Blood transfusions in palliative care patients with advanced cancer
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# GDG Membership

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<tr>
<th>Name</th>
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<td>Noreen Boyd</td>
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<td>Dr Stephen Hawkins</td>
<td>Consultant Haematologist</td>
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Introduction
Introduction

• What do we need to update our blood transfusion guidelines
  – New evidence for restricted transfusions?
  – NICE guidance Nov 2015
  – Cochrane review on restrictive transfusions (Carson, 2016)
  – TRICC trial (Herbert, 1999)
  – FOCUS trial (Carson, 2011)

• Evidence for restricted transfusion
  – Different patient groups (mostly surgical, critical care, IHD)
  – All inpatients / acute settings
Introduction

• Why have we only looked at the cancer patient cohort?
  – Management would differ in other patient groups
  – Management of anaemia in this group of patients can be challenging
  – Some treatments are part of routine management for certain patient cohorts e.g.
    • Erythropoietin-stimulating agents for patients in renal failure
    • IV iron for patients with iron deficiency anaemia (non-malignant cause) e.g. IBD, CKD

• Why do patients with cancers get anaemia? (Mercadante, 2000)
  – Direct effect of cancer (bone marrow replacement, blood loss)
  – Results of cancer treatment itself
  – Chemical factors produced by the cancer (overproduction of cytokines inhibiting erythropoiesis)
TRICC trial (Herbert, 1999)

- Liberal transfusions (n=420) vs restrictive transfusions (n=418)
- Liberal transfusion group were transfused RBC when Hb <100g/L
- Restrictive transfusion group were transfused RBC when Hb <70g/L
- [Hb] maintained between 70-90g/L
- Overall 30-day mortality similar in both groups.
- Restrictive transfusion as least as effective as and possibly superior to liberal transfusions in critically ill patients (with the exception of patients with acute MI or unstable angina)
FOCUS trial (Carson, 2011)

• 2016 patients with history/risk factor for CVD whose Hb <100g/L post surgical repair of hip fracture.
• Liberal transfusion group: Hb threshold 100g/L
• Restrictive transfusion group: Hb threshold <80g/L
• Primary outcome
  – Death
  – Unable to walk across room without human assistance on 60-day follow-up.
• Results
  – Outcomes did not differ significantly between the 2 groups
  – Rates of MI or CCF were not increased in the liberal-strategy group
Transfusing at a restrictive Hb of between 7g/dL to 8g/dL decreased proportion of participants exposed to RBC transfusion by 43%.
No evidence that restrictive transfusion strategy impacts 30-day mortality/morbidity.
Not enough data to inform safety of restrictive transfusions in certain clinical subgroups, including cancer patients.

(Carson, 2015)
Current Standards & Guidelines
Current Guidelines

• Suggests consideration of Tranexamic Acid and Etamsylate to reduce bleeding in palliative care patients [Level 4]

• Covers
  – Transfusion of red cells
  – Transfusion of platelets
  – Transfusion reactions
  – Discontinuation of transfusions
  – Erythropoietin
Current Standards

1. It is important to identify, document and treat the cause of anaemia if possible [Grade D]

2. Symptoms should be recorded before and after the transfusion to determine whether there has been any benefit. This will facilitate decision-making regarding future transfusions [Grade D]

3. The patient should give informed consent for the procedure and this should be documented in the patient notes. [Grade D]

4. Patients should be offered written information regarding their transfusion [Grade D]
Current Standards

5. All patients receiving a blood transfusion should wear a patient identity wristband or equivalent. [Grade D]

6. Each blood unit should be transfused within 4 hours of removal from refrigeration. [Grade D]

7. An infusion pump should be used to control the rate of transfusion. [Grade D]

8. All staff involved in blood transfusions should receive competency-based training in line with national targets. [Grade D]

9. Serious adverse reactions and events should be reported via the online SABRE system. [Grade D]
Literature Review
Question for the literature review

“In patients with anaemia with advanced incurable cancer receiving palliative care, does transfusion of red blood cells improve symptoms and quality of life and what evidence is there to support this compared to other interventions e.g. erythropoiesis-stimulating agents, intravenous iron, folic acid, tranexamic acid and etamsylate?”
### PICO

