Consensus guidelines for the management of anemia with erythropoesis stimulating agents (ESAs) in multiple myeloma

Anemia is a common complication in myeloma. A recent study in blood donors showed that haemoglobin levels may already decline years before the diagnosis of myeloma is established (1). At diagnosis, 30-60% of patients present with anemia but the figures vary depending on the age of the patients, their tumor stage and the definition of anemia used. With initiation of myeloma therapy up to 90% of elderly patients may become anemic (2).

1. Investigation of Anemia: The underlying cause of anemia should be carefully assessed. In particular, vitamin B12, folate and iron deficiency should be identified and treated accordingly. Other causes of anemia such severe infection, hemolysis, blood loss, bone marrow insufficiency, DIC, congenital anemia should be diagnosed and distinguished from anemia of myeloma and chemotherapy associated anemia. Also, it should be recognized that MDS may occur concomitantly with myeloma.

2. Indication for Erythropoietin therapy: Treatment with ESAs should be initiated only in patients with chemotherapy induced anemia and anemia of myeloma with Hb level ≤ 10g/dl and in those with higher levels but being symptomatic from anemia. Although the FDA and the EMEA have approved the usage of ESA therapy at Hb levels of < 10g/dl and of ≤ 10g/dl respectively, some expert committees from international societies (EORTC, NCCN) have recommended initiation of therapy at higher Hb levels (<11g/dl) with or without consideration of clinical symptoms (table 1). Of note, treatment with ESAs is only approved for patients on chemotherapy. This may be problematic in patients who present with anemia of 'chronic disease', mediated by impaired iron utilisation, inadequate erythropoetin production, and reduced responsiveness of the erythroid precursors to erythropoetin (3). In those patients treatment with ESAs may be considered in case of severe anemia - related symptoms and only after careful discussion of possible benefits and risks with the patient. Red blood cell transfusions may be administered to patients with severe anemia (Hb < 8g/dl). RBC transfusions have

not been shown to improve quality of life in patients with higher Hb levels. Their use should carefully be considered because evidence for previously unrecognized risks of RBC transfusions is increasing (4).

3. Dosage and length of Erythropoietin use: Treatment with erythropoetin should be initiated with a dose of 40.000 U once weekly or 10.000 U TIW. Darbopoetin should be administered in a dose of 150µg once weekly or 500µg every 3 weeks. Therapy should be continued until a Hb level of 12g/dl, although recommendations vary also in this respect (table 1). In case of lack of response, the dose of ESAs may be increased, but the evidence for the efficacy of dose increments is weak; in non-responding patients therapy should be discontinued within 6 - 8 weeks. In responding patients reaching the target level, treatment should be discontinued and resumed when Hb levels fall below the initiation level and/or in case of occurrence of anemia symptoms.

   ESA therapy results in reduction of transfusion need and in improved quality of life, although the latter aspect has not been confirmed in all studies. In multiple myeloma, erythropoietic response (increase in Hb ≥ 2g/dl) can be obtained in 60-80% of patients which is slightly higher than in other malignancies. This is possibly due to the high frequency of absolute or relative erythropoietin deficiency observed in myeloma. In general, responsiveness to ESAs seems to be higher in patients with well controlled disease than in those with progressive myeloma and in those with ongoing infections (5, 6).

   Recent studies in chemotherapy induced anemia showed increased response rates, shorter time to response and reduced ESA usage when intravenous iron was administered either as loading dose at the start of ESA therapy or in intervals concomitantly with ESA treatment (7). As long-term results are presently not available, intravenous iron supplementation can only be recommended in patients with absolute (TSAT <20%, ferritin <30ng/ml) iron deficiency. Use of intravenous iron in combination with ESAs may be used in patients with functional iron deficiency (defined as TSAT < 20%, ferritin ≥ 30-≤800ng/ml), but is as yet not accepted as standard.

Possible side effects of ESA therapy include an increased risk (HR: 1.65) of venous thromboembolic events (VTE). A markedly higher risk of VTE was observed in patients with myeloma being treated with ESAs and either thalidomide, doxorubicin or lenalidomide usually in combination with dexamethasone. In cancer patients, eight studies that explored ESA use in non-approved indications yielded an increased risk for progression or mortality, while no significant difference in these parameters was noted in ESA treated patients with concomitant chemotherapy (8). In myeloma, no difference in survival was noted in the VISTA trial between patients receiving or not receiving ESAs (9).

4. Monitoring: During treatment with ESAs monitoring should include Hb levels, red cell parameters (MCH, MCV), TSAT, ferritin and serum iron. In myeloma, ferritin is not a reliable marker of iron stores and levels usually increase with progressive disease and/or inflammation. Further, in inflammatory states, serum iron levels usually are depressed and do not correlate with body iron stores. TSAT is the most valuable parameter for identifying functional iron deficiency.

References

1. Edgren G. et al., Pattern of declining hemoglobin concentration before cancer diagnosis. Int J Cancer 127(6):1429-36, 2010
2. Birgegard G et al. Evaluation of anaemia in patients with multiple myeloma and lymphoma: findings of the European CANCER ANAEMIA SURVEY. Eur J Haematol 77(5):378-86, 2006
3. Spivak JL, The anaemia of cancer: death by a thousand cuts. Nat Rev. Cancer, 543-555, 2005
4. Isbister JP, et al. Adverse Blood Transfusion Outcomes: Establishing Causation. Transfus Med Rev. 2011 Feb 21. [Epub ahead of print]
5. Ludwig H, et al. Anemia in multiple myeloma. Clin Adv Hematol Oncol. 2004 2(4):233-41. Review
6. Katodritou E et al. Update on the use of erythropoiesis-stimulating agents (ESAs) for the management of anemia of multiple myeloma and lymphoma Cancer Treatment Rev, 738-743, 2009
7. Gafter-Gvili A et al. Iron Supplementation for the Treatment of Cancer-Related Anemia – Systematic Review and Meta-Analysis, Abstract 4249, ASH 2010
8. Bohlius J, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. Lancet 373(9674):1532-42, 2009
9. Richardson P. et al. Characterization of haematological parameters with bortezomib-melphalan-prednisone versus melphalan-prednisone in newly diagnosed myeloma, with evaluation of long-term outcomes and risk of thromboembolic events with use of erythropoiesis-stimulating agents: analysis of the VISTA trial. Br. J Haematol 2011

Table 1

	FDA	EMEA	ASH/ASCO	NCCN	EORTC
Initiation of ESA therapy at Hb	< 10g/dl	≤ 10g/dl	< 10g/dl	≤ 11g/dl or ≥ 2g below baseline	≤ 11g/dl
Target Hb level	Treat to a level to avoid RBC transfusion	< 12g/dl	The lowest concentration needed to avoid transfusions, reduce ESA dose when Hb increase exceeds 1/dl in any 2-week period	Not stated	12-13 g/dl
Supplementary therapy	Not stated	Not stated	Institute iron repletion when indicated	Consider iv. Iron supplementation when TSAT < 20% and ferritin ≤ 800mg/dl	Address functional iron deficiency with i.v. iron