Anaemia & Cancer

John de Vos
Consultant Haematologist
RSCH
overview

- Definitions & setting the scene
- Causes
- Consequences
- Biology
- Treatment
- Personal approach
  - Patient
  - Clinical team
Anaemia

- Definition: Decreased Hb concentration: Hb <120/130 (women/men)

- Anaemia is a result of either reduced red cell production and/or increased red cell destruction

- Decreased RBC production: secondary to impaired marrow function or lack of erythropoietin stimulus

- Increased peripheral RBC destruction
Mechanisms of Anaemia

Production Disorders:
- Factor Deficiency (RBC Size)
  - Iron, Vit. B$_{12}$, Folate
- Bone marrow conditions
  - Haematopoietic Cell Damage
  - Infiltration

Survival Disorders:
- Blood Loss: acute/chronic
- Red Blood Cell Destruction

Anaemia of chronic disease:
- multifactorial
Anaemia of Chronic Disease (AOCD)

*Classical definition*

- Anemia occurring in –
  chronic infectious, inflammatory or neoplastic disorders

- not due to –
  marrow replacement by tumor, bleeding, or haemolysis

Anaemia in cancer

- Prevalence: up to 40% of oncology patients. 60% in patients on chemotherapy (Hb <110 g/L)
- Oncology: Lung and gynae (platinum based treatment)
- Haematology patients 2x higher prevalence. 70% of patients with lymphoma on treatment
- Need for transfusion: 47-100% depending on cancer/treatment/age/premorbid condition
Anaemia is Highly Prevalent in Patients with Cancer

causes

- Common type of Anaemia of chronic disease (AOCD)
- Direct toxicity: Chemotherapy/radiation therapy
- Blood loss
- Bone marrow infiltration
  - Haematological malignancies
  - Metastatic cancer
- Nutritional deficiency
- Haemolysis
Therapy Induced anaemia

- Chemotherapy
  - Direct bone marrow suppression by most chemotherapy drugs
  - IV/oral/SC...
  - Cyclical

- Radiotherapy
  - Any area involving BM
  - Timing
Pathogenesis of anaemia in cancer

- Bone marrow involvement
- Iron distribution defect
- Shortened erythrocyte survival time
- Depression of erythropoiesis or EPO production (cytokine-mediated)
- Anaemia of Chronic Disease

- Renal failure
- Haemolysis (NHL)
- Pure red cell aplasia
- Cytotoxic chemotherapy radiotherapy
Regulation of Erythropoietin

Hypoxia + Erythropoietin

chemokines - cytokines

HIF-1 = hypoxia-induced factor-1

Ludwig (1998); Lacombe (1999)
Predicting factors

- Lower baseline levels (<120/130 (females/males)
- Lung/Gynaecological cancers
- GI/colorectal cancers
- Female patients
- Platinum based chemotherapy
- Haematological malignancies
Consequences

- Fatigue (multifactorial)
- Reduced QoL
- Hypoxia
- Impaired organ function
- Exacerbation of comorbidities
- Greater post-operative mortality
- Higher probability of blood transfusion post chemotherapy
- Radiotherapy resistance
- Lower sensitivity to chemotherapy?
- OS?
Fatigue

Jerry L. Spivak et al. The Oncologist 2009;14:43-56
QoL

- Multi-factorial
- Tools
  - Physical functioning
  - Social functioning
  - Emotional functioning
- Anaemia and QoL
  - Fatigue in patients on chemotherapy: 76% at least once a month, 24% daily. Multifactorial.
  - Hb levels < 100-120 g/L depending on trial.
- Scientific bias
Epoetin alfa phase IV studies in tumor-associated anemia: Incremental increase in quality of life and hemoglobin (Hb) level [42, 66, 76].

Jerry L. Spivak et al. The Oncologist 2009;14:43-56
consequences

- Negative impact between anaemia and QoL (/fatigue)

- Negative impact between anaemia and survival?
  - Multifactorial
  - Not evidence based (univariate)

- Anaemic patients having radiotherapy: lower OS
  - Tumour hypoxia is a measure for radiation resistance

- Tumour hypoxia: induces changes in the genes that promote angiogenesis & promotes aggressive phenotype
  - In vivo?
Biology

- Cytokines (interleukins, TNF, ...):
  - suppress erythroid progenitor cells and EPO production
  - Lead to impaired iron use: increased stores, low serum iron, reduced iron absorption, decreased serum transferrin, increased ferritin
- Iron overload suppresses EPO production
- RBC lifespan reduced in inflammatory state
Factors involved in the cause and development of anaemia in cancer patients

**Tumour cells**
- RBCs
  - Erythrophagocytosis
  - Dyserythropoiesis
  - TNF
  - IFN-α, β
  - IL-1
  - TNF

**Activated immune system**
- Macrophages
  - TNF
  - IFN-γ
  - IL-1
  - TNF
  - α1-antitrypsin

**Shortened survival**
- Anaemia
  - Reduced EPO production
  - Impaired iron utilisation
  - Suppressed BFU-e, CFU-e

TNF = tumour necrosis factor; IFN = interferon; IL-1 = interleukin-1; BFU-e = erythroid burst-forming unit; CFU-e = erythroid colony-forming unit

