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COMMENTARY

Iron and the anaemia of chronic disease: a review and strategic recommendations

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ABSTRACT

Background: The incidence of anaemia is high in many chronic conditions, yet it often receives little attention.

Scope/methods: A panel of international experts with experience in haematology, nephrology, oncology, rheumatology and pharmacy was convened to prepare strategic guidelines. A focused literature search was conducted after key issues had been identified. A series of recommendations was agreed, backed, wherever possible, by published evidence which is included in the annotations.

Recommendations: Anaemia is a critical issue for patients with chronic diseases. Healthcare professionals need to recognise that anaemia is a frequent companion of cancer and chronic conditions such as rheumatoid arthritis and heart failure. It reduces patients' quality of life and can increase morbidity and mortality. Anaemia should be considered as a disordered process in which the rate of red cell production fails to match the rate of destruction which leads eventually to a reduction in haemoglobin concentration; this process is common to all chronic anaemias. The aim of anaemia management should be to restore patient functionality and quality of life by restoring effective red cell production. Blood transfusion can elevate haemoglobin concentration in the short term but does nothing to address the underlying disorder; red cell transfusion is, therefore, not an appropriate treatment for chronic anaemia. Patients with anaemia of chronic disease may benefit from iron therapy and/or erythropoiesis stimulating agents (ESAs). Intravenous iron should be considered since this can be given safely to patients with chronic diseases while intramuscular iron causes unacceptable adverse effects and oral iron has limited efficacy in chronic anaemia.

Conclusion: The management of anaemia calls for the development of a specialist service together with education of all healthcare professionals and transfer of skills from areas of good practice. Improvement in the management of anaemia requires a fundamental change of attitude from healthcare professionals.

Introduction

Anaemia is common in patients with chronic conditions of inflammation, infection or malignancy. Despite being the commonest side effect of cancer and cancer chemotherapy, and often having a profound effect on patients' quality of life, anaemia remains an orphan issue. While lip service is paid by many clinicians to the importance of anaemia, it is often overlooked and undertreated. UK Anaemia called a meeting of experts from Europe and the United States of America with experience in haematology, nephrology, oncology, rheumatology and pharmacy to address these issues in May 2005. The aim was to develop recommendations on the approach to, and the management of, anaemia based on published evidence and practical experience.

The recommendations from the meeting take the form of a broad strategy. This should form the basis for more specific and detailed treatment guidelines which can be developed to meet the needs of different specialties and regions. Therapies are discussed generically, as the availability of treatments and diagnostic techniques vary between countries.

A focused literature search was performed after key issues had been identified. Publications were identified from Medline and from the reference lists of retrieved documents in addition to those identified by panel members. However, it became clear that the evidence base is incomplete and that many important questions about anaemia have not been raised, let alone answered. In developing the recommendations it was therefore necessary to extrapolate findings between different patient groups since the bulk of current knowledge stems from the experience of the use of erythropoietic and iron therapies in renal medicine. The recommendations are, therefore, evidence-based as far as possible but, when evidence is lacking, they are based on clinical experience. The underlying evidence is presented in the discussion/annotations section.

Discussion and annotations

1. Anaemia is a critical issue for patients, especially those with chronic diseases. It can reduce patients' quality of life and increase morbidity and mortality

- Anaemia can significantly impair quality of life and is associated with increased morbidity and mortality[1,2]. In cancer patients, fatigue has a greater impact on daily life than pain[3].
- Anaemia and its associated symptoms affect not only patients with chronic diseases but also those caring for and living with them. A study from the United States has shown that cancer patients with anaemia require more care than those without anaemia and this has a direct impact on their families[4].
- Untreated anaemia can affect economic productivity, which will also affect patients' families[5,6].

