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Predicting cancer-associated anaemia in patients receiving non-platinum chemotherapy: results of a retrospective survey

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Abstract

A 2-year retrospective chart survey of 1064 patients with colorectal, breast, lung or ovarian cancer, Hodgkin's disease, or non-Hodgkin's lymphoma was conducted at 24 centres in France to determine the prevalence of anaemia (haemoglobin (Hb) levels $\leqslant$120 g/l) and need for transfusion in patients who received non-platinum-based chemotherapy for more than three cycles or 3 months. Baseline Hb levels documented anaemia in 37.1% of patients (all tumour types). By cycle 3, the prevalence of anemia increased to 54.1% of patients and remained over 50% at cycle 4. At some time during chemotherapy 14.5% of patients were transfused. Predictive risk factors for anaemia requiring transfusion included low baseline Hb, decrease in Hb during the first month of chemotherapy, primary tumour site, prior blood transfusions and duration of chemotherapy. By early identification of patients at the highest risk of developing anaemia, interventions such as epoetin alfa can be employed to reduce or eliminate the need for transfusions.

Keywords: Anaemia; Non-platinum chemotherapy; Risk factors; Epoetin alfa; Erythropoietin

1. Introduction

Cancer-associated anaemia has numerous aetiologies. It can result from the disease itself (chronic anaemia of cancer), occur as a consequence of chemotherapy or radiotherapy, or arise from co-existing diseases that may or may not be related to the cancer. Regardless of the aetiology, anaemia can affect the cardiopulmonary, gastrointestinal, reproductive, vascular and central nervous systems, resulting in a variety of symptoms including fatigue, exhaustion, dizziness, anorexia, nausea, headache, chest pain and dyspnoea, and may lead to depression [1,2]. The traditional method of increasing haemoglobin (Hb) levels in patients with severe cancer-associated anaemia has been allogeneic blood transfusion, despite the inconvenience, cost and potential risk associated with this practice [2,3]. In addition, transfusions employed only when the Hb level reaches the critical 'transfusion trigger' of $<$80 g/l leaves thousands of patients with potentially debilitating mild-to-moderate anaemia (Hb $\geqslant$80 to $\leqslant$120 g/l) that can significantly impair quality of life (QOL), even if it is not life-threatening in itself [1]. As more effective chemotherapy regimens are developed with curative, rather than merely palliative intent, preventing and alleviating cancer-associated anaemia of any degree and its associated decrease in QOL becomes a significant goal.

An available option for treating mild to moderate anaemia in cancer patients receiving both platinum- and non-platinum-based chemotherapy is recombinant human erythropoietin (rHuEPO; epoetin alfa) [4–11]. Studies have shown that the administration of epoetin alfa not only increases Hb levels, but also reduces transfusion requirements and significantly improves patients' perception of their QOL [5–10,12]. Importantly, it has been demonstrated that the greatest incremental improvement in QOL was observed when Hb increased from 110 to 120 g/l (range 110–130 g/l), and

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this improvement in QOL was independent of the tumour type, transfusions, number of days on study, extent of chemotherapy or radiotherapy and feelings of pain and nausea [12].

The survey presented here was conducted to determine the prevalence of mild, moderate and severe anaemia in cancer patients receiving non-platinum-based chemotherapy and to identify predictive factors for the development of severe anaemia that would be associated with the probability of transfusion during a course of chemotherapy. Understanding these factors would assist in identifying patients who may benefit from early intervention with epoetin alfa therapy.

2. Patients and methods

A retrospective survey of patient charts from 24 hospitals and cancer centres throughout France provided data on patients, aged 18 to 75 years, who both started and completed non-platinum-based chemotherapy between 1 January 1994 and 31 December 1995. The survey comprised patients with a confirmed diagnosis of colorectal, breast, lung or ovarian cancer, Hodgkin's disease, or non-Hodgkin's lymphoma who received chemotherapy for more than three cycles or 3 months. Previous antineoplastic treatments were permitted including surgery, chemotherapy, radiotherapy and hormonal therapy, with or without a washout period between treatments. The only exclusion criterion was concomitant treatment with epoetin alpha. Demographic and baseline disease characteristics were recorded, along with the respective antineoplastic treatments. Transfusion history for the 3 months before the start of chemotherapy was recorded including the type of transfusion [whole blood, red blood cells (RBC) or platelets], date(s) of transfusion, number of units transfused and Hb or platelet levels prior to transfusion. The same information was collected for the chemotherapy period. Each cycle of chemotherapy comprised one treatment schedule, while a course of chemotherapy consisted of several cycles.

