Point of view about new guidelines on ESAs (erythropoiesis-stimulating agents)

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Recent concerns about the safety of erythropoietin stimulating agents (ESAs) in cancer patients have led to a reformulation of the guidelines issued by NCCN, ASH/ASCO and ESMO. The goal of this review is to comment on various safety issues like mortality or thromboembolism or iron supplementation and to summarise the views of the three working groups concerning ESA treatment in cancer patients.

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Introduction

Anaemia, defined by a haemoglobin level below 14 g/dl in men and below 12 g/dl in women is a frequent finding in cancer patients and can be subdivided into mild (Hb >10g/dl), moderate (Hb 8-10 g/dl), severe (<8g/dl) and life threatening anaemia.[1] Cancer may suppress erythropoiesis either directly by bone marrow invasion or indirectly by producing TNF-alpha and other cytokines which reduce EPO production. TNF-alpha mediated dysregulation of the GATA1/GATA2 pathways whose expression may either lead to erythrocyte differentiation or suppression of normal erythropoiesis is also thought to contribute to cancer-related anaemia.[2,3] Concurrently cancer is accompanied by various clinical states contributing to the pathogenesis of anaemia like infection denutrition or renal insufficiency.[4,5,6]

Anaemia has been recognised as an adverse prognostic factor and the management of anaemia positively affects quality of life in cancer patients.[4,5,6]

The use of erythropoiesis stimulating agents (ESAs) in cancer related anaemia was a widely used and commonly accepted treatment option in the beginning of the 2000s. At that time however first studies demonstrated an increase in mortality in cancer patients undergoing ESA therapy.[7,8] Moreover, the same studies indicated that patients whose anaemia was treated with erythropoietin were prone to venous thromboembolism. Moreover, preclinical data concerning the presence of erythropoietin receptors on tumour cells and a clinical study on head and neck cancer patients displaying reduced disease free survival in patients treated with ESA therapy raised the question of tumour progression under ESA therapy.[9,10] These concerns have led to a reformulation of the guidelines issued by ESMO, NCCN, ASH/ASCO and had a negative impact on the prescription of ESAS.[11,12] FDA initiated a risk evaluation and mitigation strategy program in which all patients receiving ESA therapy must be included prior to undergoing treatment.[4]

The goal of this review is to provide the clinician with a commented summary of current guidelines.

1. Assessment of anaemia

When faced to a cancer patient displaying anaemia, the clinician should keep in mind that cancer- or chemotherapy-induced anaemia remains an exclusion diagnosis and that the patient should be checked for any other cause of anaemia related or not to cancer,

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like blood loss, hemolysis, iron, vitamin B9 or B12 deficiency, renal insufficiency. The discovery of anaemia in a cancer patient requires a complete physical exam. Biologic assessment should contain a complete blood count, reticulocyte count, seric iron, ferritin, vitamin B12 and B9 levels, creatinine level, inflammatory parameters (CRP) and assessment of haemolysis parameters (LDH, haptoglobin, schizocytes and bilirubin.).[4,5,6]

2. Chemotherapy related anaemia

Chemotherapy may reduce erythropoiesis directly through bone marrow toxicity. Other agents like platinum salts may also reduce EPO production by renal toxicity. The toxicity of chemotherapy was shown by Groopman et al in 1999, who showed that lung and gynaecologic cancer patients displayed most severe chemotherapy related anaemia, probably because their regimens included platinum salts. The same study however showed that other chemotherapy agents displayed a more or less potent bone marrow toxicity.[13] Furthermore the incidence of anaemia seems to rise with the cycles of chemotherapy.[14]

3. Goal of ESA treatment

The goal of ESA treatment is to increase haemoglobin levels and avoid red blood cell transfusion (RBCT), thus avoiding transfusion related complications like fluid overload, non- infectious febrile transfusion reactions, infectious risk, iron overload.[15] Several studies have confirmed the reduction of RBCT need in patients receiving ESAs. Moreover, haemoglobin levels achieve higher stability under ESA treatment than with transfusions.[16-18] ESAs however take more time until the peak haemoglobin level is reached, therefore, in patients needing immediate correction of their anaemia (hemodynamically unstable or very symptomatic anaemia) RBCT remain the preferred option.[4,5]

