Original Article

Anemia at the End of Life: Prevalence, Significance, and Causes in Patients Receiving Palliative Care

Annabel Dunn, BSc, MBChB, FRNZCGP, Dip Pall Med (Melbourne), John Carter, MBChB, BMedSci, FRACP, FRCPA, and Helen Carter, BSc, MBChB, MPH, MD (Otago)
Mary Potter Hospice (A.D., H.C.), and Wellington School of Medicine (J.C.), Wellington South, New Zealand

Abstract

While data exist on the prevalence and causes of anemia in defined groups of the elderly, information on palliative care patients is limited. Compared to actively treated oncology patients, for whom anemia treatment has demonstrated improved quality of life and symptom alleviation, studies of treatment outcomes in palliative care patients are limited. Knowledge of the extent and causes of anemia in palliative care patients is needed, as correction of anemia in these patients could potentially improve their physical, emotional, and cognitive functioning. In the present study, clinical data and blood test results of 105 patients meeting specific eligibility criteria were examined to estimate the prevalence of anemia and investigate its causes. Ninety-five (90.5%) patients had advanced cancer. Based on World Health Organization criteria, anemia was found in 77% of men (Hb < 130 g/l) and 68.2% of women (Hb < 120 g/l). The diagnosis was anemia of chronic disease in 76.7% of women and 46.8% of men. Patients with prostate cancer had a significantly lower mean Hb level (P = 0.007) and more evidence of bone metastases (P = 0.0007) than those with other cancers. Neutrophil hypersegmentation, suggesting occult folate deficiency, was present in 28.6% of patients, being more common in those with major weight loss (58.3%) than those with moderate (37%) or mild/no weight loss (26%) (P = 0.019). The findings suggest that anemia is highly prevalent in the palliative care setting. Although anemia of chronic disease is most common, occult folate deficiency may be more prevalent than previously suspected. The findings suggest that a low serum folate level is an insensitive marker of occult folate deficiency. A randomized controlled trial of folic acid treatment is proposed.

J Pain Symptom Manage 2003;26:1132–1139. © 2003 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Anemia, palliative care, prevalence, causes, treatment

Introduction

In contrast to the elderly population,1–4 the prevalence of anemia in the palliative care population has not been previously described.
Although the clinical significance of anemia in palliative care patients has been receiving increasing recognition, there has been less attention given to identifying and correcting its causes. Possible reasons for this are the expense and invasiveness of treatments, and the perception that palliative patients are too ill for active treatment.

The World Health Organization (WHO) defines anemia as a hemoglobin (Hb) level of <120 g/l in women and <130 g/l in men. As in other patient groups, potential causes of anemia in palliative care patients include blood loss, impaired red cell formation by the marrow, and excess red cell destruction. Factors impairing red cell formation may include deficiencies of iron, folic acid, and vitamin B₁₂; the poorly understood processes leading to anemia of chronic disease; and marrow infiltration (disseminated malignancy).

The prevalence of anemia in groups of elderly in hospitals, rest homes, or the community has been found to range from 8% to 26%. General population-based studies of anemia have reported prevalence rates of 9% to 44%, with the highest prevalence in men 85 years or more. Recently, prevalence rates of 41% (pre-radiation) and 54% (post-radiation) have been found in cancer patients undergoing radiation. The prevalence of anemia in palliative care populations is unknown.

Anemia of chronic disease has been identified as the most common cause of anemia in the elderly, followed by iron deficiency, then folic acid or vitamin B₁₂ deficiency. Evidence exists that occult folic acid deficiency (where there is no evidence of overt erythrocyte macrocytosis) is frequent in the elderly and can contribute to cognitive impairment. Presumably, folic acid deficiency is also common in palliative care patients because of their poor dietary intake, increased demands for folic acid due to malignancy, and treatment with folic acid antagonist drugs, but this has not been previously demonstrated.

Non-controlled studies on the response of cancer patients to erythropoietin (EPO) treatment for chronic anemia have found reasonable responses (increase in Hb ≥ 20 g/l) for solid tumors and multiple myeloma, but poor responses for myelodysplasia. Randomized controlled studies have investigated the effects of EPO treatment on Hb levels and transfusion requirements in patients undergoing chemotherapy. These studies found that up to two-thirds of patients achieved an Hb increase of at least 20 g/l; there was a reduction in the numbers of patients requiring transfusion and patients’ ratings of their quality of life improved. A recent study showed incremental improvements in quality of life with every gram rise in Hb concentration, confirming that the ideal Hb target level (between 110 and 130 g/l) for enhancing quality of life is higher than previously thought.