<table>
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<tr>
<th><strong>Population</strong></th>
<th>Patients with anaemia with advanced incurable cancer receiving palliative care. Any setting.</th>
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<td><strong>Intervention</strong></td>
<td>Transfusion of <strong>red blood cells</strong></td>
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| **Comparators**  | Erythropoiesis-stimulating agents  
Iron  
Folic acid  
Tranexamic acid  
Etamsylate |
| **Outcome**      | Improved symptom control (e.g. dyspnoea, fatigue), quality of life and performance status. |
Search strategy

- Medline
- EMBASE
- CINAHL
- Cochrane
- NICE evidence
- Hand search (reference lists)
Search strategy

Exclusions

• Under 18 years old
• Non-English language articles
• Patients receiving active oncology treatment (e.g. chemotherapy, radiotherapy, biological agents)
• Patients undergoing surgery
• Non-cancer
• Case reports, editorials, letters
Medline (n=361)

CINALH (n=41)

EMBASE (n=75)

Cochrane (n=1)

Other (n=6)

Total (n=484)

Exclusions of abstracts and titles (n=460)

Articles selected for full text review (n=24)

Exclusions full text (n=11)

Study did not answer PICO 2
Poor quality study 5
Survey 1
Case studies 1
Study did not meet inclusion criteria 2

Studies included in the updated review (n=13)
NICE guidance NG24 : Published Nov 2015
NICE guidance NG24 : Published Nov 2015

• Covers
  - assessment for and management of blood transfusions in adults, young people and children over 1 year old.
  - general principles of blood transfusion
• Recommend single-unit transfusions in the absence of active bleeding (reassess after each unit).
• Recommends restrictive transfusion and lower Hb threshold (70g/dL) and target (70 - 90 g/dL).
Cochrane Review
• No RCTs. 12 before and after studies.
• 31-70% participants appeared to show some symptomatic response to blood transfusions between day 2 – day 7 with scores returning to baseline by day 14.
• 23-35% died within 14 days of transfusion.
• 3 trials showed no improvement of performance status post-transfusion.

(Preston, 2012)
Literature Review

• No evidence to suggest change in practice for blood transfusion in the palliative care population (Torres, 2014) [Level 2++].

• Significant improvement in symptoms immediately post transfusion but this effect wanes around 2 weeks (Mercadante, 2009; Cochrane review 2012) [Level 2]

• ESA may be helpful for treatment or anaemia of chronic disease in patients not receiving chemotherapy (Johansson, 2001; Smith, 2003; Gordon, 2008) [Level 1+]

• No evidence found for intravenous iron, etamsylate, tranexamic acid or folic acid as superior to blood transfusion.
Effects of red blood cell transfusion on anaemia-related symptoms in patients with cancer

- Mercadante (2009) [Level 2-]
  - Hb, wellbeing & fatigue improved at 2 days but effect partially lost 15 days after transfusion despite maintaining Hb.
  - Supports evidence for short term benefits from transfusions in terms of symptoms

- Gleeson (1995) [Level 3]
  - Wellbeing : improved at 2 days, sustained at 14 days
  - Weakness & SOB : improved at 2 days, effect waned at 14 days
  - Degree of response not related to pre-transfusion Hb

- Tanneberger (2004) [Level 3]
  - Mean duration of response (symptom control) was 18.5 days
Erythropoietin-stimulating agents

- **Smith (2003) [Level 1+]**
  - Weekly vs 3-weekly vs 4-weekly dosing schedule of Darbepoetin
  - Mean time to response 1-2 months
  - Supports work that ESAs helpful in treatment of anaemia of chronic disease (ACD) in patients NOT receiving chemotherapy
  - Q3W / Q4W regime just as effective as QW regime

- **Gordon (2008) [Level 1+]**
  - Darbepoetin vs placebo
  - Higher % patients in Darbepoetin group achieved haematopoietic response (69% vs 24%, p<0.001)
  - No difference in transfusion incidence (both 11%)
  - Subsequent Phase III trial reported reduced survival in Darbepoetin group
Erythropoietin-stimulating agents