Hb, haematocrit (Hct), RBC counts, white blood cell (WBC) total and differential counts, platelets and reticulocytes were measured at the start of, during and at the end of the treatment phase of each cycle of chemotherapy. Hb level at the start of cycle 1 was considered baseline; final Hb level was assessed approximately 1 month after the last dose of chemotherapy. Anaemia was defined as mild (Hb 105 to $\leqslant$120 g/l), moderate (Hb 80 to $<$105 g/l), or severe (Hb $<$80 g/l). The data were analysed collectively and sub-analyses were performed by primary tumour site. For each of the first six cycles of chemotherapy, the proportions of patients with no anaemia (Hb $>$120 g/l), or mild, moderate or severe anaemia were analysed. The cumulative proportion of patients with moderate-to-severe anaemia at any time after the start of chemotherapy was estimated with Kaplan–Meier curves. Mean Hb and Hct levels and RBC counts were tabulated for cycles 1 to 6 overall and for the subgroups.

The proportions of patients transfused before, during and at any time after the first cycle of chemotherapy were tabulated for the subgroups. The time to first transfusion was estimated using Kaplan–Meier curves showing the cumulative proportion of patients transfused after the start of chemotherapy and after the first cycle. The cumulative transfusion rate (units per 3 months) was calculated for the subgroups, including and excluding the first month on chemotherapy. Mean Hb levels prior to transfusion were analysed by tumour type and cycle, and the pretransfusion trigger Hb was recorded (last recorded Hb within 7 days prior to transfusion). Factors predictive of anaemia were determined by retrospective identification of those variables most frequently associated with the need for transfusion.

3. Results

3.1. Demographics and baseline characteristics

The survey included data from 1064 patients who had received a total of 5402 cycles of non-platinum-based cyclic chemotherapy for at least 3 months. Only one course of chemotherapy was assessed for each patient; therefore, all cycle data for an individual patient belong to the same course of chemotherapy. Table 1 summarises patient demographics.

Table 2 summarises chemotherapy regimens by neoplasm. Approximately half the patients had breast

Table 1
Patient demographics[a]

Characteristics	$n=1064$
Gender, no. (%)	
Male	268 (25.2)
Female	795 (74.7)
Not available	1 (0.1)
Age (years)	
Mean (S.D.)	52.1 ± 13.08
Range	17–75
Race, no. (%)	
White	446 (41.9)
Other	11 (1.0)
Not available	607 (57.0)
Previous treatments, no. (%)	
Surgery	972 (91.4)
Chemotherapy	187 (17.6)
Radiation therapy	144 (13.5)
Hormonal therapy	142 (13.4)

S.D., standard deviation.
[a] All patients receiving cyclic chemotherapy, $n=1064$.

Table 2
Chemotherapy regimens used most frequently according to primary tumour site[a]

