

# The European Cancer Anaemia Survey (ECAS): A large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients<sup>☆</sup>

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## Abstract

The European Cancer Anaemia Survey (ECAS) was conducted to prospectively evaluate the prevalence, incidence and treatment of anaemia (haemoglobin <12.0 g/dL) in European cancer patients, including the relationship of mild, moderate and severe anaemia to performance status. Patients were evaluated for up to 6 months. Data ( $N=15367$ ) included demographics, tumour type, performance status, haemoglobin levels, cancer treatments and anaemia treatments. Prevalence of anaemia at enrollment was 39.3% (haemoglobin <10.0 g/dL, 10%), and 67.0% during the survey (haemoglobin <10.0 g/dL, 39.3%). Low haemoglobin levels correlated significantly with poor performance status. Incidence of anaemia was 53.7% (haemoglobin <10.0 g/dL, 15.2%). Anaemia was treated in 38.9% of patients (epoetin, 17.4%; transfusion, 14.9%; and iron, 6.5%). Mean haemoglobin to initiate anaemia treatment was 9.7 g/dL. Anaemia prevalence and incidence in cancer patients are high. Anaemia significantly correlates with poor performance status and many anaemic patients are not treated.

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## 1. Introduction

Cancer-associated anaemia decreases patients' quality of life (QOL) and may affect clinical treatment [1–3]. Anaemia is independently associated with shorter survival times in patients with cancer [4], and correction

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of anaemia may have a positive impact on treatment outcomes [5–8]. Therefore, optimal management of anaemia appears to be a critical component of cancer treatment [1].

To date, information on the prevalence and effects of anaemia have come from clinical trials of anaemia treatments [5,9–12] or cytotoxic agents [13] that present results from protocol-defined patient populations and often have very low haemoglobin definitions for anaemia that are based on blood transfusion data. Sorely lacking has been a survey of cancer-related anaemia as it occurs in the overall cancer population, i.e., the prevalence and incidence of mild and moderate anaemia, as well as severe anaemia. The European Cancer Anaemia Survey (ECAS) was conducted to document the prevalence, incidence, evolution, severity and management of anaemia in a large, representative population of European cancer patients. Especially important is the effect of mild-to-moderate anaemia on patients who might not be treated according to the American Society of Hematology/American Society of Clinical Oncology (ASH/ASCO) guidelines, i.e., patients with haemoglobin between 10.0 g/dL and 12.0 g/dL [14].

This report describes the methodology of ECAS and provides patient data that focuses on the population enrolled, the prevalence of anaemia, the effect of mild, moderate and severe anaemia on performance status, the incidence of anaemia during the survey, and anaemia treatment patterns.

## 2. Patients and methods

### 2.1. Survey design

ECAS was a prospective, epidemiological, observational survey conducted in 24 European countries. There were no controlled conditions except that only cancer treatment centres participated. Because the protocol specified that only oncology centres be included, all cancers are well represented except prostate cancer, which in Europe frequently is treated by the urologist. Data were collected by convenience sampling defined overall by EUCAN Sampling Distribution for prevalence of tumour types by country [15]. Survey data were collected for up to six data points or 6 months of scheduled clinic visits. Survey enrollment was conducted between January 2001 and July 2001 with a follow-up of up to 6 months (February 2002).

### 2.2. Patients

Eligible patients of at least  $\geq 18$  years of age were enrolled with diagnosed solid or haematological tumours consistent with the EUCAN Sampling Distribution [15]. Patients were eligible regardless of their disease

status or type of cancer treatment. Patients enrolled in a clinical trial were ineligible. All procedures were in compliance with local regulations regarding Ethical Committee Approval for epidemiological surveys at the time the survey was done. The procedures were conducted in accordance with the ethical principles defined in the Declaration of Helsinki.

### 2.3. Data definitions and collection

Patient data were collected at enrollment, at up to six follow-up visits and at completion of the survey. Enrollment data included age, gender, tumour type (according to International Classification of Diseases [ICD]-9 code) and stage, date of initial cancer diagnosis, disease status, performance status, weight and haematological laboratory values. Cancer and anaemia treatments within 30 days of survey enrollment and at enrollment were recorded.

Patients receiving chemotherapy or concomitant chemo-radiotherapy had follow-up data collected at the end of each chemotherapy cycle to a maximum of six cycles or 6 months following enrollment. For patients receiving radiotherapy, the first radiotherapy treatment was at enrollment or at a subsequent data-point; follow-up data were collected 3–6 weeks after initiation of radiotherapy, at the end of treatment and at any clinical follow-up visit to a maximum of six visits. For patients not receiving chemotherapy or radiotherapy, data were collected at each clinic visit, with a maximum of one per month for the 6-month survey period. Survey completion data were recorded at the last follow-up evaluation at 6 months or after the sixth follow-up evaluation.

Follow-up data included weight, performance status, cancer treatment, number of current cycle for patients receiving chemotherapy and whether current cycle was delayed by 7 days or more due to anaemia, laboratory values (as at enrollment) and anaemia treatment. At survey completion, radiotherapy data (start/stop dates, whether therapy was completed, fractions/day, total tumour dose), chemotherapy at that time, reason for completion of survey (end of survey period, death, lost to follow-up, or patient withdrawal), and last laboratory values (as at enrollment) were recorded. Performance scores throughout the survey were recorded according to the World Health Organization (WHO) scale of 0–4 [16].