• Mystakidou (2005) [Level 1+]
  – Weekly Epo + oral iron led to statistically significant (p<0.05) improvements in Hb (increased by ave of 2.4g/dL in week 24) and QOL vs oral iron alone

• Johansson (2001) [Level 1+]
  – High dose vs low dose Epo (+ oral iron)
  – High dose: Epo dose doubled if Hb <15 after 4/52 or <20 after 8/52
  – Hb values increased in both groups
  – Transfusion incidence: 54% in low dose group, 40% in high dose group
  – Improved QOL
  – More adverse events in high dose group
Proposed Updated Standards and Guidelines
Introduction

• Anaemia commonly occurs in patients with both advanced malignant and non-malignant disease (Ludwig, 2004). It is important to understand the cause(s) of anaemia if possible, although investigations to determine the cause may be inappropriate.

• Potential causes of anaemia in palliative care patients include blood loss, impaired red cell formation by the marrow and excess red cell destruction. (Dunn, 2003)

• Symptoms of anaemia may be very debilitating and can significantly affect patients’ quality of life. Symptoms commonly associated with anaemia include fatigue, dyspnoea, decreased exercise capacity, diminished overall wellbeing and decreased appetite. (Mercadante, 2000)
Proposed New Guidelines

Transfusion of red cells

- Consider transfusion when Hb < 10g/dL [Level 3]
- If prognosis less than 14 days, transfusion for weakness may not be appropriate [Level 3]
- The patient should give informed consent for the procedure and this should be documented in the case notes. They should also be offered written information regarding their transfusion [Level 4]
- All patients receiving a blood transfusion should wear a patient identity wristband or equivalent [Level 4]
- Furosemide 20-40mg PO/IV with alternate units should only be prescribed for patients at risk of fluid overload [Level 4]
Proposed New Guidelines

Transfusion of red cells

• 1 unit of blood will raise Hb level by approximately 1 g/dL. The pre-transfusion Hb level and other clinical indicators should influence the number of units transfused. [Level 4]

• The red cells should be transfused within 4 hours of removal from cold storage and each unit should therefore be prescribed over 2-3 hours. [Level 4]

• The use of an infusion pump is recommended to ensure the transfusion is completed within safe time limits. [Level 4]

• Pulse, BP and temperature should be recorded at least before and 15 minutes after starting the transfusion. Further observations may be appropriate depending on the clinical situation. [Level 4]

• All staff involved with the blood transfusions process should receive competency-based training in line with national targets [Level 4]
Proposed New Guidelines

Transfusion of red cells

- Blood transfusions should only be considered in patients with symptomatic anaemia. There has been recent evidence to suggest restrictive red blood cell transfusion thresholds and targets, and single unit transfusions in patients who do not have active bleeding. However there was not enough data to inform the safety of this transfusion policy in certain clinical subgroups, including patients with cancer. [Level 4]

- If the estimated prognosis is expected to be short weeks, a blood transfusion may not be appropriate. Studies have shown that pre-transfusion haemoglobin levels do not correlate with response to transfusion. [Level 2]

- There is some evidence around restrictive thresholds and targets and restrictive transfusions however these randomised controlled trials have not been carried out in the palliative care population. It would be the responsibility of individual units to decide whether or not to implement a restrictive transfusion policy. [Level 4]
Proposed New Guidelines

Transfusion of red cells (continued)

• There is limited evidence that patients with better functional status and prognosis seem to derive the most benefit from blood transfusions [Level 2]

• The Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) recommends that ‘valid consent’ for blood transfusion should be obtained and documented in the clinical record (signed consent for transfusion is not mandatory, but may be a local requirement). [Level 4]
Proposed New Guidelines

Transfusion reactions

• If a patient becomes febrile or develops a mild urticarial reaction, consider stopping the transfusion for a short period of time. The use of Hydrocortisone 100mg IV or Chlorpheniramine 10mg IV may be required. If the reaction does not settle, discuss with the local transfusion laboratory and consider stopping the infusion [Level 4]