Chemotherapy regimen	No. patients (%)	No. cycles	Mean (days) duration ± S.D.
Total	1064 (100)	5402	144.4 ± 82.2
Breast	534 (50.2)	2802	145.7 ± 73.8
5-FU + cyclophosphamide + doxorubicin/epirubicin	301 (56.4)		
Docetaxel/paclitaxel only	76 (14.2)		
Doxorubicin/epirubicin + cyclophosphamide	24 (4.5)		
5-FU + cyclophosphamide + methotrexate	23 (4.3)		
5-FU + cyclophosphamide + mitozantrone	22 (4.1)		
5-FU + folinic acid	3 (0.6)		
Other combinations	85 (15.9)		
Colorectal	153 (14.4)	871	175.2 ± 84.3
5-FU + folinic acid	128 (83.7)		
5-FU + cyclophosphamide + doxorubicin/epirubicin	1 (0.7)		
Other combinations	24 (15.7)		
Lung	17 (1.6)	105	104.5 ± 34.9
Vinorelbine	8 (47.1)		
Doxorubicine/epirubicin + cyclophosphamide + vincristine/vinblastine	6 (35.3)		
Doxorubicine/epirubicin + cyclophosphamide	2 (11.8)		
Other combinations	1 (5.9)		
Ovarian	47 (4.4)	230	129.5 ± 66.6
Docetaxel/paclitaxel only	33 (70.2)		
5-FU + folinic acid	2 (4.3)		
Other combinations	12 (25.5)		
Hodgkin's disease	93 (8.7)	363	131.2 ± 93.8[b]
Doxorubicin/epirubicin + bleomycin + vincristine/vinblastine	64 (68.8)		
Doxorubicin/epirubicin + bleomycin + vincristine/vinblastine + cyclophosphamide	17 (18.3)		
Doxorubicin/epirubicin + bleomycin + cyclophosphamide	1 (1.1)		
Other combinations	11 (11.8)		
Non-Hodgkin's lymphoma	220 (20.7)	1031	131.2 ± 93.8[b]
Doxorubicin/epirubicin + cyclophosphamide + vincristine/vinblastine	92 (41.8)		
Doxorubicin/epirubicin + cyclophosphamide + bleomycin	57 (25.9)		
Doxorubicin/epirubicin + cyclophosphamide	31 (14.1)		
Doxorubicin/epirubicin + bleomycin + cyclophosphamide + vincristine/vinblastine	10 (4.6)		
Other combinations	30 (13.6)		

5-FU, 5-fluourouracil; S.D., standard deviation.
[a] All patients receiving cyclic chemotherapy, $n = 1064$.
[b] Patients with Hodgkin's disease and non-Hodgkin's lymphoma were combined for the calculation of mean duration of chemotherapy.

cancer (50.2%); non-Hodgkin's lymphoma was the second most frequently occurring cancer (20.7%). Patients received a variety of regimens and chemotherapeutic agents; the most frequently employed agents (≥20%) were cyclophosphamide (57%), 5-fluorouracil (49.5%), epirubicin (35.5%), doxorubicin (25.1%). Prednisolone was administered to 25.0% of patients. 402 patients (37.0%) received adjuvant chemotherapy, and 379 (34.9%) received chemotherapy intended to be curative. Chemotherapy was considered palliative in only 275 (25.3%) patients; the intent of chemotherapy for the remaining 31 (2.9%) was not recorded.

Baseline haematology for 953 patients with recorded values is shown in Table 3. Most patients (63%) had no anaemia, 22.5% had mild anaemia, 13% had moderate anaemia, and 1.6% had severe anaemia. Mean baseline Hb levels were >120 g/l for all primary tumour types except ovarian cancer (Hb 110 ± 18 g/l) and colorectal cancer (Hb 119 ± 18 g/l). The prevalence of anaemia (Hb < 120 g/l) at baseline was greatest in patients with ovarian cancer (64.4%), colorectal cancer (48%), Hodgkin's disease (44.8%) and non-Hodgkin's lymphoma (41.7%). The prevalence of anaemia at baseline was lowest in patients with lung cancer (16.7%) and breast cancer (28.7%).

3.2. Changes in Hb levels

Mean Hb levels for patients with all tumour types combined remained relatively constant over successive chemotherapy cycles; at the start of cycle 1, mean Hb was 123 ± 17 g/l ($n = 953$) and at the start of cycle 6 mean Hb was 120 ± 14 g/l ($n = 326$). Examination of the data by tumour type, however, revealed that patients

Table 3
Baseline haematologic characteristics by primary tumour site[a]

