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Estimating prevalence of functional iron deficiency anaemia in advanced cancer

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Abstract

Purpose

Anaemia is a common complication of cancer causing symptoms including fatigue. It is also associated with shorter survival. Cancer causes systemic inflammation which interrupts iron metabolism leading to a functional iron deficiency (FID). There are few data on prevalence or aetiology of anaemia in those with advanced cancer. We aimed to establish the prevalence of anaemia and estimate extent of FID anaemia in patients with advanced cancer.

Methods

All patients with advanced cancer referred to two UK specialist palliative care services over one year were identified. Demographic and clinical data were linked with routinely collected haematological and biochemical profiles. We assessed the numbers of patients with abnormal values for haemoglobin, %hypochromic red cells (>5% indicates iron restricted erythropoiesis) and CRP (>10 indicates systemic inflammation). We judged that FID anaemia was likely when patients had all three abnormalities and ferritin 30-800ng/ml.

Results

1797/2416 patients had a cancer diagnosis and laboratory data available. Mean haemoglobin was 116g/L. 63% of patients were anaemic; mild 25%, moderate 35% and severe 3%. Women had significantly higher mean haemoglobin than men and there was wide variation in anaemia prevalence across tumour sites. Thirty nine percent of patients' who had all four parameters checked met our criteria for FID anaemia. There were significant relationships between haemoglobin, %hypochromic red cells and CRP (p=0.0001).

Conclusions

Anaemia was common in this population and we estimate this was caused by FID in 66% of anaemic patients. Further research is needed to validate our diagnostic criteria before this approach can be used in clinical practice.

Key Words

anemia; functional iron deficiency; advanced cancer; palliative care

Introduction

Anaemia is a common complication of cancer and causes symptoms including fatigue and breathlessness, with fatigue being the most frequently reported symptom [1]. Studies have shown that prevalence of anaemia is related to both stage of disease and tumour site [2]. In the European Cancer Anaemia Survey (ECAS) of over 15,000 patients, 39% of cancer patients were anaemic at baseline and this increased to 67% of those undergoing chemotherapy (Hb<120g/L) [3]. However, in patients with advanced cancer, fewer data are available. In a study of 105 palliative care patients, the majority of which had cancer, 77% of men and 68.2% of women were anaemic [4]. Aetiology of anaemia in advanced cancer has not been well described.

Normal erythropoiesis relies on utilising iron stored in macrophages, and absorbed from the intestine via enterocytes, a process regulated by ferroportin. Ferroportin is a transmembrane protein that exports iron [5] and is the only known vertebrate cellular iron exporter [6]. Pro-inflammatory cytokines, especially interleukin-6 (IL-6) and tumour necrosis factor (TNF) induce hepcidin, a small peptide produced by the liver. Hepcidin causes the destruction and endocytosis of ferroportin which results in inhibition of intestinal iron absorption and iron release from macrophages and hepatocytes. Cancer induced inflammation elevates hepcidin which may result in insufficient iron availability for erythrocytes despite adequate levels of total body iron (and adequate oral iron intake), a state known as Functional iron deficiency (FID) which can result in anaemia of chronic disease [7]. Patients with advanced cancer (and increasing systemic inflammation) are likely to have FID as the predominant aetiology of anaemia. Understanding the cause of anaemia in advanced cancer can direct more tailored treatment.

There are current guidelines on identifying FID [8] but no consensus on diagnosing or treating FID. A large study of 1528 patients with stage I-IV cancer found FID to comprise 81.9% of those with any sign of iron deficiency combined with haemoglobin ≤120g/l [2]. In another study that included 76 (72.3%) patients with metastatic cancer in the palliative care setting, FID was diagnosed in 76.7% of anaemic women and 46.8% of anaemic men [4]. In that study, FID was defined as low iron stores and low iron binding capacity in those with a haemoglobin ≤120g/l. These two studies illustrate the differing diagnostic criteria used for establishing FID. Table I demonstrates a sample of parameters and thresholds which have been used in studies of FID. There is a lack of agreement even when using the same tests, and parameters can also differ depending on disease studied [9].

INSERT TABLE I

Anaemia is important not just because of its influence on symptoms but because of its association with shorter survival times for patients [10]. Anaemia may simply reflect more advanced disease, but these data also serve to highlight the need for early detection and instituting correct treatment. We aimed to establish the prevalence of anaemia and estimate extent of FID anaemia in a large population of patients with advanced cancer using routinely reported haematological data to guide clinicians without the need for additional investigations.