• Severe transfusion reactions are rare but occur in about 1 in 7000 units transfused. In the event of a severe transfusion reaction, i.e. anaphylaxis or shock, the transfusion should be stopped immediately. Emergency treatment with IV fluids and adrenaline should be administered as appropriate. The reaction should be reported immediately to the local transfusion laboratory and local procedures followed. Serious adverse reactions and events should be reported via the online SABRE system. [Level 4]
Proposed New Guidelines

Transfusion reactions

• For patients who develop a mild transfusion reaction, defined as having no or limited change in vital signs e.g. isolated fever greater than 38°C and rise of 1–2°C from baseline and/or pruritus or rash but without other features (e.g. new hyper- or hypotension, nausea, malaise, collapse, flushing, pain, respiratory distress), it is reasonable to restart the transfusion following appropriate treatment under direct observation. [Level 4]

• Patients with mild isolated febrile reactions may be treated with oral Paracetamol (500-1000mg in adults). Patients with mild allergic reactions may be managed by slowing the transfusion and treatment with an antihistamine. [Level 4]
Proposed New Guidelines

Assessments post-transfusion(s)

- Assessment post transfusion should be undertaken within a week after the blood transfusion, including a review of relevant symptoms. [Level 4]
Proposed New Guidelines

Discontinuation of transfusions

• Some patients with a low haemoglobin level do not respond symptomatically to blood transfusion or may only respond for a short period of time. Decisions regarding the continuation of blood transfusions should be made on an individual basis, taking into account symptoms, prognosis, response to previous transfusions and patient wishes. [Level 3]

• Where possible, response to transfusion and discussions regarding future transfusions should be recorded in the case notes to aid future decision-making. This may form part of advance care planning conversations with patients. [Level 4]
Proposed New Guidelines

Erythropoietin

• There is evidence suggesting that the mean time of haemopoietic response to erythropoietin stimulating agents (ESAs) is between 1-2 months. Complications of ESAs include an increased risk of thromboembolic events. [Level 1]

• If you are considering use of ESAs, please liaise with your local haematologist for specialist advice [Level 4]
Proposed New Guidelines

• Patients receiving palliative radiotherapy should have a Hb >10g/dL [Level 1+]

• Iron supplements may be used for patients with iron deficiency anaemia. They may be poorly tolerated and prognosis should be considered [Level 4]

• The following may be used to reduce bleeding in palliative care patients [Level 4]
  – Tranexamic acid 1g TDS PO. Dose reduced to 500mg TDS once bleeding stopped. Avoid if massive haematuria & severe renal impairment. Reduce in renal failure.
  – Etamsylate 500mg QDS PO.
Proposed New Standards

1. It is important to identify, document and treat the cause of anaemia if possible [Grade D]
   The cause of anaemia must be identified and documented in all patients receiving blood transfusions. [Grade D]

2. Symptoms should be recorded before and after the transfusion to determine whether there has been any benefit. This will facilitate decision-making regarding future transfusions [Grade D]
   All patients should have an assessment of their symptoms pre- and post- transfusion to determine benefits of the transfusion and this should be clearly documented in the patients’ case notes. [Grade D]
Proposed New Standards

3. The patient should give informed consent for the procedure and this should be documented in the patient notes. [Grade D]

Informed consent (verbal or written) must be obtained from all patients receiving blood transfusions and this must be documented in the patients’ case notes. [Grade D]

4. All patients should be offered written information regarding their transfusion [Grade D]
Proposed New Standards

5. All patients receiving a blood transfusion should wear a patient identity wristband or equivalent. [Grade D]

6. Each blood unit should be transfused within 4 hours of removal from refrigeration. [Grade D]

7. An infusion pump should be used to control the rate of transfusion. [Grade D]

8. All staff involved in the blood transfusions process should receive competency-based training in line with national targets. [Grade D]

9. Serious adverse reactions and events should be reported via the online SABRE system. [Grade D]
National Blood Transfusion Audit
Patient and public representative:
Angela Fell
Invited Expert
Discussion
Discussion

1. Should the guidelines advise a transfusion threshold? If so, what should this threshold be?

2. When should the effect of the blood transfusion be assessed? (Consider the different settings)

3. How does the group feel about restrictive transfusions (i.e. single-unit transfusions)?