Key Issues and Strategic Recommendations

- Anaemia is a critical issue for patients, especially those with chronic diseases. It can reduce patients' quality of life and increase morbidity and mortality.
- Anaemia is a frequent companion of cancer and chronic conditions such as rheumatoid arthritis.
- Healthcare professionals too often accept anaemia and its consequences with equanimity – it is the patient who pays the price.
- There is a need to raise awareness of anaemia, its detection, investigation and management among healthcare professionals who treat patients with chronic diseases.
- Anaemia should be considered as a disordered process in which the rate of red cell production fails to match the rate of destruction, which eventually leads to a reduction in haemoglobin concentration – whatever the causation. This process is common to all chronic anaemias.
- The aim of anaemia management should be to restore patient functionality and quality of life, and to reduce morbidity and mortality, by restoring effective red cell production.
- Blood transfusion can elevate haemoglobin concentration in the short term but does nothing to address the underlying disorder. Red cell transfusion is not an appropriate treatment for chronic anaemia.
- Patients with anaemia of chronic disease may benefit from iron therapy and/or erythropoiesis stimulating agents (ESAs).
- Oral iron causes side-effects, is associated with drug–drug interactions, and has limited efficacy in chronic anaemia.
- Intramuscular iron is associated with unacceptable adverse effects and should not be given.
- Intravenous (iv) iron can be given safely to patients with chronic diseases.
- The management of anaemia calls for the development of a specialist service, education of all healthcare professionals and transfer of skills from areas of good practice.

- People with anaemia may not have access to information about their condition and may, therefore, be unaware of the treatment possibilities.
- The long-term and widespread under-treatment of chemotherapy-induced anaemia may have contributed to the misconception that anaemia is an unavoidable consequence of cancer and its treatment[7].
- Until recently there have been no organisations representing people with anaemia. This contrasts with the rise of successful advocacy groups such as those for breast cancer which have lobbied effectively for better and more patient-centred care.
- The World Health Organization estimates that 'as many as 4–5 billion people, 66–80% of the world's population, may be iron deficient; 2 billion people – over 30% of the world's population – are anaemic'[8].

2. Anaemia is a frequent companion of cancer and chronic conditions such as rheumatoid arthritis

- The recent European Cancer Anaemia Survey (ECAS), which involved over 15 000 patients in 24 countries, found that about 40% of adult cancer patients had haemoglobin (Hb) concentration < 12 g/dL at the start of the survey. The incidence of anaemia rose to around 60% over the course of the survey[9]. A literature review has suggested that 30–90% of patients with cancer are anaemic[10].
- Similarly, a Dutch study has found that about 60% of patients with rheumatoid arthritis (RA) are anaemic[11,12].
- Long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) can cause gastrointestinal blood loss resulting in iron-deficiency anaemia[13].
- Patients with chronic inflammatory conditions such as RA may also have inflammation-related anaemia[14].
- Renal impairment can cause anaemia; Hb concentrations are correlated with the glomerular filtration rate. The incidence of anaemia is relatively low in people with mild renal impairment but rises to over 90% in those receiving dialysis (if left untreated) and is independently associated with an increased risk of death.
- Anaemia can be both a cause and a consequence of chronic heart failure (CHF) and can exacerbate symptoms of breathlessness and fatigue[15]. Falling haemoglobin concentrations in patients with CHF have been associated with increased morbidity and mortality[16].
- In patients with HIV, anaemia is a predictor of progression to AIDS and is independently associated with an increased risk of death[17].
- A survey in the United States found that anaemia prevalence increased with age and that more than 20% of those aged over 85 years were anaemic[18].
- Patients with chronic infection, inflammation or malignancy may also be prone to anaemia because of poor dietary intake and poor absorption of dietary iron.

3. Healthcare professionals too often accept anaemia and its consequences with equanimity – it is the patient who pays the price

- Clinicians often underestimate the effects of anaemia on patients. However, studies have shown that cancer patients are often more concerned by fatigue than by pain or nausea[3].