The definition of anaemia for ECAS was haemoglobin  $< 12.0$  g/dL based on toxicity grading criteria from the National Cancer Institute (NCI) and the European Organisation for Research and Treatment of Cancer (EORTC). As most major clinical studies of anaemia in cancer patients do not differentiate between age or gender [5,9–12], haemoglobin  $< 12.0$  g/dL was the standardised definition of anaemia. Anaemia was further categorized as mild: 11.9–10.0 g/dL; moderate: 9.9–8.0 g/dL; or

severe:  $<8.0$  g/dL, based on the Common Toxicity Criteria from the NCI [17].

Malignancies were categorised into nine groups: breast; lung; head and neck; gynaecological (cervix, ovary, uterus); gastrointestinal/colorectal; urogenital (prostate, male genital organs, bladder, kidney); lymphoma/myeloma (included chronic lymphocytic leukaemia); leukaemia (included acute lymphocytic leukaemia and acute myelogenous leukaemia); and an “other” category that included significant malignancies not specifically in any of these categories (e.g., skin cancer or brain tumour). For disease status, patients were categorised as “newly diagnosed” if this was their first occurrence of cancer; these patients were further categorised into newly-diagnosed/not receiving treatment or newly-diagnosed/receiving treatment. Patients were categorised as “persistent/recurrent” if their initial tumour had returned or metastasised, or as “in remission” if they were being followed after successful cancer treatment.

To avoid multiple counts of any patient when calculating the frequency of anaemia, patients were categorised into one of the following five treatment groups: no cancer treatment; only chemotherapy; only radiotherapy; concomitant chemo-radiotherapy (i.e., these treatments were administered during the same time period); and a combination of cancer therapies.

#### 2.4. Statistical methods

Sampling was stratified by tumour type with minimum targets for aggregate and by-country (sub-) sample sizes. The patient population was defined based on EUCAN Sampling Distribution [15] for population by country and prevalence of tumour types, and validated by GLOBOCAN 2000 [18].

Data were analysed as an aggregate with all countries included. Descriptive statistics were used to explore sample characteristics and baseline haemoglobin. Chi-square statistics were used to examine differences between dichotomous variables, including comparison of patient characteristics in various subpopulations for analysis. Two-way ANOVA models were used to determine WHO performance score at enrollment from haemoglobin at enrollment, treatment status at enrollment and the interaction between haemoglobin and treatment status.

### 3. Results

Results are reported for data from 748 cancer centres in 24 European countries with over 1000 physicians participating. Fig. 1 summarises the disposition of the patient population. For the *enrollment population* of 15367 patients, only enrollment demographics are reported. Of patients enrolled, 10476 (68.2%) finished

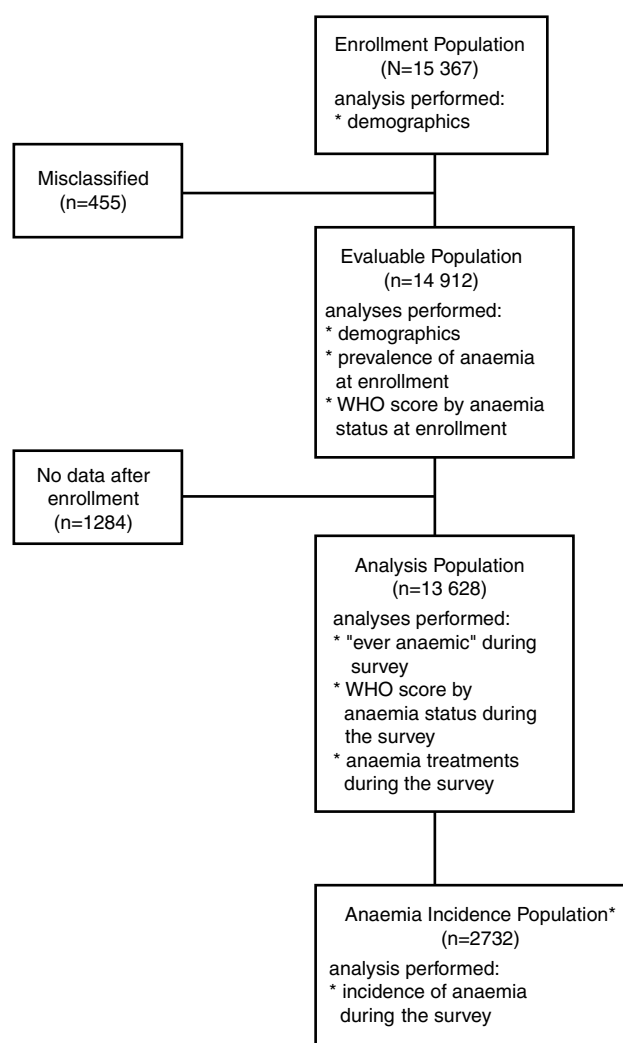


Fig. 1. Flow chart of patient disposition. \*Not anaemic at enrollment, received first cancer treatment during the survey period, and had a minimum of two cancer treatments during the survey. WHO, World Health Organization.

the survey and had an end-of-survey form, 1431 (9.3%) died, 1470 (9.6%) were lost to follow-up or withdrew, 1858 (12.1%) were missing an end-of-survey form, and 132 (0.9%) had an incomplete end-of-survey form.