4. Safety concerns

Two studies indicated that in the palliative setting, patients treated with erythropoietin had a higher mortality rate than patients whose anaemia was treated with RBCT.[7,8] This study led several working groups to recommend against the use of ESAs in patients displaying cancer related anaemia not treated with chemotherapy.[4-6]

Six studies and three meta-analyses showed that patients treated with chemotherapy for various types of cancer displayed a reduction in overall survival if treated with ESAs as compared to patients treated with RBCT.[10,19-26] It must however be noted that, in these patients, ESA treatment was performed with a target haemoglobin level higher than 12g/dl and that the studies where ESAs were used off label weighed for more than 20% in the above mentioned meta-analysis. One recent meta-analysis by Glaspy failed to show any statistically significant difference in survival between patients treated with ESA and patients treated with RBCT. [27] Moreover, recent pharmacovigilance studies on Darbepoietin beta and Epoetin alpha failed to show any increase in mortality in patients treated by ESA.[28-30] Although in the third of these studies, which was a revision of the PREPARE trial, no difference in survival could be found, a trend towards reduced disease free survival was still present in those patients treated with darbepoietin, raising the question of tumour progression in patients receiving ESAs.[31] Recently published studies on patient treated for ovarian cancer, small cell lung cancer and lymphoid malignancies likewise did not display any increase in mortality or reduction in progression-free survival in ESA patients.[32-34] On the contrary, an analysis published presented under abstract form at ASCO 2011 on patients with non Hodgkin's lymphoma treated with R-CHOP (LMNH 03 study) indicates a trend towards prolonged progression free survival in patients receiving Darbepoietin.[35] Although evidence remains inconclusive and despite recent contradictory studies, the concern about increased mortality in patients receiving ESAs is not entirely cleared. Therefore, NCCN recommends against the use of ESA in cancer patients treated with a curative intent, while ESMO recommends caution in these patients.[4,5] ASH/ASCO guidelines stress that the clinician often faces a dilemma as to know whether a patient is treated with a curative or a supportive intent and recommends that erythropoietin be used with caution in these patients.[6]

In patients treated supportively with chemotherapy, ESAs remain an option. All working groups recommend that the patient must be included in the decision making and be aware of the potential harms caused by erythropoietin. The potential benefits of ESA treatment in terms of RBCT reduction and quality of life must be weighed against potential side-effects.[4, 5, 6]

The meta-analyses performed by Bohlius, Tonelli, Bennet and Glaspy proved that the use of ESA could increase the risk of TED.2[4-27] This risk had been quantified in a ODAC meeting in 2007. Relative risk for venous thromboembolism was evaluated as 1,71

Table 1. Indications of ESA therapy according to NCCN, ESMA and ASH/ASCO guidelines. (REMS risk evaluation and mitigation strategy concerning the use of ESAs)

	NCCN	ESMO	ASH/ASCO
Indication			
Chemotherapy with curative intent	ESAs not recommended	ESAs are to be used with caution	ESAs not recommended though the term of curative intent is subject to debate
Palliative chemotherapy	Initiation of ESA therapy under REMS guidelines using the lowest dose necessary to avoid transfusions RBCT remain an option	ESAs may be considered	Initiation of ESA therapy with informed consent as to potential risks. RBCT remain an option
Cancer induced anaemia (untreated patient)	ESAs not recommended RBCT preferred	ESAs not indicated due to an increase in mortality especially if target hemoglobin 12-14g/dl	Not recommended
Initiation			
Hb level at initiation	<10g/dl or reduction of 2g/dl from baseline >10g/dl if symptomatic or high risk patient.	≤10g/dl to increase the Hb level to<2g/dl or to stabilize Hb level to avoid RBCT	<10g/dl In patients with Hb 10-12g/dl, ESAS are to be used according to circumstances and clinical judgement.
Unstable patient	RBCT recommended	Not assessed	RBCT recommended
Iron supplementation			
Type of supplementation	Parenteral iron only	Parenteral iron therapy yields a better increment than oral therapy	Not enough evidence to favour parenteral over oral iron supplementation
Initiation	If functional iron deficieny is present (ferritin<800ng/ml and transferrin saturation<20%)	If signs of functional iron deficiency are present (ferritin<100ng/ml and transferrin saturation<20%)	If signs of functional iron deficiency are present.