Haematological characteristics	Breast ($n=534$)	Colorectal ($n=153$)	Hodgkin's disease ($n=93$)	Non-Hodgkin's lymphoma ($n=220$)	Ovarian ($n=47$)	Lung ($n=17$)	Total ($n=1064$)
Hb (g/l) Mean (S.D.) (Range)	126±14 (55–159)	119±18 (73–151)	122±18 (79–154)	123±22 (62–185)	110±18 (74–150)	133±16 (109–151)	123±17 (55–185)
Hct (%) Mean (S.D.)	37.6±4.1	36.0±4.9	37.1±4.7	36.9±6.3	32.2±5.4	40.1±4.5	36.9±5.0
Previous transfusion, no. (%)							
Whole blood	6 (1.1)	17 (11.1)	0	13 (5.9)	13 (27.7)	0	49 (4.6)
Platelets	1 (0.2)	0	0	3 (1.4)	4 (8.5)	0	8 (0.8)
Hb group, no. (%)							
<80 g/l	2 (0.4)	2 (1.7)	1 (1.1)	8 (3.9)	2 (4.4)	0	15 (1.6)
80 to <105 g/l	32 (6.6)	23 (19.0)	14 (16.1)	39 (18.9)	16 (35.6)	0	124 (13.0)
105 to ⩽120 g/l	106 (21.7)	33 (27.3)	24 (27.6)	39 (18.9)	11 (24.4)	1 (16.7)	214 (22.5)
>120 g/l	348 (71.3)	63 (52.1)	48 (55.2)	120 (58.3)	16 (35.6)	5 (83.3)	600 (63.0)
Unknown	46	32	6	14	2	11	111

Hb, haemoglobin; Hct, haematocrit; S.D., standard deviation.
[a] Calculated as a percentage of patients with known values ($n=953$).

with lung cancer, Hodgkin's disease, non-Hodgkin's lymphoma, and breast cancer had mean decreases in Hb of 34, 16, 06, and 05 g/l, respectively, from the start of cycle 1 to the start of cycle 6. Patients with colorectal and ovarian cancer had increases in Hb levels over these cycles (mean 11 g/l and 09 g/l, respectively).

3.3. Prevalence of anaemia

Of the patients whose Hb was known at baseline ($n=953$), 353 (37.1%) had anaemia. This increased to 48.1% (358/745) of patients at the start of cycle 2, and further increased to 54.1% (413/764) of patients at the start of cycle 3 and 52.6% of patients (302/574) at the start of cycle 4. Extended duration of chemotherapy tended to increase the probability of developing moderate or severe anaemia (Fig. 1). After 2 months of treatment, approximately 30% of patients had experienced at least one episode of moderate or severe anaemia; that prevalence increased to approximately 43% of patients after 8 months. At the start of cycle 4, the prevalence of moderate anaemia was highest in patients with non-Hodgkin's lymphoma (34.9%), lung cancer (33.3%), and Hodgkin's disease (25.7%) compared with ovarian (16.7%), breast (14.4%) and colorectal (3.2%) cancer.

3.4. Transfusion requirements

49 (4.6%) patients had received transfusions prior to the start of chemotherapy and 154 (14.5%) were trans-

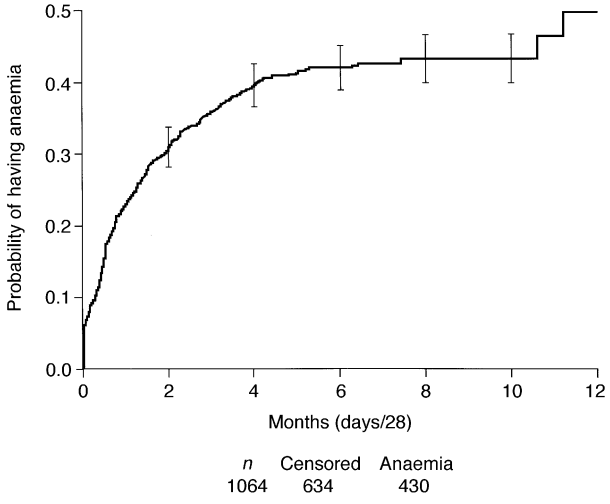

Fig. 1. Incidence of patients with moderate to severe anaemia after start of chemotherapy.