The *evaluable population* ( $n=14912$ ) excluded 455 ineligible patients with inconsistent diagnoses and treatment, or retrospective data. Demographics and haemoglobin levels, prevalence of anaemia and WHO scores at enrollment are reported for the evaluable population. The *analysis population* ( $n=13628$ ) further excluded 1284 patients with no data beyond enrollment. During the survey, the frequency of reported anaemia (“ever anaemic”), WHO scores, and anaemia treatments are reported for the analysis population.

Demographics and patient characteristics for the three patient populations were similar (Table 1). Statistical analyses confirmed no meaningful differences between these groups.

Table 1  
Patient demographics for the enrollment, evaluable and analysis populations

|   | Enrollment <i>n</i> = 15367 | Evaluable <i>n</i> = 14912 | Analysis <i>n</i> = 13628 |
|---|-----------------------------|----------------------------|---------------------------|
| <i>Age, <sup>a</sup><i>n</i> (years)</i>          |                             |                            |                           |
| Median (range)                                    | 59.0 (18–96)                | 59.0 (18–96)               | 59.0 (18–96)              |
| Mean (SD)   | 58.0 (13.2)                 | 58.0 (13.2)                | 57.8 (13.2)               |
| <i>Gender, <sup>b</sup><i>n</i> (%)</i>           |                             |                            |                           |
| Male  | 6080 (43.8)                 | 5882 (43.6)                | 5415 (43.6)               |
| Female  | 7789 (56.2)                 | 7600 (56.4)                | 7014 (56.4)               |
| <i>Disease status, <sup>c</sup><i>n</i> (%)</i>   |                             |                            |                           |
| Newly-diagnosed, no treatment                     | 4877 (32.1)                 | 4768 (32.3)                | 4433 (32.8)               |
| Newly-diagnosed, with treatment                   | 3424 (22.5)                 | 3257 (22.1)                | 2966 (22.0)               |
| Persistent/recurrent                              | 5231 (34.4)                 | 5089 (34.5)                | 4684 (34.7)               |
| In remission                                      | 1666 (11.0)                 | 1636 (11.1)                | 1417 (10.5)               |
| <i>Tumour type, <sup>d</sup><i>n</i> (%)</i>      |                             |                            |                           |
| Breast  | 3278 (21.7)                 | 3216 (21.9)                | 2923 (21.8)               |
| Lung  | 2176 (14.4)                 | 2057 (14.0)                | 1900 (14.1)               |
| Gastrointestinal-colorectal                       | 2566 (17.0)                 | 2469 (16.8)                | 2245 (16.7)               |
| Head and neck                                     | 754 (5.0)                   | 710 (4.8)                  | 625 (4.7)                 |
| Gynaecological                                    | 1741 (11.5)                 | 1702 (11.6)                | 1564 (11.6)               |
| Lymphoma/myeloma                                  | 2360 (15.6)                 | 2316 (15.8)                | 2179 (16.2)               |
| Leukaemia   | 650 (4.3)                   | 640 (4.4)                  | 601 (4.5)                 |
| Urogenital  | 938 (6.2)                   | 917 (6.2)                  | 810 (6.0)                 |
| Other   | 671 (4.4)                   | 660 (4.5)                  | 587 (4.4)                 |
| <i>Treatment status, <sup>e</sup><i>n</i> (%)</i> |                             |                            |                           |
| Without treatment                                 | 7947 (52.8)                 | 7781 (53.3)                | 7211 (53.7)               |
| Chemotherapy                                      | 5986 (39.8)                 | 5759 (39.4)                | 5265 (39.2)               |
| Radiotherapy                                      | 682 (4.5)                   | 663 (4.5)                  | 578 (4.3)                 |
| Concomitant chemo-radiotherapy                    | 435 (2.9)                   | 409 (2.8)                  | 362 (2.7)                 |
| <i>WHO score, <sup>f</sup><i>n</i> (%)</i>        |                             |                            |                           |
| 0   | 5408 (35.5)                 | 5248 (35.5)                | 4818 (35.7)               |
| 1   | 6583 (43.3)                 | 6418 (43.4)                | 5876 (43.5)               |
| 2   | 2528 (16.6)                 | 2439 (16.5)                | 2241 (16.6)               |
| 3   | 609 (4.0)                   | 582 (3.9)                  | 502 (3.7)                 |
| 4   | 89 (0.6)                    | 86 (0.6)                   | 73 (0.5)                  |
| Missing data                                      |                             |                            |                           |
| Enrollment population                             | Evaluable population        |                            | Analysis population       |
| <sup>a</sup> <i>n</i> = 71                        | <i>n</i> = 66               |                            | <i>n</i> = 58             |
| <sup>b</sup> <i>n</i> = 1498                      | <i>n</i> = 1430             |                            | <i>n</i> = 1199           |
| <sup>c</sup> <i>n</i> = 169                       | <i>n</i> = 162              |                            | <i>n</i> = 128            |
| <sup>d</sup> <i>n</i> = 233                       | <i>n</i> = 225              |                            | <i>n</i> = 194            |
| <sup>e</sup> <i>n</i> = 317                       | <i>n</i> = 300              |                            | <i>n</i> = 212            |
| <sup>f</sup> <i>n</i> = 150                       | <i>n</i> = 139              |                            | <i>n</i> = 118            |