for a target haemoglobin between 13 and 14 g/dl, 1.92 if target haemoglobin lay between 14 and 15 g/dl and 1.66 fir a target haemoglobin of 15-16 g/dl.[36] The risk of thromboembolism in patients receiving ESA corresponds to a class effect and exists for any target haemoglobin used.[4-6] Most working groups advise caution in patients displaying additional risk factors for TED, like old age, history of thromboses surgery, prolonged period of immobilisation.[4-6,37] Caution is also recommended in certain diseases where venous thromboembolism is more frequent (myeloma, metastatic disease and ductal histology in breast cancer).[37-39] Pure red blood cell aplasia has been described in the past with some preparations of epoetin alfa in dialysis patients. No case has been described in cancer patients. It is however recommended to suspect PRBC in those patients presenting sudden loss of reticulocyte response to ESAs.[4] Other side effects like seizures or hypertension have also been described in ESA patients.[4-6] Recently, the risk of increased strokes in ESA patients has also been addresses in dialysis patients but also in cancer patients receiving ESAs. [40,41]

5. Initiation of therapy (Table 1)

Therapy should be initiated in patients treated for cancer displaying moderate anaemia who are moderately symptomatic. ASCO/ASH and NCCN consider ESA therapy in patients whose haemoglobin has fallen below 10 g/dl.[4,5] ESMO guidelines recommend the initiation of ESA treatment in patients below 10 g/dl or approaching this limit.[6] In certain patients considered at risk (old age, previous radiotherapy, severe comorbidities) or who are symptomatic between 10 and 12 g/dl, ESAs can be initiated in selected patients depending on clinical circumstances.[4,5,6] A recent retrospective study assessed that the most important benefit is obtained in those patients in whom ESA therapy is started early when Hb levels approach 10 g/dl.[39] Initial dosing of ESAs recommended are 150 units/kg of Epoetin alpha three times weekly or 40000 units

Table 2. Dose initiation and tapering algorithm according to ESMO and ASH/ASCO guidelines. Legend: qw: once a week q3w once every three weeks, tiw: twice a week, RBCT: red blood cell transfusions, Hb: haemoglobin. (adapted from Rizzo et al and Schrijvers et al.)

Doses of ESAs according to ESMO based on EMEA label					
	Epoetin alpha		**Epoetin beta**	**Darbepoietin alfa**	
Initial dose	150 IU/kg sc tiw	450 IU/kg qw	30000 IU sc qw	2.25 ug/kg SC qw	500 ug sc q3w
Dose increase	300IU/kg tiw		60000 IU sc qw	Not recommended	
Dose reduction	If result achieved: 25-50% If Hb>12g/dl: 25-50% If Hb rise >2g/dl/4weeks: 25-50%		If result achieved: 25-50% If Hb>12g/dl: 25-50% If Hb rise >2g/dl/4weeks: 25-50%	If result achieved: 25-50% If Hb>12g/dl: 25-50% If Hb rise >2g/dl/4weeks: 25-50%	
Dose withholding	If Hb>13 g/dl until 12g/dl		If Hb>13 g/dl until 12g/dl	If Hb>13 g/dl until 12g/dl	
Doses of ESAS according to ASH/ASCO					
Initial dose	150 UI/kg sc tiw	450 IU/kg sc qw	Epoetin beta not available in the US	2.25 ug/kg SC qw	500 ug sc q3w
Dose increase	300 UI/kg sc tiw If no reduction in RBCT requirements, If increase in Hb after 4 weeks to achieve lowest Hb sufficient to avoid RBCT	60000 IU sc qw If no increase of >1g/dl after 4 weeks of treatment to achieve and maintain the lowest Hb level sufficient to avoid RBCT		4.5 ug/kg if increase <1g/dl after 6 weeks	Not recommended
Dose reduction	Decrease by 25% when Hb reaches a level needed to avoid transfusion or Hb increases >1 g/dl in 2 weeks.			Decrease by 40% when Hb reaches a level needed to avoid transfusion or Hb increases >1 g/dl in 2 weeks.	
Dose withholding	If Hb exceeds a level needed to avoid transfusion. Restart at 25% below previous dose when approaching levels where transfusions might be needed.			If Hb exceeds a level needed to avoid transfusion. Restart at 40% below previous dose when approaching levels where transfusions might be needed.	
Discontinue	After completion of chemotherapy or if no response after 8 weeks of therapy			After completion of chemotherapy or if no response after 8 weeks of therapy	