4. There is a need to raise awareness of anaemia, its detection, investigation and management among healthcare professionals who treat patients with chronic diseases

- In the assessment of anaemia, many clinicians rely on one or two measurements taken from the blood count and chemistry. The selection of these measurements is often determined by history and availability.
- Haemoglobin concentration is the key measurement, but it is a late reflection of the anaemic process, and in some circumstances, chiefly pregnancy, may not reflect changes in the red cell mass. In some cultures, the haematocrit is used as a surrogate for measuring Hb concentration.
- The productivity of the erythroid marrow can be assessed reliably using the reticulocyte count. The reticulocyte percentage can give an inverse reflection of red cell life span (when it is > 2.5% this is evidence of haemolysis).
- The adequacy of iron supply to the developing erythron can be assessed from a variety of parameters, the most direct of which is the MCH (mean cell Hb). This is available as part of every full (complete) blood count but is rarely used. MCH is, however, a late reflection of the adequacy of iron supply. Mean cell volume (MCV) may mirror changes in MCH but can be confounded by a variety of factors. A more immediate measure of iron supply is provided by the reticulocyte Hb content while the percentage of hypochromic red cells offers an intermediate assessment (where these parameters are reported).
- The adequacy of iron in reticuloendothelial iron 'stores' can be assessed by measuring serum ferritin levels, but again there are a number of confounding factors. Ferritin is an acute phase reactant so this measure may be unreliable in sick patients. Moreover, the presence of iron in

these 'stores' does not mean it is available for erythropoiesis. The flow of iron from these 'stores' to the marrow may be assessed by measurement of serum iron and Total Iron Binding Capacity (TIBC) but this measurement is biologically labile and methodologically often flawed.

- In some circumstances, it may be appropriate to assess the stimulus to the marrow by measuring serum EPO or the degree of erythroid inhibition by an indicator of inflammation such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

5. Anaemia should be considered as a disordered process in which the rate of red cell production fails to match the rate of destruction which eventually leads to a reduction in haemoglobin concentration – whatever the causation. This process is common to all chronic anaemias

- The red cell mass is maintained at a constant level by the balance of red cell production and destruction. Changes in this balance will be manifest as a change in Hb concentration. However, the relatively slow turnover of mature red cells means that this process has a high degree of inertia and a fall in Hb concentration is a very late reflection of the anaemia process[19].
- The making of red cells and the control of red cell production is fundamentally the same whatever the condition. In chronic conditions associated with infection, inflammation and malignancy, erythropoiesis will be suppressed by a common process involving the inflammatory cytokines. These counter the pro-erythropoietic activity of erythropoietin[20].
- A low Hb concentration is a consequence of a disordered erythropoietic process. Anaemia may be predicted from measures of erythropoietic activity by the reticulocyte count before Hb concentrations reach traditional levels at which anaemia is diagnosed[21].
- A low reticulocyte count (e.g. $< 30 \times 10^9$/L), or falling Hb concentration should, therefore, be the stimulus to correct the disorder and prevent symptoms of anaemia.
- Use of erythropoiesis stimulating agents (ESAs) without adequate iron support can create a Functional Iron Deficiency (FID) in which, although total iron storage levels may be normal, insufficient iron is transported to the bone marrow to support erythropoiesis[22]. FID is suggested by MCH < 28, reticulocyte Hb content < 29, hypochromic red cells > 5–10%; the transferrin saturation may be < 20%. Measurement of serum ferritin alone cannot indicate FID, since this can occur when the serum ferritin concentration is normal or even high.

6. The aim of anaemia management should be to restore patient functionality and quality of life, and to reduce morbidity and mortality, by restoring effective red cell production

- Several studies in patients with cancer, renal failure or inflammatory diseases have shown a correlation between correcting anaemia and improved quality of life[23-26].
- Anaemia is often diagnosed and treated by reference to the Hb concentration, but this is not directly related to what patients feel. Clinicians should, therefore, concentrate on preventing and alleviating the associated symptoms such as fatigue and breathlessness which can markedly impair functionality and lead to a vicious spiral of reduced physical and social activity.