### 3.1. Prevalence of anaemia

For 14520 patients with haemoglobin levels available at enrollment, 39.3% were anaemic. Most patients (29.3%) had mild anaemia, with haemoglobin levels between 10.0 and 11.9 g/dL; moderate anaemia was recorded for 8.7% (haemoglobin 8.0–9.9 g/dL), and severe anaemia for 1.3% of patients (haemoglobin <8.0 g/dL). Fig. 2 displays anaemia by tumour type. For all these tumour types, most anaemic patients had haemoglobin levels between 10.0 and 11.9 g/dL. As shown in Fig. 3, patients with persistent/recurrent disease were most frequently anaemic (48.5%). Between 24% and 34% of patients had haemoglobin levels between 10.0 and 11.9 g/dL. When analysed by cancer treatment sta-

tus at enrollment, almost one-third (31.7%) of patients who were not receiving cancer treatment at enrollment were anaemic; for patients receiving cancer treatment, 50.5% of patients receiving chemotherapy, 43.5% of patients receiving chemo-radiotherapy, and 28.7% of patients receiving radiotherapy were anaemic.

### 3.2. Performance status and haemoglobin level

As shown in Fig. 4, there were more patients at enrollment with poor performance status (i.e., higher WHO score) at lower haemoglobin levels than at higher haemoglobin levels. WHO scores of 2–4 were recorded for 50.7% of patients with haemoglobin <8.0 g/dL and 40.0% of patients with haemoglobin 8.0–9.9 g/dL.

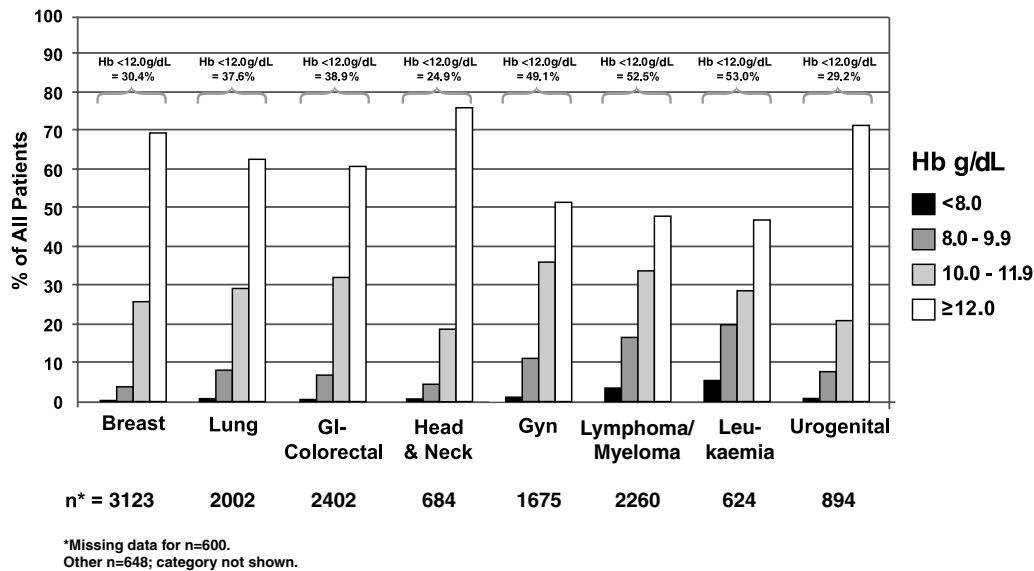


Fig. 2. Haemoglobin (Hb) at enrollment according to tumour type. Data based on the evaluable population ( $n=14912$ ). Gyn, gynaecological; GI, gastrointestinal.

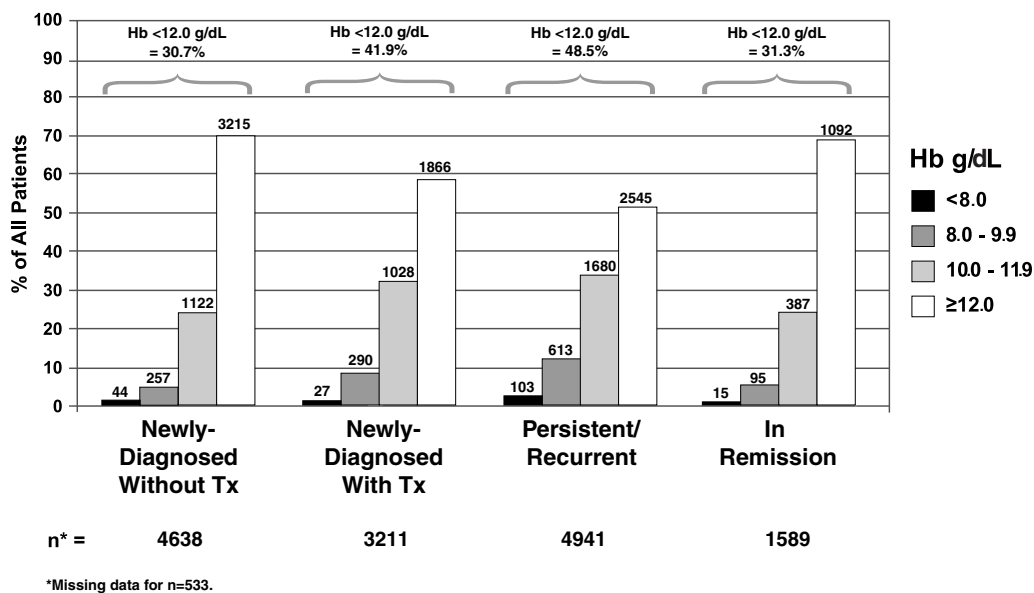


Fig. 3. Haemoglobin (Hb) at enrollment according to disease status. Data based on the evaluable population ( $n=14912$ ) Tx, therapy.