Treatment
Treatment of anaemia

- Treatment required?
- Treat cause
- Transfusion
- Erythropoietin
- Other supportive measures
- Chemotherapy/radiotherapy?
- Palliative setting / Symptomatic
Transfusion

- Low risk
- Availability
- Extra visits/chair-time
- Validity of cross-match sample
- ‘1 Unit and assess’
- Special requirements
Erythropoietin
Erythropoietin

Timeline:

- 1993: EPO approved on the basis of 413 patients in 3 small studies
- 2001-2005: studies showed QoL and apparent OS advantage.
- 2007: Black box warning (FDA – USA)
Erythropoietin- adverse effects

- 2007: ‘black box’ warning (FDA)
  - Increased mortality
  - Thrombo-embolic events
  - Cardiovascular events
  - Tumour progression?

- Trials: (aimed for normal Hct or even started with normal Hct)
  - ENHANCE: H&N patients: higher mortality
  - BEST: breast cancer patients: patients on chemo/DXT
  - NSCLC patients: patients not on chemo
EPO and adverse effects

- Increased risk of VTE
  - Cancer patients are hypercoagulable
  - RBC mass (threshold 120 g/L (regardless of cause of anaemia)).
  - Plasma volume effect: decreased with EPO (same as Tx).

- “Tumour progression resulting from Stimulation of Tumour Cell EPO-receptors”.
  - Research on immortalised cell lines rather then primary tissue
  - Forced overexpression of EPO-R
  - Non-physiological concentrations
  - EPO does not stimulate tumour growth in vitro or in vivo
MHRA/CHM advice (December 2007 and July 2008) Erythropoietins—tumour progression and survival in patients with cancer

Clinical trial data show an unexplained excess mortality and increased risk of tumour progression in patients with anaemia associated with cancer who have been treated with erythropoietins. Many of these trials used erythropoietins outside of the licensed indications (i.e. overcorrected haemoglobin concentration or given to patients who have not received chemotherapy): erythropoietins licensed for the treatment of symptomatic anaemia associated with cancer, are licensed only for patients who are receiving chemotherapy

The decision to use erythropoietins should be based on an assessment of the benefits and risks for individual patients; blood transfusion may be the preferred treatment for anaemia associated with cancer chemotherapy, particularly in those with a good cancer prognosis
2014
NICE TA323: Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy.

Technology appraisal guidance [TA323] Published date: 26 November 2014
All trials showed benefit of ESA over non-ESA.
- Benefit greater in platinum based therapy
- All but one trial showed reduction in transfusion need
- Haematological responses >10-20 g/L
- No difference in cancer outcome
- No difference in OS
- No difference in risk of death
- Adverse events
- Improved QoL
  - Improvement only in patients on chemotherapy
  - FACT-F: Functional Assessment of Cancer-Therapy-Fatigue
Overall Survival - discussion

- Unlicensed use
- Promoting tumour growth
- Higher starting levels of Hb
- Aiming too high
- Overall conclusion: OS not affected
Conclusion

1.1 Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta, and darbepoetin alfa) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy.

1.2 If different erythropoiesis-stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used.
But…

- “The committee considered the need for treatment in people with anaemia who receive chemotherapy and how it is managed. It heard from the patient expert that symptomatic anaemia is associated with fatigue and the inability to perform everyday tasks; the patient expert explained that when haemoglobin concentration rises, quality of life improves.”

- “The committee heard from a clinical expert that standard treatment for anaemia in people having chemotherapy includes blood transfusions and that people now have fewer units of blood because of risks associated with blood transfusion, which, although rare, could worsen quality of life and potentially shorten survival”
And...

- Clinical expert: Hb <90 g/L.
- Trials average: 103 g/L
- EMA (European Medicines Agency): 100 g/L
summary

- EPO:
  - ONLY IN PATIENTS ON CHEMO
  - Alleviate anaemia
  - Improve QoL
  - Reduce Tx
  - Never Hb >120 g/L
  - Not together with transfusions
  - Increased VTE risk: risk/benefit assessed per patient
Recombinant erythropoietin effect on haemoglobin level

Hb (g/dL)

Days of treatment

0  30  60  90  120  150  180  210

Epoetin
Transfusions

Comparison of the pharmacokinetics of exogenously administered erythropoietin.

Jerry L. Spivak et al. The Oncologist 2009;14:43-56
Treatment of anaemia

- Treatment required?
- Treat cause
- Transfusion
- Erythropoietin
- Other supportive measures
- Chemotherapy/radiotherapy ?
- Palliative setting / Symptomatic
Hb Triggers
- <70 g/L
- <80 g/L
- <100 g/L
- Not if 100-120 g/L
- Dangerous if >120 g/dL
Don’t treat blindly/on a number
Individual decision
Extra visits
Cost
Endgame?
What are we trying to achieve?
To check or not to check?
Questions?
References/reading

- Littlewood et al, Effects on hematologic parameters and QoL in cancer patients receiving non-platinum chemotherapy: results of a randomised, double-blind, placebo-controlled trial. JCO 2001