once a week subcutaneously.[8,16,19,20] Higher dosages have been used to some avail (80000 units every two weeks and 120000 every 3 weeks).[42,43] Darbeopoietin alpha is currently initiated at the dose of 2.25 ug/kg.[17,44] Dosage of 500 ug every thee weeks have also shown efficacy.[44] Different algorithms of dose tapering are listed on *Table 2*. Currently, given the concerns about erythropoietin, it is recommended to use the lowest dose able to maintain stable haemoglobin level.[4-6]

6. Iron deficiency

Functional iron deficiency is present in most cancer patients and may impair the efficacy of erythropoietin. The adjunction of intravenous iron has shown superior to oral or no iron supplementation at all.[45] In a recent study on darbepoietin beta, however, iron supplementation did not seem to affect response to ESA treatment.[46] Nonetheless, most working groups recommend the use of intravenous iron in patients receiving ESA therapy especially if they display relatively low ferritin levels. Though oral forms of iron supplemen-tation are commonly used, intravenous forms should be preferred.[4-6]

7. ESA in myelodysplasia

The use of ESA in low IPSS myelodysplasia has been investigated over the last decades. In 1995 Hellström-

Key messages:

1) Cancer-or chemotherapy induced anaemia remains an exclusion diagnosis. Patients should be checked for other causes of anaemia. (blood loss denutrition, haemolysis, iron deficiency renal insufficiency or inflammation).
2) ESAs are recommended in cancer patients undergoing supportive chemotherapy. They are generally not recommended in patients not receiving chemotherapy (with the exception of myelodysplasia).
3) In patients receiving chemotherapy with a curative intent, most guidelines recommend against the use of ESAs.
4) Most studies indicating a negative effect of ESA therapy on overall survival had a Hb target>12g/dl. Recent data do not seem to support these suspicions.
5) The risk of venous thromboembolism is raised in patients receiving ESA treatment.
6) Parenteral iron should be given to patients receiving ESA especially if they display functional iron deficiency

Lindberg and colleagues discovered that serum Epo level and lower transfusion burden were predictive of favourable response to ESAs and implemented their findings in a decision model which was validated in 2003.[46,48] Other favourable prognostic factors include blast count below 10%, IPSS low or intermediate 1.[47] Expression of CD7, CD5, CD56, or loss of CD 33 expression have been described as adverse prognostic factors.[49,50] Some cytogenetic findings like del(5q) also predict lower response rates to ESAs.[51]
Response rates to ESA therapy lie between 20-30% in a general MDS population and can reach up to 64,5% in selected low risk patients.[51,52]
Currently most working group recommend the use of ESA therapy in low risk MDS patients displaying Epo serum level <500Ul.[4-6] It must however be noted that this indication is not yet reimbursed in Belgium.

Conclusions

In the last years clinical practice guidelines concerning the use of ESA treatment have undergone major changes. Conflicting datas exist concerning the risk of an increase in overall mortality, thromboembolic disease and cancer progression have led to extreme caution towards erythropoietin in the clinical setting. Even if recent data seem to indicate that ESAs are supportive medication which do not change the course of the underlying disease, patients must be informed of the putative risks and the benefits of ESA treatment must be carefully weighed out against potential harms.

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