Published studies on the treatment of anemia in the terminally ill are limited. However, non-controlled studies on the effectiveness of transfusing anemic palliative care patients found that transfusion alleviated some symptoms and improved patients’ well-being. Fatigue is recognized as a common symptom of cancer-related anemia, with other symptoms also being attributed to anemia. Fatigue has also been shown to have a negative effect on patients’ quality of life.

Despite the emphasis on symptom alleviation and improvement in quality of life in palliative care, the extent, causes, effects, and treatment of anemia have received limited attention. This review aimed to determine the prevalence and causes of anemia in patients admitted to a hospice facility and to identify patient groups that could be involved in future trials of treatment for anemia.

**Methods**

**Sample**

A prospective audit of clinical/demographic information and routine blood test results was undertaken for all patients admitted to Mary Potter Hospice’s inpatient unit from June 1 to November 30, 2001. Those excluded from the review included: 1) children (aged < 16 years); 2) those who had been transfused less than four weeks prior to admission or who were currently receiving a transfusion; 3) patients who had completed chemotherapy less than four weeks prior to admission; and 4) very ill patients who would not normally have had routine blood tests done.

Wellington Ethics Committee approval was obtained for the procedures, which involved access to patients’ medical file information.
and laboratory test results and close examination of blood films.

**Review of Blood Test Results**

The following tests were included in the review: 1) full blood count (FBC) and complete automated parameters; 2) serum iron studies (iron, total iron binding capacity, ferritin); 3) serum vitamin B<sub>12</sub> level; 4) red blood cell folate level and serum folate; and 5) serum creatinine and albumin.

Standard MGG stained blood films, routinely prepared by the Laboratory at the time of a request for a FBC, were collected and stored by the Hematology Laboratory at Wellington Public Hospital. The films were examined in batches using a ‘blinded’ methodology by one of the investigators (JC). Evidence of marrow infiltration (leucoerythroblastic features), tumor-associated microangiopathic hemolytic anemia (schistocytes) and folate/vitamin B<sub>12</sub> deficiency (hypersegmented neutrophils) were specifically recorded, as were other non-specific abnormalities. Neutrophil hypersegmentation was objectively determined by observing 100 consecutive neutrophils and calculating the segmentation index.29

**Clinical and Demographic Data**

An audit form was prepared for the purposes of recording demographic and clinical information extracted from the patients’ medical files. The following data were documented: patients’ age and sex, stage of illness, receipt of chemotherapy less than four weeks prior to admission, alcohol dependency, and drugs causing folate deficiency including antibiotics and antiepileptics. Symptoms commonly associated with anemia were routinely recorded as absent or present by hospice doctors at the time of the patients’ admission, using a standard medical assessment form. Doctors judged whether these symptoms were present on the basis of clinical examination as well as discussions with patients. They also recorded degree of symptoms as absent, mild, moderate and severe.

**Data Analysis**

The data were entered into a computer database and analyzed using the EPI 6 and SAS statistical programs. Chi-square tests were used for group comparisons which involved categorical variables and Fisher’s exact tests were used where cell numbers were less than 5. Pearson correlations were performed on Hb versus blood test values. As serum folate, iron, and vitamin B<sub>12</sub> appeared to be log-normally distributed, analysis was performed on the log of the values. In contrast, serum albumin and patients’ age appeared to be normally distributed. Unpaired t tests were used to compare mean Hb levels between 1) patients with and without the presence of particular anemia-related symptoms and 2) patients with and without anorexia. An unpaired t test was performed to compare mean serum folate levels between patients with neutrophil hypersegmentation and those without.

**Results**

**Patients**

The review included 105 patients. Exclusions comprised two children, 25 ‘very ill’ patients who died within four days of admission, and four patients who were transfused on admission.

Forty-four of the 105 (41.9%) patients were women and 61 (58.1%) were men. The mean age was 70.1 ± 12.8 years. The median age was 74.0 years (range, 29–90). While the study population was largely elderly (73.3% older than 65 years), more than one quarter (26.6%) of patients were aged less than 65 years.

Ninety-five of the 105 (90.5%) patients had a primary cancer diagnosis, and 10 (9.5%) had a non-cancer diagnosis. Non-cancer diagnoses included end-stage respiratory disease (4), end-stage heart disease (2), end-stage heart and respiratory disease (1), motor neuron disease (1), pseudomyxoma peritonei (1), and chronic liver failure (1). The most common diagnoses were gastrointestinal tract cancer (26.7%), urogenital cancer (21%), lung cancer (21%) and breast cancer (8.6%). Five patients (4.8%) had a primary hematological disorder, which included non-Hodgkin’s lymphoma (3), multiple myeloma (1), and chronic lymphatic leukemia (1). There were no patients with a prior history of thalassemia or sickle cell anemia.