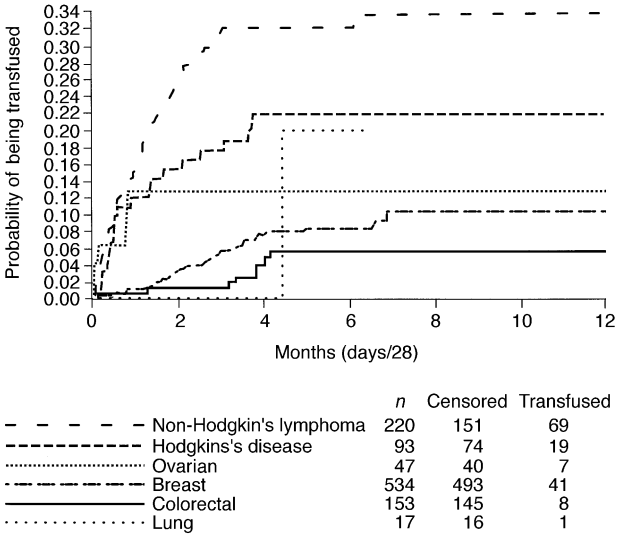

Fig. 2. Probability of being transfused after beginning chemotherapy by tumour type.

fused during the course of chemotherapy. The mean cumulative transfusion rate for the transfused patient population only was 3.83±3.90 units/3 months. Fig. 2 depicts the Kaplan–Meier estimates of the probability of being transfused after beginning chemotherapy by tumour type. The percentage of patients who required transfusion at any time from cycle 1 onwards increased from pretreatment for patients with breast cancer (from 1.1 to 8.4%), non-Hodgkin's lymphoma (from 5.9 to 33.2%), Hodgkin's disease (from 0 to 20.4%), and lung cancer (from 0 to 5.9%). Patients with non-Hodgkin's lymphoma, Hodgkin's disease and ovarian cancer had higher transfusion rates at any time from cycle 1 onwards (33.2, 20.4 and 17.0%, respectively) than did patients with breast (8.4%), lung (5.9%) or colorectal (5.2%) cancer. The mean Hb trigger level for transfusion ranged from 77 g/l for non-Hodgkin's lymphoma to 88 g/l for lung cancer. The time to first transfusion was shortest for patients with non-Hodgkin's lymphoma, Hodgkin's disease or ovarian cancer. Fig. 3 depicts the Kaplan–Meier estimates for the incidence of patients transfused after beginning chemotherapy by baseline Hb categories. Patients with baseline Hb levels <105 g/l had a shorter time to first transfusion than those with baseline Hb levels $\geqslant 105$ g/l.

3.5. Predictive factors for transfusion

Based on the findings of this survey, five factors were identified that might signal the potential for developing severe anaemia during non-platinum chemotherapy, with the consequent need for a blood transfusion.

3.5.1. Baseline Hb levels

More patients with baseline Hb <105 g/l (44.6%) received transfusions at any time from cycle 1 onwards than did patients with baseline Hb $\geqslant 105$ g/l (10.6%).

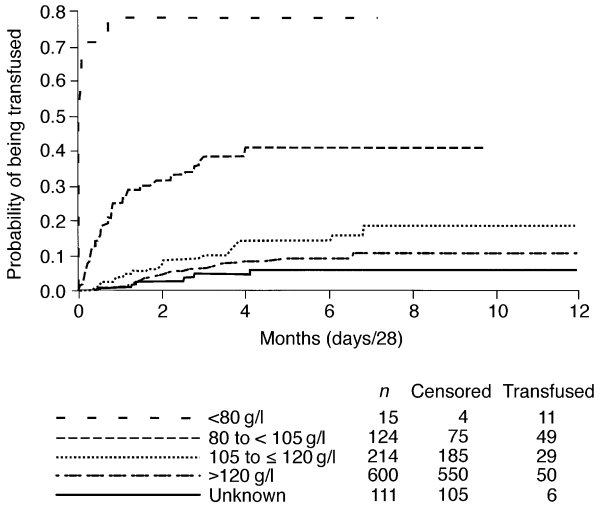

Fig. 3. Probability of being transfused after beginning chemotherapy by baseline haemoglobin (Hb) categories.