Almost one-quarter (24.8%) of patients with haemoglobin 10.0–11.9 g/dL had low WHO scores of 2–4. For patients with haemoglobin  $\geq 12.0$  g/dL, 15.9% had WHO scores of 2–4. The difference in the proportion of patients in each haemoglobin category with WHO scores 0–1 versus 2–4 was significant ( $P<0.001$ ). There was a significant difference between mean haemoglobin for WHO score 0 ( $12.8 \text{ g/dL} \pm 17$ ) and WHO score 4 ( $10.2 \text{ g/dL} \pm 23$ ) ( $P<0.001$ ).

Also shown is the mean WHO score for each haemoglobin category. Low haemoglobin levels correlated with high mean WHO scores at enrollment ( $P<0.001$ ). Decreased haemoglobin correlated with poor performance score for all tumour types at enrollment (Pearson

$R=-0.24$ ). Similar trends were seen during the survey, with low haemoglobin levels correlating significantly ( $P<0.001$ ) with high mean WHO scores at all data-points (Pearson  $R$  range =  $-0.27$  to  $-0.30$ ).

### 3.3. Frequency of anaemia during the survey

The frequency of anaemia was determined by the number of patients in the analysis population in whom low haemoglobin values ( $<12.0 \text{ g/dL}$ ) were recorded at least once during the survey ("ever anaemic"). Table 2 shows patients ever anaemic at enrollment or during the survey by tumour type and cancer treatment group. For the 13628 patients included, 67.0% were anaemic at some

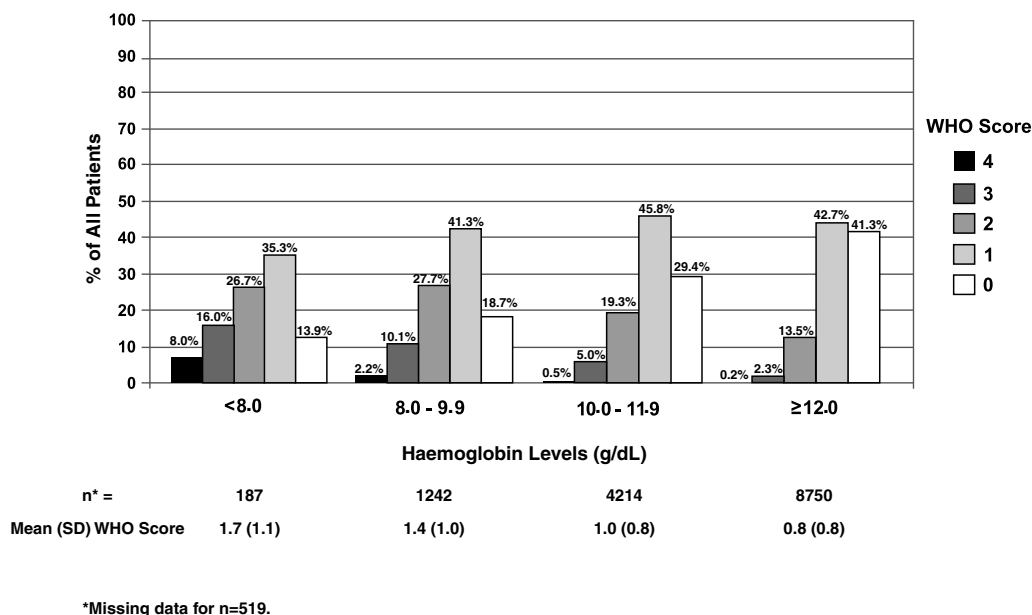


Fig. 4. Distribution of haemoglobin levels by category according to World Health Organization (WHO) performance status at enrollment. Percentages are cumulative to 100% within haemoglobin category. SD, standard deviation.

Table 2

Percentage of all patients in analysis population who were anaemic at least once (ever anaemic) during the survey

| Tumour type   | Overall <sup>a</sup> |             | Chemotherapy |             | Radiotherapy |             | Concomitant <sup>a</sup> |             | No treatment |             | Combination <sup>b</sup> |             |
|---------------|----------------------|-------------|--------------|-------------|--------------|-------------|--------------------------|-------------|--------------|-------------|--------------------------|-------------|
|               | Total (n)            | %           | Total (n)    | %           | Total (n)    | %           | Total (n)                | %           | Total (n)    | %           | Total (n)                | %           |
| Breast        | 2912                 | 62.2        | 1651         | 70.8        | 335          | 34.6        | 29                       | 55.2        | 248          | 29.4        | 649                      | 67.5        |
| Lung          | 1898                 | 77.0        | 1147         | 83.3        | 182          | 50.5        | 25                       | 56.0        | 137          | 42.3        | 407                      | 84.0        |
| GI/Colorectal | 2241                 | 60.8        | 1715         | 62.4        | 86           | 48.8        | 93                       | 51.6        | 93           | 43.0        | 254                      | 64.2        |
| Head/neck     | 625                  | 51.7        | 102          | 71.6        | 251          | 31.9        | 68                       | 69.1        | 56           | 26.8        | 148                      | 73.0        |
| Gynaecol      | 1563                 | 81.4        | 1154         | 88.3        | 192          | 53.6        | 65                       | 75.4        | 52           | 34.6        | 100                      | 83.0        |
| Lymph/myeloma | 2178                 | 72.9        | 1570         | 79.7        | 94           | 41.5        | 3                        | 33.3        | 283          | 51.9        | 228                      | 65.4        |
| Leukaemia     | 601                  | 67.7        | 454          | 73.6        | 1            | 100.0       | –                        | –           | 131          | 45.0        | 15                       | 86.7        |
| Urogenital    | 807                  | 50.7        | 362          | 71.8        | 277          | 25.6        | 6                        | 66.7        | 97           | 25.8        | 65                       | 75.4        |
| Other         | 587                  | 59.8        | 315          | 70.2        | 125          | 36.0        | 10                       | 60.0        | 48           | 41.7        | 89                       | 66.3        |
| Total         | 13412                | <b>67.9</b> | 8470         | <b>75.0</b> | 1543         | <b>38.2</b> | 299                      | <b>61.9</b> | 1145         | <b>39.7</b> | 1955                     | <b>71.8</b> |