Seventy-six (72.3%) patients had known metastatic cancer and 32 (30.5%) had bone metastases. Fourteen (13.3%) of patients died within 10 days of admission.
No patients had received chemotherapy less than four weeks prior to admission. One patient had a history of alcohol dependency, two were prescribed antibiotics that inhibit folate absorption, and one was prescribed phenytoin (which can affect folate utilization).

Prevalence of Anemia

The mean Hb level ± standard deviation (SD) for all patients was 114.2 ± 18.0 g/l. For patients with a primary cancer diagnosis, the mean Hb level ± SD was 113.5 ± 16.9 g/l. Based on WHO criteria, anemia was present in 47 (77%) of men and 30 (68.2%) of women.

Major weight loss was present in 12 of the 105 (11.4%) patients, four women and eight men. Anemia was present in all of these women and five of the eight (62.5%) men.

Twenty-eight of the 41 female patients (68.3%) with a cancer diagnosis were anemic, compared to two of three women (66.7%) with a non-cancer diagnosis (\(P = 0.671\)). Forty-four of 54 male patients (81.5%) with a cancer diagnosis were anemic compared to three of seven men (42.8%) with a non-cancer diagnosis (\(P = 0.002\)). Of the seven male patients with a non-cancer diagnosis, 3 had chronic respiratory disease with a correspondingly normal/high Hb (\(\geq 130\) g/l).

Factors Associated with a Low Hb (\(<120\) g/l)

There was no significant inverse association between age and Hb level (\(r = 0.032, P = 0.741\)). Table 1 shows correlations between Hb levels and blood test values. There were significant associations between low serum iron levels and low Hb levels (\(r = 0.336, P = 0.0005\)) and low serum albumin levels and low Hb levels (\(r = 0.387, P < 0.0001\)). There were no significant associations between low serum folate levels and low Hb levels (\(r = 0.112, P = 0.258\)), and low vitamin \(B_{12}\) levels and low Hb levels (\(r = -0.124, P = 0.208\)).

Of the 22 patients with urogenital cancer, 50% had prostate cancer. Compared to patients with other cancer types whose mean Hb level ± SD was 115.3 ± 16.5 g/l, patients with prostate cancer had a significantly lower mean Hb level (99.5 ± 13.7 g/l, \(P = 0.007\)). A significantly higher proportion (81.8%) of patients with prostate cancer had bone metastases compared to those with other cancer types (27.4%, \(P = 0.0007\)).

Seven (6.7%) patients had evidence of a low vitamin \(B_{12}\) level (\(<130\) pmol/l) and 23 (21.9%) had a low serum folate level (\(<6.5\) nmol/l). No patients had evidence of a low red blood cell (RBC) folate (\(<295\) nmol/l). A low serum albumin (\(<34\) g/l) was found in 63 (60%) patients.

Five of the 12 patients (41.7%) with a major weight loss had a low serum folate, one patient (8.3%) had a low serum vitamin \(B_{12}\) and 8 patients (66.7%) had a low serum albumin.

Hb Levels and Symptoms

Symptom ratings were recorded in the files of 103 patients. Symptoms present on admission were fatigue (84.5% of patients), weakness (78.6%), anorexia (75.7%), weight loss (72.8%), and breathlessness (42.7%). Table 2 shows differences in mean Hb levels between patients with and without a particular symptom. Patients with anorexia had a significantly lower mean Hb (112.0 g/l) than those without anorexia (121.6 g/l), (95% CI = 1.5, 17.7, \(P = 0.02\)). For other symptoms, there were no significant differences between those with and those without the symptom.

Causes of Anemia

Blood parameters (i.e., low iron, low ferritin, increased iron binding capacity) showed no evidence of uncomplicated iron deficiency anemia. Anemia of chronic disease (i.e., low iron, low iron binding capacity) was found in 23 (76.7%) women and 22 (46.8%) men with anemia.

Erythrocyte macrocytosis (\(>98\) fL) was evident in 10 (9.5%) of patients. Of these 10 patients, 3 had a low serum folate level and 4 had evidence of neutrophil hypersegmentation. Of

---

**Table 1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Patients</th>
<th>Pearson Correlation Coefficient ((r))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>105</td>
<td>0.032</td>
<td>0.741</td>
</tr>
<tr>
<td>Serum iron(^b)</td>
<td>105</td>
<td>0.356</td>
<td>0.0005</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>105</td>
<td>0.387</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum folate(^a)</td>
<td>104</td>
<td>0.112</td>
<td>0.258</td>
</tr>
<tr>
<td>Serum vitamin (B_{12})(^b)</td>
<td>104</td>
<td>(-0.124)</td>
<td>0.208</td>
</tr>
</tbody>
</table>

\(^a\)Age and blood test values.