Methods

Sampling

We identified all patients with cancer referred to two UK specialist palliative care services between April 2013-March 2014 using electronic medical records. Both services provide community and inpatient care to a predominantly urban population. We linked palliative care electronic records with laboratory data on routinely collected haematological and biochemical profiles taken within 4 weeks of first referral to palliative care services. We only included patients once in our analysis (at the time point closest to referral) even if multiple blood testing had occurred. Patients were excluded if they had a non-cancer diagnosis or if no laboratory data were available. We did not have access to full clinical records to obtain data on symptoms or treatments such as medication or blood transfusions.

Laboratory data

Routinely reported items collected were:

Haematological: haemoglobin (Hb), white cell count, platelets, mean cell haemoglobin, mean cell volume, red cell distribution width and % red cell hypochromia. Ferritin was not recorded in many patients but results have been analysed due to its clinical importance for assessing anaemia aetiology. Transferrin saturation was only measured in two patients so not included in the analysis although useful for the diagnosis of FID. We used WHO criteria [11] to determine normal and abnormal values for haemoglobin, Table II.

INSERT TABLE II

Biochemical: Creatinine, C-reactive protein (CRP), bilirubin, B12, folate

Other parameters were recorded when measured but were not found in a significant proportion of patients so were not reported in detail: iron studies, LDH, reticulocytes. Please see appendix 1 for normal values of parameters recorded.

Analysis

We assessed the numbers of patients with abnormal values for Hb, %hypochromic red cells (values >5% indicate iron restricted erythropoiesis), CRP (values >10 indicate systemic inflammation [12, 13] and ferritin.

After reviewing the ferritin parameters used in other studies of FID we judged those with a value between 30-800ng/ml to be in keeping with FID [2,9,20,21]. Using % hypochromic red cells to detect FID has been well described [14, 15, 16]. Ferritin was only measured in 246/1797 patients (14%). Therefore two algorithms are used to estimate FID:

1) Ferritin, Hb, % hypochromic red cells and CRP
2) Hb, % hypochromic red cells and CRP.

We developed a pragmatic clinical algorithm based on presence of three routinely reported haematological parameters: anaemia, iron restricted erythropoiesis and systemic inflammation. This method has not been used in previous studies in this area. We judged that FID anaemia was likely when patients had all three abnormalities: anaemia

(Hb<110g/L), iron restricted erythropoiesis (%hypochromia >5) and systemic inflammation (CRP>10). From this, we estimated the proportion of patients with advanced cancer that were likely to have FID anaemia. We calculated mean or median values and standard deviations or interquartile ranges for each of these parameters to explore the relationship with clinical characteristics.

Results

Patient characteristics

In the one year period, 2416 patients were referred to the two palliative care services. 1920/2416 (79%) patients had a cancer diagnosis and of these 1797 (94%) had relevant haematological data. Mean age of the included cancer patients was 71 years and there were equal proportions of men and women. 97 patients (5%) had a haematological malignancy with the majority (1699, 95%) having a solid tumour. Tumour site distribution is outlined in the table 4; the most common tumour sites were lung (which included mesothelioma), upper gastro-intestinal, and colorectal.

FID parameters

Mean haemoglobin for the whole sample was 116g/L (SD 25.46). 63% of patients were anaemic (see table II). No relationship was found between age and haemoglobin (correlation -0.066, 95% CI -0.11 to -0.02 p=0.0051). A significant difference between the mean Hb in females and males was found (female mean Hb 118g/L, SD 21.38 95% CI 117 to 120; male mean Hb 113g/L, SD 20.63, 95% CI 111 to114, p < 0.0001).

Median value of hypochromic red cells was 7% (IQR 2-17). 803 (45%) of patients had values >5%. CRP was recorded in 1246 (69%) of patients with a median value of 63 (IQR 21-128). 1052 (84%) had an elevated CRP (>10).

Ferritin was recorded in 246 patients. Of these 179 had also had a CRP checked. Of these 70 met all four criteria (ferritin 30-800ng/ml; anaemia; hypochromic red cells <5%; CRP >10.) Using these four criteria (algorithm 1) 39% (70/179) had FID anaemia. Two patients had TSAT measured which were both <20%.

Using algorithm 2, data for all three parameters were available in 1246 / 1797 cancer patients. We identified 536 patients who had abnormal values for all three parameters. Based on our sample, we estimate that 43% of patients with advanced cancer have anaemia caused by FID.

When the whole sample was grouped by level of anaemia (Table III), we found statistically significant associations between severity of anaemia, % hypochromic cells, and CRP, (p=0.001, Kruskal-Wallis test).