Each patient is counted only once in the cancer treatment groups. GI, gastrointestinal; Gynaecol, gynaecological; Lymph, lymphoma.

<sup>a</sup> Patients who received chemotherapy and radiotherapy at the same time.

<sup>b</sup> Patients who received chemotherapy and radiotherapy at different times.

\* Data missing for n=216.

time during the survey. Fig. 5 shows haemoglobin categories according to the lowest recorded haemoglobin value during the 6-month survey. Haemoglobin levels were <10.0 g/dL for 39.3% of patients who were ever anaemic.

Anaemia was most frequently reported in patients with gynaecological cancer (81.4%) and lung cancer (77.0%). Most of these patients had haemoglobin levels of 10.0–11.9 g/dL (gynaecological cancer, 57.2%; lung cancer, 53.9%). A large proportion of patients (gynaecological cancer, 35.3%; lung cancer, 39.3%) had haemoglobin levels between 8.0 and 9.9 g/dL; the remaining patients had haemoglobin levels <8.0 g/dL. A high frequency of anaemia was also reported for patients with lymphoma/myeloma (72.9%). Anaemia was most

frequently reported in patients who received chemotherapy (75.0%) or a combination of therapies (71.8%). Anaemia occurred in 39.7% of patients who did not receive cancer treatment at any time during the survey. Frequency of anaemia was 75.4% for patients with persistent/recurrent disease, 67.2% for patients newly-diagnosed/receiving treatment at enrollment, 64.1% for patients newly-diagnosed/not receiving treatment at enrollment, and 47.9% for patients in remission.

### 3.4. Anaemia incidence

The incidence of anaemia was calculated from an incidence population (n=2732) who were not anaemic



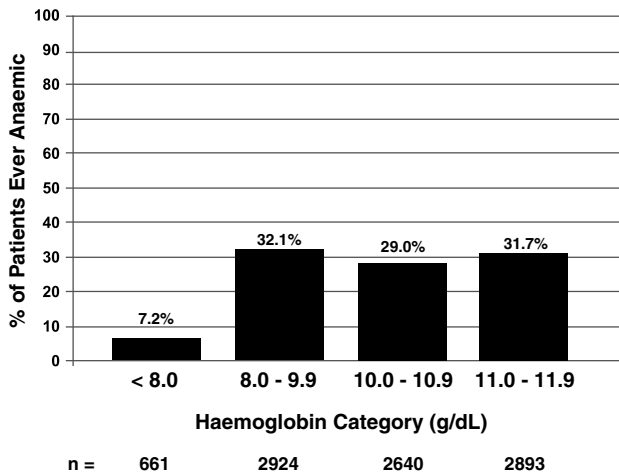


Fig. 5. Haemoglobin nadir distribution for patients ever anaemic ( $n=9118$ ).

at enrollment, received their first cancer treatment during the survey period, and had a minimum of two cycles of chemotherapy or two follow-up data-points for radiotherapy during the survey (chemotherapy,  $n=2101$ ; radiotherapy,  $n=514$ ; concomitant chemo-radiotherapy,  $n=117$ ) (Fig. 1).

The overall incidence of anaemia was 53.7%; 38.5% of patients had haemoglobin levels between 10.0 and 11.9 g/dL, 13.8% had haemoglobin levels between 8.0 and 9.9 g/dL, and 1.4% had haemoglobin levels <8.0 g/dL. Patients who received chemotherapy had the high-

est incidence of anaemia (62.7%) compared with concomitant chemo-radiotherapy (41.9%) or radiotherapy (19.5%). The incidence of anaemia increased with increasing chemotherapy cycles. In cycle 1, incidence of anaemia was 19.5%. Incidence steadily increased to 34.3% at cycle 2, 42.0% at cycle 3, and to 46.7% in cycles 4 and 5. The proportion of patients with lower haemoglobin levels (i.e., <10.0 g/dL) increased as the cycles increased.

The incidence of anaemia was highest in patients with lung cancer (70.9%) and gynaecological malignancies (64.6%). For patients who received chemotherapy, incidence of anaemia was 67.7% for those with persistent/recurrent disease, 61.3% for those newly-diagnosed/not receiving cytotoxic treatment at enrollment, and 48.3% for those in remission. For patients who received radiotherapy, incidence of anaemia was 23.3% for those with persistent/recurrent disease, 19.2% for those newly-diagnosed/not receiving cytotoxic treatment at enrollment, and 17.6% for those in remission.