\(^b\)Log of the values.
Table 2
Comparisons Between Mean Hb Levels for Patients With and Without Anemia-Related Symptoms and Anorexia

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of Patients</th>
<th>Mean Hb (g/l)</th>
<th>(95% CI)</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>16</td>
<td>110.6</td>
<td>(−14.2, 5.4)</td>
<td>−0.89</td>
<td>0.373</td>
</tr>
<tr>
<td>Present</td>
<td>87</td>
<td>115.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakness*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>22</td>
<td>113.1</td>
<td>(−10.3, 7.1)</td>
<td>−0.37</td>
<td>0.714</td>
</tr>
<tr>
<td>Present</td>
<td>81</td>
<td>114.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breathlessness*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>59</td>
<td>111.7</td>
<td>(−13.4, 0.83)</td>
<td>−1.75</td>
<td>0.083</td>
</tr>
<tr>
<td>Present</td>
<td>44</td>
<td>117.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>25</td>
<td>114.6</td>
<td>(1.5, 17.7)</td>
<td>2.35</td>
<td>0.020</td>
</tr>
<tr>
<td>Present</td>
<td>78</td>
<td>107.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Anemia-related symptoms.

the 30 patients with neutrophil hypersegmentation, 26 (86.7%) had no evidence of macrocytosis.

There was no evidence of marrow infiltration or microangiopathic hemolytic anemia on blood film examination. Sixty films (57.1%) showed rouleaux formation.

Neutrophil hypersegmentation (index > 30), suggesting occult folate deficiency, was evident in 30 (28.6%) of films. Neutrophil hypersegmentation was more common in those with a major weight loss (58.3%) compared to those with a moderate (37%) or mild/absent weight loss (26%), P = 0.019.

There was no significant difference in mean serum folate levels between those with neutrophil hypersegmentation and those without (P = 0.567). Serum folate levels in those without neutrophil hypersegmentation were 1.07 (95% CI = 0.84, 1.38) times the level of those with neutrophil hypersegmentation.

Discussion

Nearly 80% of men and 70% of women were anemic on the basis of the WHO criteria, indicating that it is a common entity in this hospice group. As the study excluded patients who were very ill, the prevalence of anemia in the total inpatient group was likely to have been even higher.

This prevalence was high compared to the rates found in defined groups of the elderly and large general population studies, and comparable to the rates found in cancer patients following chemotherapy or radiotherapy. For example, a recent study of patients with advanced cancer showed a rate of anemia of 41% prior to radiotherapy, rising to 54% post radiotherapy. Tas et al. found that the prevalence of anemia in cancer patients pre-chemotherapy varied by cancer type. Breast cancer patients had a rate of anemia of 44% pre-chemotherapy, increasing to 60% post-chemotherapy. The highest rate of anemia was found in lymphoma patients; 82% were anemic pre-chemotherapy with little change occurring after chemotherapy. A significant difference between hospice cancer patients and advanced cancer patients undergoing therapy is that, in the latter group, anemia may recover over a period of weeks following chemotherapy or radiotherapy if the disease responds to treatment, while in hospice cancer patients, anemia is likely to worsen as the disease progresses.

Anemia was found to be significantly more prevalent in male patients with cancer than men with a non-cancer diagnosis. An explanation for this was that three of the seven men with a non-cancer diagnosis had chronic respiratory disease with a corresponding normal/high Hb. The lack of difference found between women with cancer and those without cancer was probably attributable to the small study numbers in the non-cancer group.

Anemia of chronic disease was found to be a common cause of anemia in this palliative care group, being present in almost 50% of men and over 70% of women with anemia. A probable cause of anemia of chronic disease is a complex interaction of inflammatory cytokines
released as part of the inflammatory process, causing a blunting of the usual erythropoietin response to anemia and the impaired release of iron from the reticuloendothelial system. The rates of anemia of chronic disease in this study were higher than the rates (up to 45%) reported in anemic elderly patients in hospitals and in cancer patients, which have been found to vary from 10% to 60% depending on the type of cancer and whether or not patients are receiving chemotherapy. Similar mechanisms to those producing the anemia of chronic disease are presumably responsible for the high prevalence of hypoalbuminemia and rouleaux found in this study.