This trend was evident for all of the tumour types except lung cancer (only 1 patient with lung cancer was transfused, and this occurred at cycle 6). In addition, more patients with baseline Hb levels <80 g/l received transfusions at any time from cycle 1 onwards, compared with patients who had Hb levels of 80 to <105 g/l (80% versus 40.3%).

3.5.2. Early changes in Hb levels

Overall, 13.7% (98/716) of patients had a decrease in Hb $\geqslant 15$ g/l during cycle 1 and 49.3% (353/716) had a decrease in Hb of <15 g/l during this cycle. Patients who experienced a decrease in Hb of at least 15 g/l during the first month of chemotherapy were more likely to require transfusion after cycle 2 (34.7%) than patients whose Hb decreased by <15 g/l (12.2%).

3.5.3. Duration of therapy

As the duration of chemotherapy increased, so did the probability that the patients would need to be transfused. Based on Kaplan–Meier estimates (Fig. 2), the probability that patients would need transfusion increased within the first 2 months of chemotherapy to 0.25 for non-Hodgkin's lymphoma, 0.15 for those with Hodgkin's disease, and 0.13, 0.03 and 0.01 for those with ovarian, breast, and colorectal cancer, respectively. The increase in probability of transfusion for patients with lung cancer (0.2) occurred after 4 months of chemotherapy; however, this finding was based on just 1 of 17 lung cancer patients. For patients who were transfusion-independent at baseline, an increase in the probability of transfusion occurred with time.

3.5.4. Tumour type

Transfusions were given most frequently to patients with non-Hodgkin's lymphoma (33.2%), Hodgkin's disease (20.4%) and ovarian cancer (17.0%). The mean cumulative transfusion rate for patients with non-Hodgkin's lymphoma (5.35±5.03 units/3 months for transfused patients) was greater than that of all the other tumour types.

3.5.5. Previous transfusion

Patients who had previously received whole blood transfusions were more likely to receive subsequent transfusions than those who had not (44.9% versus 13.0%).

Using various regression models, age, gender, pre-survey surgery, previous chemotherapy, previous radiotherapy and immunotherapy were not found to be predictive for transfusion.

4. Discussion

Anaemia is a frequent and significant cause of comorbidity in patients with cancer, occurring in a

majority of patients at some point in their illness [4]. Symptoms range from fatigue, exhaustion, weakness and drowsiness to respiratory distress and cardiac decompensation [1,2]. The causes of cancer-associated anaemia are multifarious. Chemotherapy appears to contribute to the pathogenesis of anaemia through its direct effect on erythroid progenitors or precursors, and repeated cycles of chemotherapy may impair erythropoiesis cumulatively [4,13]. A recent and comprehensive review of the incidence and treatment of chemotherapy-related anaemia confirmed a relatively high incidence (often 70% or greater) of mild to moderate treatment-related anaemia with commonly used single-agent and combination chemotherapy regimens, including the newer-generation chemotherapy agents (e.g. taxanes, vinorelbine, camptothecins) [13]. In addition to neoplastic natural history and treatment processes, anaemia in cancer patients can be caused by infections, gastrointestinal blood loss, nutritional deficiencies, renal impairment, clonal disorders of haematopoiesis, microangiopathy, autoimmune haemolysis, excessive bone marrow fibrosis and displacement, or inflammatory status that causes default in iron stock use [2]. Because erythropoietin production by the kidney in response to tissue hypoxia is often blunted, cancer patients may have an inadequate erythropoietin response for their degree of anaemia [2].

Cancer-associated anaemia has traditionally been treated with blood transfusion, but this approach has two major problems: risk and timing. Approximately 20% of transfusions are associated with acute complications [14], including haemolytic reactions, febrile episodes and infections, iron overload and possible adverse effects on the immune system [3,15], as well as transmission of viral hepatitis [3,14,16]. Furthermore, because anaemia is present for a period of time before the Hb level reaches the transfusion threshold or trigger of 70 to <80 g/l, cancer patients with less severe anaemia (mild: Hb 105 to <120 g/l; moderate: Hb 80 to <105 g/l) are often untreated despite the presence of anaemia-associated symptoms and a negative impact on patients' QOL [9,10].

