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Diagnosis and management of anaemia and iron deficiency in patients with haematological malignancies or solid tumours in France in 2009–2010: The AnemOnHe study

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ABSTRACT

Objective: To describe the management of anaemia in 2009–2010 in France in patients with haematological malignancies (HM) or solid tumours (ST).

Methods: Retrospective observational study in 57 centres, enrolling adult patients with HM or ST treated for an episode of anaemia (duration of the episode $\geqslant$3 months occurring in the last 12 months).

Results: 220 patients with ST (breast, 18%; lung, 18%) and 56 with HM (lymphoma, 60%) were included (median age, 68 years; female, 53%). Mean haemoglobin level at anaemia diagnosis was 9.3 ± 1.4 g/dL (<8 g/dL for 16%) and 9.8 ± 1.1 g/dL (<8 g/dL for 6%) in HM and ST patients, respectively. At least one parameter of iron deficiency (ferritin, transferrin saturation) was assessed in 26% of HM and 19% of ST patients. Treatment of anaemia included erythropoiesis-stimulating agents (ESA) for 98% of HM and 89% of ST patients. Iron was prescribed to 14% (oral, 12%; intravenous, 2%) of HM patients and to 42% (oral, 17%; intravenous, 25%) of ST patients. The rates of blood transfusions were high: 70% in HM and 46% in ST patients; transfusions alone or administrated with ESA were more frequent in patients with Hb <8 g/dL.

Conclusion: Although recent guidelines recommend evaluating iron deficiency and correcting anaemia by using intravenous iron, our study in cancer patients evidenced that ESA and blood transfusions are still frequently used as the treatment of anaemia in cancer patients. Iron deficiency is insufficiently assessed (only one patient among five) and as a consequence iron deficiency is most likely insufficiently treated.

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1. Introduction

Anaemia is a frequent condition in patients with cancer and it has negative consequences on disease outcome and quality of life.[1,2] The European cancer anaemia survey (ECAS) performed in 2001 reported that anaemia was present in 54% of cancer patients; for patients receiving chemotherapy treatment, this rate achieved up to 75%.[2] In patients with haematological malignancies, anaemia is twice more frequent than in patients with solid tumours.[3]

The main mechanisms of anaemia in cancer are related to the production of inflammatory cytokines, which inhibit both the production of erythropoietin and erythropoiesis, and to functional and absolute iron deficiencies.[4,5] Functional iron deficiency is common during chronic diseases such as cancer or chronic kidney disease. It is the consequence of inflammatory mechanisms that lead to an imbalance between iron needs of the bone marrow erythroblast cells and iron supply. Recently, the short peptide hepcidin has been involved in functional iron deficiency. Indeed, this peptide is synthesised by liver during inflammatory processes: it inhibits iron absorption by intestinal cells and blocks iron release from intracellular stocks in liver cells and macrophages.[6] Absolute iron deficiency is related to depletion of iron stores due to blood loss or insufficient iron uptake from food. Functional and absolute iron deficiencies are diagnosed by blood serum ferritin and transferrin saturation. Serum ferritin >100 ng/mL and transferrin saturation <20% indicate functional iron deficiency anaemia whereas absolute iron deficiency is defined by serum ferritin <100 ng/mL and transferrin saturation <20%.[7]

In contrast to patients with chronic kidney diseases, iron supplementation remains infrequent in cancer patients. Thus, in the study of Ludwig et al., which examined anaemia management in European cancer patients treated with erythropoiesis-stimulating agents (ESA), only 20–28% of patients had iron supplementation.[8] Shord et al. studied patients with chemotherapy-induced anaemia receiving ESA and reported that biological tests of iron metabolism were not commonly measured before the start of ESA therapy and only a few patients received iron supplementation.[9] Therefore iron supplementation remains unsatisfactory in cancer patients despite the fact that many studies have convincingly demonstrated that intravenous iron supplementation enhances ESA efficacy, reduces ESA requirements and improves quality of life.[10–15]

The safety of ESA in cancer patients was recently questioned through possible increased risk of thromboembolic events and stimulation of tumour growth.[16,17] The meta-analysis of Bohlius et al. concluded that ESA treatment in cancer patients increased mortality.[18] As a consequence, the American Society of Clinical Oncology (ASCO) updated their guidelines and recommended ESA only in chemotherapy-induced anaemia when Hb level is below 10 g/dL.[19] Moreover, monitoring iron stores and supplementing iron intake in patients treated with ESA were considered as valuable, but there was a need for additional clinical evidence. In Europe, the European Medicines Agency (EMEA) recommended that, in cancer patients with a reasonably long life-expectancy, anaemia should be corrected with blood transfusions.[20]

With these new guidelines that recommend monitoring iron stores and limiting the use of erythropoietin-stimulating agents (ESA) in cancer patients, it was of interest to describe their potential impact in the management of anaemia.