7. Blood transfusion can elevate haemoglobin concentration in the short term but does nothing to address the underlying disorder. Red cell transfusion is not an appropriate treatment for chronic anaemia

- Transfusion of allogeneic blood or blood products is a logical approach to acute situations of blood loss such as trauma or surgery when patients require haemodynamic support. However, in cases of chronic inflammation, infection or malignancy, or when anaemia is caused iatrogenically by myelosuppression, the administration of blood or blood products has no effect on the disordered process and is, therefore, inappropriate.
- The benefits of red blood cell transfusions have never been properly assessed, and their legendary life-saving properties have never been tested. Indeed, some studies have shown that transfusion is associated with a poorer prognosis in cancer patients[1,27].
- Clinical trials in which anaemic patients were randomised to receive an ESA or standard treatment (the control group) which consisted of blood transfusion have shown significant differences in quality of life between the ESA and control group. Patients in the control group received significantly more blood transfusions than those receiving an ESA yet tended to have a poorer quality of life[24,26].
- Clinical experience also suggests that transfusion-dependent patients may have a poor quality of life despite maintaining Hb concentrations at acceptable levels. This contrasts with patients treated with ESAs supported with intravenous (iv) iron who often experience a noticeable improvement in quality of life almost immediately after starting treatment for their anaemia.

8. Patients with anaemia of chronic disease may benefit from iron therapy and/or erythropoiesis stimulating agents (ESAs)

- A number of ESAs have now been licensed for use in various countries, including darbepoetin alfa and two forms of recombinant human erythropoietin. The range of iv iron preparations available to clinicians has also increased recently with the introduction of iron sucrose and sodium ferric gluconate in addition to iron dextran.
- In most countries, ESAs are used most extensively in renal dialysis patients, although their use in oncology is increasing, especially in patients receiving myelosuppressive chemotherapy[28]. The experience built up in renal units, including the optimisation of ESA therapy by the use of iv iron, should be transferred to other specialties. However, specific clinical trials should be performed in a number of chronic conditions for confirmation and to determine special considerations for different populations. Similarly, the different ESAs and iron preparations should be compared systematically to determine the best and most cost-effective treatment strategies[29,30].
- A study of 30 patients with rheumatoid arthritis and Hb < 12 g/dL (for women) or < 13 g/dL (for men) showed benefits of treatment with an ESA and iv iron in terms of the proportion of hypochromic red blood cells, serum ferritin concentration and quality of life (SF-36 measure of vitality)[30].
- The effectiveness of ESA treatment is enhanced by the co-administration of iv iron. Use of iv iron can accelerate or increase the response to the ESA[31–34].
- Use of iv iron may reduce the dose of ESA required to achieve a given response[34].
- In some cases, use of iv iron alone (i.e. without an ESA) can provide substantial improvements[35–37].
- Other adjuncts to ESAs (e.g. vitamin C, vitamin E, androgens, carnitine, pentoxifylline and statins) have not consistently been shown to be useful, or have been shown to pose an unacceptable risk of adverse effects, and are, therefore, not recommended[38].

9. Oral iron causes side-effects, is associated with drug–drug interactions, and has limited efficacy in chronic anaemia

- In one study of 155 cancer patients (whose compliance with oral iron treatment was carefully monitored), the increase in Hb concentration in those receiving oral iron and an ESA was not significantly different from those who received no iron, whereas those receiving iv iron plus an ESA experienced a significant increase in Hb[31].
- In another study of dialysis patients receiving an ESA, those receiving oral iron did not have a significantly different response from those receiving no iron in terms of Hb and ferritin concentrations[34].
- Oral iron has several disadvantages including poor compliance and a high incidence of adverse gastro-intestinal effects (nausea, vomiting, constipation, bloating and bleeding) and a high potential for interactions with other treatments.
- Oral iron should, therefore, be avoided.

10. Intramuscular (im) iron is associated with unacceptable adverse effects and should not be given

- Intramuscular iron is no more effective than iv iron but is painful to deliver and may cause staining of the injection site and has been associated with gluteal sarcomas[39–41].