### 3.5. Anaemia treatment

Of patients who were ever anaemic ( $n=9118$ ), 61.1% did not receive treatment for their anaemia. Most patients who were not treated (47.2%) had haemoglobin levels between 10.0 and 11.9 g/dL; 12.9% who were not treated had haemoglobin levels between 8.0 and 9.9 g/dL, and 0.9% had haemoglobin levels <8.0 g/dL. As shown in Fig. 6, anaemic patients with breast cancer

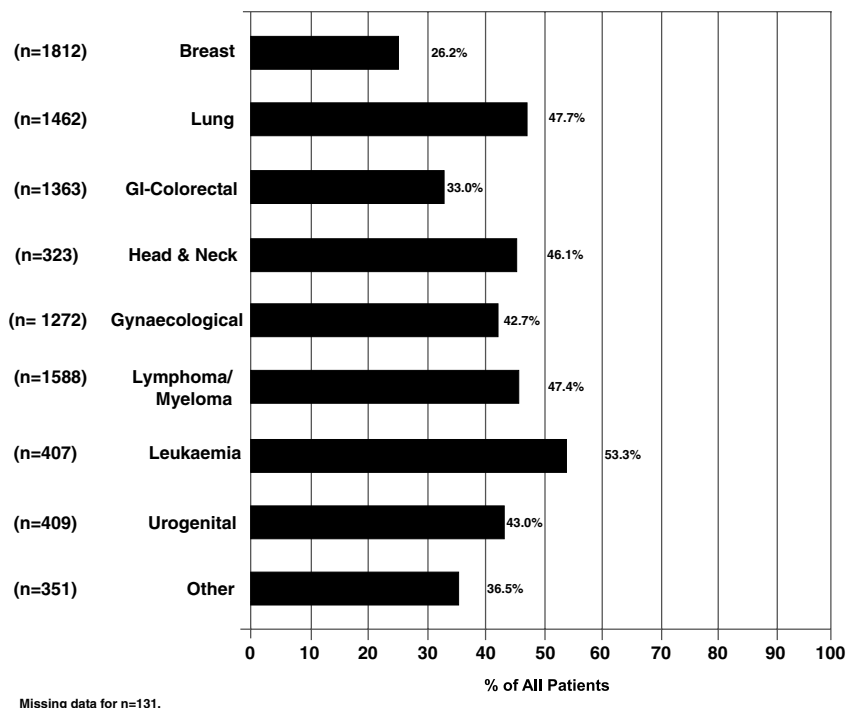


Fig. 6. Percentage of patients who received anaemia treatment if ever anaemic ( $n=9118$ ) by tumour type. GI, gastrointestinal.

were least likely to receive anaemia treatment (73.8%). Impaired functional status was no guarantee of treatment for anaemia; 51% of anaemic patients with WHO performance score  $\geq 2$  did not receive anaemia treatment.

For the 38.9% of patients ( $n=3545$ ) who received anaemia treatment, the most frequent treatment was epoetin, either alone or in combination with iron and/or transfusion (17.4%). Frequency of transfusion alone or with iron was 14.9%, and iron alone was 6.5%. Mean haemoglobin decreased to 9.7 g/dL before anaemia treatment was initiated. Table 3 shows the percentage of patients who received anaemia treatment by haemoglobin nadir in those patients receiving chemotherapy only during the survey. For one-third of patients who received epoetin (33.5%) and over one-half of patients who received transfusion (52.7%), treatment was not initiated until haemoglobin was  $<9.0$  g/dL. Of the 5877 patients analysed who did not receive anaemia treatment, 38.9% had haemoglobin nadirs  $\leq 10.9$  g/dL.

#### 4. Discussion

ECAS has revealed a high prevalence and incidence of anaemia in cancer patients in Europe. At ECAS enrollment, 39.3% of patients had haemoglobin levels  $<12.0$  g/dL. The prevalence of anaemia increased to 67.0% for patients in whom low haemoglobin values ( $<12.0$  g/dL) were recorded at least once during the survey. Most patients who began chemotherapy during ECAS became anaemic, most likely a reflection of the type and intensity of cancer therapy. The incidence of anaemia in a well-defined incidence population was 53.7% overall and 62.7% for patients who received chemotherapy. The longer patients received chemotherapy, the greater the risk of developing anaemia. Anaemia was reported in 19.5% of patients in the first chemotherapy cycle and 46.7% of patients in the fifth chemotherapy cycle.

Haemoglobin levels for most patients categorised as anaemic were between 10.0 and 11.9 g/dL. However, even this level of anaemia had a significant impact on performance status. Using the physician-reported WHO Performance Score, it was shown that as haemoglobin decreased, performance status worsened and there was a significant correlation between these variables. Over half the patients with severe anaemia (haemoglobin  $<8.0$  g/dL) at enrollment had a WHO score of 2–4; poor performance scores of 2–4 were also noted for one-quarter of patients with haemoglobin between 10.0 and 11.9 g/dL. The correlation between performance score and haemoglobin remained, regardless of the disease status or cancer treatment.

The relationship between anaemia and low performance status that was demonstrated in ECAS is consistent with findings that report a significant correlation between increasing haemoglobin and improving QOL, [5,9–12,19]. In these studies increased or higher haemoglobin levels were associated with improved quality of life, using a variety of QOL measures.

