should not exceed 12 g/dl (II, B).

ESMO guidelines for symptomatic anaemic patients with myelodysplastic syndromes:

- In patients with low-risk myelodysplastic syndromes based on bone marrow blast percentage, number of cytopenias and cytogenetic analysis, ESAs [+/- granulocyte-colony stimulating factor (G-CSF)] can be used to improve anaemia (off-label indication).
- The low-risk designation is based on set criteria that take into account bone marrow blast percentage, number of cytopenias and cytogenetic analysis.

Safety and tolerability

The influence of ESAs on tumour response and overall survival in anaemic cancer patients remains unclear. Several randomised trials have demonstrated decreased survival times and worse progression-free survival rates. Specifically,

Table 3: Referral guide based on blood clotting

	Epoetin α	Epoetin β	Darbepoetin
Initial treatment	150 IU/kg SC TIW 450 IU/kg SC QW	30,000 SC QW	2.25 μ g/kg SC QW 500 μ g (6.75 μ g/kg) SC Q3W
Dose increase	300 IU/kg SC TIW	60,000 SC QW	Not recommended
Dose reduction	If result achieved: 25–50% If Hb >12 g/dL: 25–50%	If result achieved: 25–50% If Hb >12 g/dL: 25–50%	If result achieved: 25–50% If Hb >12 g/dL: 25–50%
	If Hb rise >12 g/dL/4 weeks: 25–50%	If Hb rise >12 g/dL/4 week: 25–50%	If Hb rise >12 g/dL/4 weeks: 25–50%
Dose withholding	If Hb >13 g/dL until 12 g/dL	If Hb >13 g/dL until 12 g/dL	If Hb >13 g/dL until 12 g/dL
SC: subcutaneous; TIW: thrice weekly; QW: once weekly; Q3W: once every three weeks			

safety concerns regarding increased mortality or tumour progression have been noted in eight ESA studies, which have led to changes in the label of all ESAs in most countries, including the European Union and the US. However, the implications of this data are ambiguous because the studies raising concerns were conducted in off-label settings such as ESA use in patients with Hb levels greater than 12 g/dL or in the absence of chemotherapy. In contrast, adverse effects by ESAs have not been observed in other well-controlled studies in cancer induced anaemia. Meta-analyses in over 8,000 subjects do not indicate a clear negative effect by ESAs on mortality or tumour progression. This lack of a consistency suggests further studies are required to define the safety profile of ESAs when used according to appropriate guidelines and labelled indication.

It is important to note that restrictions on the use of ESAs in chemotherapy-induced anaemia could lead to severe pressure on the current blood supply. In a recent publication, a modelling simulation looked at the packed red blood cell requirement if ESAs were limited or discontinued. The model predicted that up to 15% of the blood supply would be required to cover the demand that would arise from a 25% decrease in ESA use. The impact of limiting ESA usage could even be more significant in periods of high blood demand or low supply. Therefore, the public health consequences of limiting ESA usage could be quite significant, especially for patients with an acute need for blood to correct Hb levels [9].

In regards to safety, ESMO recommends the following guidelines:

- ESAs should not be used in patients with a known hypersensitivity to this class of medication.
- ESAs should be avoided in patients with poorly controlled hypertension (B).
- At this time, it is unclear the effect ESAs has on the liver and should be used with cautions in patients with liver disease (D).
- The relative risk for thromboembolic events is increased by 67% in patients treated with ESAs compared with placebo (I). Their use should be carefully reconsidered in patients with a high risk of thromboembolic events. This includes patients with a history of recent surgery, prolonged immobilisation or previous thrombotic event.
- Patients with multiple myeloma and treated with thalidomide or lenalidomide in combination with doxorubicin and corticosteroids should avoid the use of ESAs (D).
- There are no data on the preventive use of anticoagulants or aspirin.
- Pure red cell aplasia caused by neutralising anti-EPO antibodies has been observed in association with ESAs in patients with chronic renal failure (V). This has not been reported in cancer patients, but remains a concern.
- Other side effects of ESAs are rare allergic reactions including dyspnoea, skin rash, urticaria, arthralgia, peripheral oedema; and mild and transient injection site pain (I).

Biosimilarity

Although biological differences between

products were seen during clinical trials, there were no clinically significant differences identified. The different products all successfully corrected anaemia and maintained the target haemoglobin, but different dosing structures were required.

According to ESMO, there was no significant difference between different ESAs in relation to effectiveness and safety (I). However, since every biological product is different, treating healthcare professionals should exercise caution and analyse the available data prior to interchanging biosimilar products. Pharmacovigilance, as part of a comprehensive European risk management programme, will need to include regular testing for consistent manufacturing of the different drugs. Clinical trials and post-authorisation pharmacovigilance are essential to guarantee the product's safety and efficacy over time. This includes proper documentation of the actual product (brand) administered. Hospital pharmacies are in a favourable position to implement a track-and-trace system, to facilitate the identification of the right product and batch in case a problem occurs. Such a system should be based on a unique identifying name and cannot be based on the INN (generic drug name), as different products carry the same INN, like erythropoietin alpha.

Risk management and pharmacovigilance

Given the complexity of the new guidelines and the potential for life threatening complications, the hospital pharma-

cist has an essential role in monitoring compliance and ensuring appropriate dosing. All hospital pharmacies should develop a risk management plan specific for ESAs. This should focus on communicating ESA specific risk-benefit information to the prescriber and the patient, guiding appropriate distribution, implementing a track-and-trace system and monitoring any adverse events or outcomes. Stringent pharmacovigilance can allow for the detection of effects that were not initially recognised during safety trials. The hospital pharmacist is in the unique position to provide guidance and ensure adherence to the ESMO prescribing and dispensing requirements.