2. Patient and methods

2.1. Study design

The *Anaem*ia in *On*cology–*Hae*matology (AnemOnHe) study was a retrospective study conducted in 57 French oncology and haematology centres. The centres were selected on the basis of a significant activity in oncology or in haematology, type (academic, general or private centre) and region. The eligibility criteria of the patients were: (1) diagnosis of haematological malignancy or solid tumour and (2) treatment of an anaemia episode during the last 12 months with duration of the episode $\geqslant$3 months.

The main objective was the description of the different treatment strategies for anaemia management: transfusions, erythropoiesis-stimulating agents (ESA), oral iron, intravenous iron, folates. The main secondary objectives were the description of the biological tests of anaemia, Hb level at diagnosis and therapeutic strategies according to different subgroups of patients (e.g. Hb <8 g/dL or >8 g/dL, solid tumour or haematological malignancy).

The following data were registered: age, gender, weight, height, type and stage of cancer, date of cancer diagnosis, on-going anticancer treatments, clinical signs of anaemia for the last episode, dates of anaemia episode, biological tests for anaemia (total blood count, Hb, ferritin, serum iron, transferrin saturation, C-reactive protein) at diagnosis and at end of treatment (or end of follow-up), treatments for anaemia. The cause of anaemia was classified as chemotherapy, radiotherapy or surgery when the anaemia episode occurred less than 6 weeks after the end of the related treatment.

2.2. Statistical analysis

Data from the French Anemia Cancer Patient (F-ACT) study were used to estimate the sample size.[21] It was estimated that a sample size of 300 patients would provide 90% power to detect a difference (with alpha-risk at 5%) in the proportion of patients treated with iron alone in different subgroups of patients: patients with haematological malignancy versus solid tumours and patients with Hb <8 g/dL versus Hb $\geqslant$8 g/dL.

No formal statistical hypothesis was tested and the statistical analysis was essentially descriptive. Groups were compared using Student's *t*-test or Wilcoxon's test for quantitative variables and Fisher's exact test or Chi-2 test for qualitative variables. All tests were bilateral at the level 0.05. The analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Characteristics of patients

From July 2009 to October 2010, 50 patients with haematological malignancies and 226 patients with solid tumours were included in the study (Table 1). According to the eligibility criteria (anaemia episode treated during the last 6 months), all patients were treated for anaemia after the warning on ESA and new recommendations limiting the use of ESA in cancer patients. Patients had a median age of 68 years and 53% of women were included. Breast (18%) and lung (18%) tumours were the most frequent solid tumours; lymphoma was the most frequent (60%) haematological malignancy.

Cancer duration was comparable between groups (mean, 2.9 years for haematological malignancies and 2.7 years for solid tumours).

As expected, therapeutic strategies differed markedly between groups. Thus, chemotherapy alone was more frequent for haematological malignancies than for solid tumours (76% versus 19.9%); chemotherapy plus surgery (32% versus 6%), chemotherapy plus radiotherapy (17% versus 4%) or surgery plus radiotherapy (29% versus 0%) were more frequent for solid tumours compared to haematological malignancies, respectively. Twenty percent of patients with haematological malignancies received bone marrow graft.

Cancer treatment was curative for 76% of patients with haematological malignancies and was palliative for 88% of patients with solid tumours (Table 1).

3.2. Clinical characteristics of last treated anaemia episode

The last treated anaemia episode was still on-going (investigator's assessment) for 36% of patients with haematological malignancies and 50% of patients with solid tumours. The median duration of the treated anaemia episode was not significantly different between the two groups: 3.4 and 2.5 months for haematological malignancies and solid tumours, respectively. In contrast, when anaemia episode was still on-going, its duration was longer in haematological malignancy group compared to solid tumours group (median, 6.7 versus 4.4 months, respectively; $p < 0.0001$).

The last anaemia episode was the first episode for 44% of patients with haematological malignancies and 59% of patients with solid tumours ($p = 0.048$). For first episodes, the median duration between diagnosis of cancer and anaemia episode was shorter for haematological malignancies compared to solid tumours (1.6 versus 4.7 months, $p = 0.0003$).