INSERT TABLE III

Variation by tumour site

Table IV illustrates variation in anaemia, iron restricted erythropoiesis and inflammation by

tumour site. Anaemia was most prevalent among patents with leukaemia, myeloma and prostate cancer followed by GU and colorectal malignancies. Most tumour sites had a high level of systemic inflammation with over 50% of patients having abnormal values of CRP, except for those with brain tumours or 'other' cancer sites. Proportions of those with anaemia and raised % hypochromic red cell were not always congruous, indicating there are multiple processes influencing haemoglobin levels in patients. Levels of estimated FID anaemia (using algorithm 1) also varied by tumour site ranging from 4.6% in those with lymphoma to 62% of those with prostate cancer.

INSERT TABLE IV

Discussion

We found that 63% of patients with advanced cancer in our large sample were anaemic, with 38% having moderate to severe anaemia. This is consistent with a smaller study in palliative care cancer patients in which 65% of patients were anaemic [17]. Prevalence of FID was 39-43% in all cancer patients, and 66% of those with anaemia highlighting the importance of this aetiology in advanced cancer. However, prevalence of FID anaemia varied significantly by tumour site and was highest in patients with genitourinary, colorectal, melanoma, and head and neck cancers.

Comparisons with existing literature are complicated by differences in patient sampling and diagnostic criteria for FID. Ludwig et al found the prevalence of iron deficiency to be up to 53.6% in advanced cancer and FID to comprise 81.9% of those with any sign of iron deficiency [2]. However, these authors also found lower overall prevalence of anaemia than in our study: 41.2% in advanced cancer compared to 63% in our study. Comparing Ludwig et al with our data, there was lower reported prevalence of anaemia by tumour type; for example lung cancer (41.3% vs 57.8%), colorectal cancer (34.6% vs 70.1%) and breast cancer (26.5% vs 46.2%). These results highlight the effect of advancing disease on anaemia. Information on survival in relation to anaemia severity would also be of interest in order to make more direct comparisons. .

The strengths of our study include the large number of patients included with a diverse range of cancer types, and the sole use of routine haematological data compared to less commonly used or research techniques for diagnosing FID. We found that assessing for FID with or without ferritin results did not lead to a big discrepancy in our estimate of FID anaemia in this population. Our method of diagnosing FID is not one which has been used before but given the lack of consensus on how to identify FID in routine clinical care we wanted to test this pragmatic approach. Using algorithm one or two led to similar results (39% FID anaemia when ferritin included and 43% FID anaemia without). Alternative approaches include reticulocyte haemoglobin content (CHr) which is an early marker of iron-restricted erthyropoesis because it measures the haemoglobin content of the erythrocytes most recently produced (reticulocytes exist in the circulation for only 1-2 days). However this test is not available routinely in our area. The relative proportion of hypochromic mature red cells (% hypochromia; i.e. cells with a mean corpuscular haemoglobin concentration of less than 26 pg/ml) provides ongoing information over a several-week period. It is a late indicator of iron-restricted erythropoiesis because erythrocytes have a lifespan of around 120 days [16, 18]. Therefore our use of this parameter to diagnose iron restricted erythropoesis may

lead to the under diagnosis of FID. The availability of iron is reflected by transferrin saturation (TSAT), %HYPO and the CHr. The combination of low TSAT (<20%) and normal/elevated serum ferritin may indicate FID but TSAT was only measured in two patients and ferritin in 246. Future studies in advanced cancer comparing our pragmatic method with TSAT would provide a means to evaluate the diagnostic accuracy of our method.

There are some limitations to our findings. The retrospective collection of data meant that not all parameters were recorded in each patient. Our population from two UK hospices may not represent all patients with advanced cancer. Having used the WHO criteria for anaemia (Hb <110g/L) we may have underestimated anaemia levels compared to previous studies which used a threshold of 120g/L. We did not have data on patients' symptoms or physical function, nor their clinical management in order to understand the clinical context more fully. Patients' may have a mixed cause of their anaemia as many had a raised %hypochromic red cells indicating iron restricted erythropoesis but may also have another cause of their anaemia, which would be better understood with more clinical information.

This study highlights the high prevalence of anaemia in advanced cancer and importance of FID as a common aetiology. Further validation of our diagnostic criteria is required before this approach can be used in routine clinical practice. Given the apparent large proportion of patients with FID anaemia, red cell transfusion may not be an appropriate first line strategy in advanced cancer Alternative treatments which target the mechanism of FID should be investigated, which may include the use of intravenous iron.

Conflict of Interest Statement – none declared.

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