EMA describes risk management as a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent and minimise risks. It goes on to define risk minimisation as a set of activities used to reduce the probability and severity of an adverse reaction occurring. Although EMA describes the need for robust risk management systems, they do not define or enforce pharmacy specific programmes [10].

All risk management systems should include four steps:

1. risk detection
2. risk assessment
3. risk minimisation and
4. risk communication.

In addition to these standard medication risk management procedures, ESA specific pharmacy programmes should consider the following [11]:

- Discussions with doctors and patients regarding ESAs and the risk of venous thrombotic events (VTEs). Ensure all parties are aware of new labelling instructions specific to VTEs.
- Educate patients on the benefits and risks of treatment and provide them with a medication guide. Patients should be aware of concerns regarding shortened survival times and disease progression.
- Ensure ESAs are only used for the treatment of anaemia associated with

chemotherapy and that other causes of anaemia have been ruled out.

- Ensure a programme of haemoglobin monitoring is in place prior to dispensing ESAs. Verify doses are adjusted for Hb level and rate of increase according to ESMO guidelines.
- Do not exceed a haemoglobin level of 12 g/dL. Use the lowest dose possible to improve symptoms and avoid transfusion. Decrease the dose when target levels are met. Withhold the dose when levels exceed 12 g/dL.
- When haemoglobin levels begin to drop, consider restarting the dose at 25% of the original dose.
- Consider the addition of iron therapy to reduce the overall ESA requirement.
- Distinguish between low-risk and high-risk patients. High-risk individuals include patients who are overweight, have had recent surgery, have a history of deep vein thrombosis (DVT)/pulmonary embolism or are taking thalidomide and dexamethasone as treatment for multiple myeloma.
- Although there are no ESA specific guidelines to date, consider recommending DVT prophylaxis in high-risk patients.
- Consider the risks versus the benefits of substituting ESAs for blood transfusion. Although the possibility of transfusion associated infections remain, the risks have decreased substantially with better screening. However, as described in the 2008 UK SHOT report, there remains significant morbidity and mortality associated with transfusion-related reactions and other adverse events [6].
- The use of ESAs will differ depending on national medical practices and there is already significant European variation in the use of ESA versus transfusion. For example, Spain tends to utilise blood transfusion as the preferred treatment option for chemotherapy-associated anaemia. However, the effect on the current blood supply must be taken into account given the increased demand that could result with decreased ESA use.
- Monitor treatment lengths and ensure active renewal of prescriptions according to treatment timelines, laboratory

data and symptom relief. Discontinue treatment with the completion of chemotherapy.

- Understand the product stability during transport from the pharmacy to the ward and storage on the ward prior to administration. Ensure procedures are in place to maintain cold chain distribution and understand the methods of delivery within the hospital to optimise biological function.
- Educate health professionals on ESA specific delivery systems to prevent needlestick injuries.
- Consider initiating protocol sheets to ensure the ESMO guidelines are complied with. Limit enrolment into the ESA programme to prescribers and patients that agree to follow the guidelines.

Given the new labelling changes for ESAs and concerns regarding potential complications associated with their use, renewed pharmacovigilance is critical to minimise the risk of adverse outcomes. The ESMO guidelines provide clear recommendations for the use of ESAs to maximise their benefit and protect the patient from potential side effects [1]. The Committee for Medicinal Products for Human Use from EMA concluded in 2008 after reviewing the new safety data that the benefits of ESAs continue to outweigh the risks in their approved indications. However, the decision to administer ESAs should be based on an informed assessment of the benefits against the risks on an individual basis, taking into account the type and stage of tumour, the degree of anaemia, the patient's life-expectancy, the environment in which the patient is being treated and the patient's preference [8]. The hospital pharmacist remains an essential component of the overall risk management system and ensuring compliance with these recommendations.

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References

1. Schrijvers D, Roila F. On behalf of the ESMO Guidelines Working Group. Ery-

- thropoiesis-stimulating agents in cancer patients: ESMO Recommendations for use. *Ann Oncol.* 2009;20(Suppl 4): iv159-iv161.
2. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. *J Natl Cancer Inst.* 1999;91(19): 1616-34.
 3. Glaspy J. Erythropoietin in Cancer Patients. *Annu Rev Med.* 2009;60:181-92.
 4. Rizzo JD, Somerfield MR, Hagerty KL, et al. Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update. *Blood.* 2008;111(1):25-41.
 5. Spiess BD. Blood transfusion: the silent epidemic. *Ann Thorac Surg.* 2001;72: S1832-7.
 6. Taylor C (Ed), Cohen H, Mold D, Jones H, et al. On behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2008 Annual SHOT Report (2009).
 7. Cook DJ, Guyatt GH, Laupacis A, Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest.* 1992;102(Suppl 4):305S-311S.
 8. <http://www.emea.europa.eu/pdfs/human/press/pus/49618807en.pdf>
 9. Vekeman F, Bookhart B, et al. Impact of limiting erythropoiesis-stimulating agent use for chemotherapy-induced anemia on the United States blood supply margin. *Transfusion.* 2009;49(5):895-902.
 10. <http://www.emea.europa.eu/pdfs/human/euleg/9626805en.pdf>
 11. Dicato M. Venous Thromboembolic Events and Erythropoiesis-Stimulating Agents: An Update. *Oncologist.* 2008;13 (Suppl 3):11-5.