In the survey presented here, we have attempted to establish the prevalence of anaemia in patients who received non-platinum-based chemotherapy. At baseline, approximately 37% of patients had some degree of anaemia. Mean Hb levels generally decreased during chemotherapy and the percentage of patients with anaemia increased after the first cycle of chemotherapy. However, an inherent problem is that the observed prevalence and severity of anaemia over time is confounded by the use of transfusion to increase Hb levels in severely anaemic patients (14.5% of patients received transfusions during chemotherapy), as well as to artificially raise baseline Hb levels (4.6% of patients received prechemotherapy transfusions). This may give the impression of a decreased prevalence or less severe anaemia when, in fact, the opposite is true.

We also attempted to define the factors predictive of cancer-associated anaemia, thereby identifying high-risk patients at an early stage, when interventions can be employed to reduce or eliminate the need for transfusions. This retrospective survey identified five predictive factors for anaemia that may lead to the need for transfusion: low baseline Hb, decrease in Hb during the first month of chemotherapy, duration of chemotherapy, prior blood transfusion and primary tumour site. More patients received blood transfusions after the first cycle of chemotherapy if their baseline Hb level was <80 g/l (80%) or was between 80 and <105 g/l (40.3%), compared with patients who had Hb levels $\geqslant 105$ g/l (10.6%). Patients who had a decrease in Hb of 15 g/l or greater during the first month of chemotherapy were more likely to require transfusion after cycle 2 (34.7%) than patients whose Hb decreased by <15 g/l (12.2%). The probability of anaemia severe enough to require transfusion increased as the duration of chemotherapy increased.

Primary tumour site had a significant impact on the probability of transfusions. The patients most likely to require transfusions at any time from cycle 1 onwards were those with non-Hodgkin's lymphoma (33.2% or 73/220 patients transfused) and Hodgkin's disease (20.4% or 19/93 patients transfused). Patients with non-Hodgkin's lymphoma were the most affected by the duration of chemotherapy and had the highest mean cumulative transfusion rate (5.35 ± 5.03 units/3 months for transfused patients). Despite the large number of transfusions, the largest decrease in mean Hb levels from baseline to the beginning of cycle 4 was observed in these patients. Less dramatic but similar trends were observed in patients with Hodgkin's disease. For solid tumours, the incidence of transfusion at any time from cycle 1 onwards was greatest for ovarian cancer (17.0% or 8/47 patients). For breast and colorectal cancers, the number of patients who received blood transfusions increased with each cycle of chemotherapy up to cycle 4, resulting in fewer anaemic patients.

Epoetin alfa is efficacious and well tolerated in alleviating anaemia and reducing transfusion requirements in cancer patients receiving platinum- and non-platinum-based chemotherapy [5–10,12]. Quality-of-life assessments utilising the Linear Analog Scale Assessment (LASA, also known as the Cancer Linear Analog Scale, or CLAS) in three studies of 4757 cancer patients who received platinum or non-platinum chemotherapy [9,10] or non-platinum chemotherapy only [17] demonstrated a significant improvement in energy, activity level and overall QOL [9,10,17] that was directly related to increases in Hb with epoetin alfa treatment [9,10]. Interestingly, analyses based on incremental increases in Hb of 10 g/l demonstrated that the greatest

improvement in QOL for each 10-g/l change in Hb occurred when Hb level increased from 110 to 120 g/l (range 110–130 g/l). Even patients with mild cancer-associated anaemia can benefit from early intervention with epoetin alfa.

In addition to increasing Hb levels in patients with anaemia, epoetin alfa has been shown to be effective in preventing anaemia in patients at risk [18,19]. Recognising predictive risk factors and instituting preventive Hb maintenance strategies, such as the administration of epoetin alfa, may be the key to eliminating the need for crisis intervention in the management of cancer-related anaemia and ensuring good patient QOL.

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Appendix

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