In other studies, there has been evidence that higher haemoglobin levels (some increased by epoetin) are correlated with improved outcome measures, including survival [4–8,20]. However, two recent studies with epoetin increasing haemoglobin levels to a higher range [21,22] have not shown the same positive survival benefit. One study was terminated early because of observed higher early mortality in the epoetin-treated group [21] and the other revealed better outcome in the placebo patients [22]. The interpretation of these results is complicated due to differences in study and patient populations. Reassuringly, a reduction in the risk of dying in erythropoietin treated cancer patients (Hazard Ratio (HR): 0.80) compared with untreated controls was found in a recent Cochrane analysis with a total of 1624 patients reviewed [23]. Still, there is a need for further prospective studies about the potential survival benefit of anaemia treatment.

Table 3  
Haemoglobin nadir by anaemia treatment for patients receiving chemotherapy only

| Hb nadir (g/dL) | Epoetin <sup>a</sup> |       | Transfusion <sup>a</sup> |       | Iron only <sup>b</sup> |       | No treatment <sup>c</sup> |       |
|-----------------|----------------------|-------|--------------------------|-------|------------------------|-------|---------------------------|-------|
|                 | <i>n</i>             | (%)   | <i>n</i>                 | (%)   | <i>n</i>               | (%)   | <i>n</i>                  | (%)   |
| $<9.0$          | 408                  | 33.5  | 562                      | 52.7  | 71                     | 16.6  | 275                       | 4.7   |
| 9.0–9.9         | 335                  | 27.5  | 316                      | 29.6  | 100                    | 23.3  | 682                       | 11.6  |
| 10.0–10.9       | 301                  | 24.7  | 130                      | 12.2  | 112                    | 26.1  | 1330                      | 22.6  |
| 11.0–11.9       | 115                  | 9.4   | 32                       | 3.0   | 86                     | 20.0  | 1590                      | 27.1  |
| $\geq 12.0$     | 58                   | 4.8   | 27                       | 2.5   | 60                     | 14.0  | 2000                      | 34.0  |
| Total           | 1217                 | 100.0 | 1067                     | 100.0 | 429                    | 100.0 | 5877                      | 100.0 |

<sup>a</sup> Includes patients who received transfusion only and transfusion + iron; data missing for  $n=1$ .

<sup>b</sup> Data missing for  $n=1$ .

<sup>c</sup> Data missing for  $n=10$ .

\* Includes patients who received epoetin only, epoetin + transfusion, epoetin + iron, or epoetin + transfusion + iron; data missing for  $n=1$ .



As cancer treatment regimens improve, patients are surviving longer, but more often with the unwanted complication of anaemia [13,24]. Selecting the optimal haemoglobin level for intervention with anaemia treatment becomes critical for maximising QOL and possibly other outcomes for cancer patients [25]. The decision to initiate anaemia treatment depends on the actual haemoglobin level, but consideration of symptoms due to anaemia is also important. The ASH/ASCO guidelines recommend starting anaemia treatment with epoetin when haemoglobin levels decline to  $\leq 10.0$  g/dL [14]. Treatment initiation in patients with haemoglobin between 10.0 g/dL and 12.0 g/dL, and symptomatic due to anaemia, is left to the discretion of the physician.

In ECAS, anaemia treatment was initiated in approximately 40% of anaemic patients. Of the 60% who were not treated, most had haemoglobin levels between 10.0 and 11.9 g/dL. Correlations with WHO performance score demonstrated that 25% of patients with this level of anaemia had functional decline; this may suggest that they should have received treatment. Almost 14% of anaemic patients who were not treated for their anaemia had haemoglobin  $< 10.0$  g/dL. Overall, 51% of anaemic patients with WHO performance score of 2 or greater did not receive anaemia treatment. Although other factors than anaemia may have contributed to impaired performance score, it seems that the ASCO/ASH guidelines have not been followed in many patients.

When anaemia treatment was administered, use of transfusion was similar to epoetin (14.9% *versus* 17.4%, respectively); iron alone accounted for a minority of anaemia treatment. Of those patients who had Hb  $< 12.0$  g/dL and were most likely clinically symptomatic (WHO performance score  $\geq 2$ ), 50% received no anaemia treatment.

ECAS was specifically designed to provide a representative profile of anaemia in cancer patients in Europe and has revealed interesting information. Results show that the prevalence and incidence of anaemia are high and correlate significantly with poor performance status. Importantly, treatment for anaemia may not be optimised: many anaemic patients, including those with haemoglobin levels  $< 10.0$  g/dL and therefore in the category where they should be treated according to ASH/ASCO guidelines, were not treated for their anaemia. Recognition of these results may lead to better management of anaemia in cancer thereby optimising overall patient care and improving patients' QOL during cancer treatment.

## 5. Conflict of interest statement

Peter Barrett-Lee, Gunnar Birgegård, Carsten Bokemeyer, Pere Gascón, Paris Kosmidis, Maciej Krzakowski, Heinz Ludwig, Johan Nortier, Patrizia Olmi,

Maurice Schneider, Dirk Schrijvers and Simon Van Belle do not have any financial interests, such as owning stock, consulting or performing contracted work for any company.

Gunnar Birgegård, Carsten Bokemeyer and Heinz Ludwig have received honoraria from Amgen.

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