11. Intravenous (iv) iron can be given safely to patients with chronic diseases

- Data from over 32 000 haemodialysis patients in the United States have shown no association between all-cause mortality and cumulative 6-month iv iron dose[42].
- A French study of over 6000 patient-months of haemodialysis found no association between total dose of iv iron, or ferritin levels, and risk of infection[43].
- Serious adverse reactions to all iv iron preparations are rare[44]. Two studies have suggested that anaphylactic reactions with iron dextran occur with 0.6–0.7% of doses[33,41]. Another study reported lower rates of adverse events associated with low molecular weight iron dextran than with high molecular weight dextran[44].
- A recent analysis suggests rates of anaphylaxis of around three per million doses with iv iron dextran and less than one per million doses of iron gluconate or iron sucrose[45].
- The real clinical consequences of oxidative stress associated with free iron release after iv administration have not been determined.
- Use of iv iron was traditionally avoided in RA because of concerns about disease flares. However, a more recent study has shown that not only may iv iron be given safely to people with RA, but its use, in combination with ESAs, is associated with a reduction in disease activity score[30].
- IV iron should not be given to patients with active sepsis[46].
- Animal studies using very high doses have suggested that iron may promote tumour growth but these findings have not been reflected in clinical experience and probably do not apply

to patients with normal levels of transferrin saturation. They may also not be relevant to the doses of iv iron given in normal clinical practice[47]. However, caution should be exercised in patients with high transferrin saturation (above 50%) since use of iv iron in this population may, theoretically, be associated with enhanced tumour growth or unwanted effects such as increased cardiotoxicity of chemotherapeutic agents[48].

- Bone marrow and tumour cells may compete for available iron. However, in patients with normal levels of transferrin saturation nearly all the iron from a therapeutic dose will be taken up by the bone marrow cells since their transferrin receptors are much more numerous, and have a greater affinity for iron, than those present on tumour cells. In addition, exposure of tumour cells to excess transferrin iron will be short-lived because it will be rapidly quarantined in the reticuloendothelial 'stores'.

12. The management of anaemia calls for the development of a specialist service, education of all healthcare professionals and transfer of skills from areas of good practice

- Following the recognition of the high prevalence of anaemia in patients undergoing dialysis, management is currently coordinated best in renal medicine. According to international clinical practice guidelines, patients receiving dialysis now receive treatment with ESAs and iv iron[2]. However, in other specialties, training and experience in these therapies may be lacking and anaemia management is ill coordinated. The increasing specialisation within haematology has resulted in advances in the treatment of leukaemia but a decline in the treatment of anaemia[49]. The development of nurse consultants in anaemia (in the UK) serving a wide range of specialties, or other models involving other healthcare professionals with a focus on anaemia, may be the way forward.

Conclusions

Anaemia is important to patients. This is not generally appreciated in the clinical community. The need for specialist understanding and management of chronic anaemia is, as yet, poorly recognised and treatment is often poorly organized. We believe that it is now time to rectify these deficiencies. This may require funding but, more importantly, it will require a fundamental change in attitude: anaemia really does matter.

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Competing interest statements

Michael Auerbach has acted as a consultant for Watson Pharmaceutical. George R. Bailie has been a consultant for American Regent, Inc. and Vifor International and has received honoraria from Amgen, Inc. He is a member of the Advisory Board for NKF's K/DOQI and is a member of the workgroup for the K/DOQI Anaemia Clinical Practice Guidelines. Peter Barrett-Lee has taken part in advisory boards and received honoraria from Amgen and Roche, and received research funding from Roche. Yves Beguin has been on advisory boards for Amgen, Roche and Vifor. Ivor Cavill has acted as a consultant for Vifor International and Syner-Med and has received honoraria for speaking from American Regent, Amgen UK, Roche Pharmaceutical Products and Ortho Biotech (Janssen-Cilag). His position at the University of Cardiff is supported by UK Anaemia. J. P. Kaltwasser has taken part in an advisory board for Amgen and received recombinant human erythropoietin (Recormon) from Boehringer Mannheim (now part of Roche) for a clinical trial. Tim Littlewood has acted as a consultant for Amgen, Ortho Biotech and Roche. Iain Macdougall has acted as a consultant for Affymax Ltd, Amgen UK, Roche Pharmaceutical Products and Ortho Biotech (Janssen-Cilag).

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