It should be noted that, in palliative care patients, the causes of anemia may be difficult to determine, as anemia is often a mixed picture, including anemia of chronic disease, bone marrow infiltration with neoplasia, and blood loss. Although there was no evidence of uncomplicated iron deficiency anemia in this group, iron deficiency anemia was likely to have been common. The detection of iron deficiency anemia based on blood parameters is complicated because of the mixed etiology of anemia. Serum ferritin, which is traditionally low in iron deficiency, can be raised by co-existent inflammation, malignancy and hepatic disease and can mask iron deficiency. A more definitive test for iron deficiency anemia is examination of the bone marrow aspirate for iron content, although this test may now be superseded by the transferrin receptor assay.

Nearly 7% of patients had a low vitamin B12 level, which is similar to the percent found in some elderly populations. Although just over 20% of patients had a low serum folic acid level, blood film examinations suggested that occult folic acid deficiency occurred in nearly 30% of patients. In contrast to vitamin B12 stores, which last up to two years, body stores of folic acid can be depleted in four to five months. The theoretical likelihood that folic acid deficiency is common in palliative care patients (where dietary deficiency, increased tissue demands resulting from neoplasia and the effects of folate-depleting drugs are often present) was confirmed by this study.

Examination of blood films for neutrophil hypersegmentation has been recommended as a reliable method for identifying deficiencies in folate and vitamin B12, as well as the presence of uremia. Furthermore, hypersegmentation is reportedly the first hematological abnormality to appear in folate deficiency. In this study, examination of the peripheral blood film for neutrophil hypersegmentation provided a convenient method for investigating folic acid tissue deficiency, as blood films are routinely prepared by the laboratory on the request of a full blood count. In line with previous studies, these study findings suggested that a low serum folate acid level is not a sensitive indicator of tissue folic acid deficiency. This study also confirmed previous observations that neutrophil hypersegmentation often occurs in the absence of erythrocyte macrocytosis. Although serum homocysteine and methylmalonic acid levels are reportedly better indicators of folate acid and vitamin B12 deficiency, these assays are not routinely performed by the laboratory.

The proportion of palliative care patients in this study with suggestive folic acid deficiency (nearly 30%) was high compared to rates of 5–10% which have been found in elderly European populations. The findings also suggested that the presence of folic acid deficiency becomes progressively higher as weight loss increases. These findings are significant, as folic acid deficiency is reportedly associated with neuropsychiatric disorders and improvements in cognition and depression in elderly patients have been found after folic acid supplementation.

Fatigue and weakness were found to be common symptoms in this palliative care group, occurring in 85% and 79% of patients, respectively. In contrast to other studies, this study did not find a significant association between anemia and presence of fatigue. This may have been because physicians did not use an instrument that was sensitive to measuring anemia-related fatigue. Given the multifactorial cause of fatigue in terminally ill patients, the use of an instrument specifically designed to measure anemia-related fatigue is recommended for future studies. The Functional Assessment of Cancer Therapy Anemia (FACT-An), which has been validated in cancer patients, has been found to successfully discriminate patients on the basis of Hb levels and performance status.

The study found that patients with advanced prostate cancer were significantly more likely to have a lower mean Hb level and presence of bone metastases than other cancer patients.
prostate cancer patients are commonly represented in palliative care populations, further research is recommended to investigate the effectiveness of treatments for anemia in this group.

In conclusion, the findings confirmed the relatively high prevalence of anemia in this inpatient palliative care group. They also suggested a high prevalence of occult folic acid deficiency, which progressively increased as weight loss increased. Clinicians working in palliative care have long emphasized the need to treat the patient and not just the blood test. Perhaps the time has come for closer attention to be paid to the blood test as a means of improving the quality of life of palliative care patients. This recommendation is supported by the growing evidence that raising Hb levels to within normal parameters (e.g., women ≥120 g/l, men ≥130 g/l) in cancer patients significantly improves their quality of life scores. However, when treating anemia in palliative care patients, factors such as the cost effectiveness and degree of invasiveness of the treatments must be considered.

On the basis of the findings, a randomized controlled trial is proposed to determine whether or not folic acid treatment is effective in improving the quality of life and cognitive functioning of folic acid deficient patients receiving palliative care. In undertaking this trial, there is a need to carefully monitor the effects of folic acid treatment on the sub-groups of patients with moderate and major weight loss, in whom there is suggestive evidence of high rates of folic acid deficiency.

Acknowledgments

Our thanks to the Wellington Hospital Laboratory staff and the Medical Laboratory staff for assisting with the blood test results, in particular, Glenys White (Capital and Coast DHB). We are also grateful to Robin Green and Gordon Purdie, statisticians, Wellington School of Medicine, for their advice on the data analysis.

References

18. Littlewood TJ, Bajetta E, Norton JWR, et al. Effects of epoietin alfa on hematologic parameters and