Clinical signs of anaemia were reported more frequently for patients with haematological malignancies than with solid

Table 1 – Characteristics of the cancer patients of the *Anaemia* in *Oncology–Haematology (AnemOnHe)* study.

	Haematological malignancies[a] N = 50	Solid tumours[b] N = 226
Age, years		
Mean (SD)	66.8 (11.9)	66.3 (11.8)
Median (range)	68 (30–86)	67 (23–95)
Female gender, *n* (%)	21 (42)	126 (56)
Body mass index, mean (SD), kg/m^2	25.1 (4.4)	24.0 (4.5)
Cancer duration, years, mean (SD)	2.9 (3.8)	2.7 (3.1)
Cancer stage at inclusion, *n* (%)		
New diagnosis	10 (20)	39 (17)
Stable	8 (16)	54 (24)
Progressive disease	16 (32)	89 (40)
Remission	14 (28)	14 (6)
Relapse	2 (4)	28 (13)
Distant or lymph node metastases, *n* (%)	16 (33)	192 (85)
Therapeutic strategy, *n* (%)		
Chemotherapy alone	38 (76)	45 (20)
Surgery alone	0	1 (0.4)
Chemotherapy + surgery	3 (6)	73 (32)
Chemotherapy + radiotherapy	2 (4)	38 (17)
Surgery + radiotherapy	0	1 (0.4)
Chemotherapy + radiotherapy + surgery	0	66 (29)
No treatment	7 (14)	2 (1)
Bone marrow transplant, *n* (%)	10 (20)	5 (2)
Cancer treatment, *n* (%)		
Adjuvant or neoadjuvant therapy	0	20 (9)
Curative	38 (76)	7 (3)
Palliative	7 (14)	199 (88)
No treatment	5 (10)	0

[a] Haematological malignancies: lymphoma, 60%; multiple myeloma, 16%; leukaemia, 8%; others, 16%.

[b] Solid tumours: breast, 18%; lung, 18%; uterus and ovary, 12%; colon and rectum, 8%; prostate, 7%; urinary bladder, 7%; pancreas and liver, 10%; gastrointestinal tract, 6%; kidney, 2%; others, 11%.

tumours (80% versus 52%; $p = 0.0003$). Asthenia was the main clinical symptom reported with a high frequency in both groups (88% and 94%, respectively). Pallor (60% versus 25%; $p < 0.0001$), dyspnoea (40% versus 23%; $p = 0.038$) and tachycardia (15% versus 4%; $p = 0.004$) were more frequent for haematological malignancies than solid tumours, respectively.

The cause of anaemia was reported to be chemotherapy for 47% of patients with haematological malignancies and 70% of patients with solid tumours; the cause was unknown for 49% and 16% of cases, respectively (Table 2).

3.3. *Biological tests for diagnosis of anaemia and exploration of iron metabolism*

Mean Hb level at diagnosis of anaemia was 9.3 ± 1.4 g/dL (range, 6.1–11.8 g/dL) and 9.8 ± 1.1 g/dL (range, 4.6–11.9 g/dL) for patients with haematological malignancies and solid tumours, respectively. Hb was <8 g/dL for 16% of patients with haematological malignancies and Hb was <8 g/dL for 6% of patients with solid tumours (Table 2).

Only total blood count was performed for anaemia diagnosis (with occasionally C-reactive protein (CRP)) for 80% of patients. Complete blood count with at least one biological test of iron metabolism (ferritin, serum iron, transferrin saturation coefficient) was performed for only 20% of patients (Table 2).

3.4. *Treatments of last episode of anaemia*

A large majority of patients were treated with ESA, most frequently without iron supplementation: 98% of patients with haematological malignancies (including 84% without iron supplementation) and 89% of patients with solid tumours patients (including 52% without iron supplementation) (Table 3).

Prescription of iron alone was infrequent, both in patients with haematological malignancies (0%) and in patients with solid tumours (3%). Overall, iron was prescribed to 14% (oral, 12%; intravenous, 2%) of patients with haematological malignancies and to 42% (oral, 17%; intravenous, 25%) of patients with solid tumours (Table 3).

The rates of blood transfusions were high and more frequent in patients with haematological malignancies (70%) than in patients with solid tumours (46%, $p = 0.004$) (Table 3). In patients with solid tumours, transfusions (alone or administrated with ESA) were more frequent in patients with Hb <8 g/dL: 85% (11/13) and 44% (93/213) in patients with Hb

Table 2 – Characteristics and diagnosis of the last anaemia episode.

	Haematological malignancies $N = 50$	Solid tumours $N = 226$
Duration of last anaemia episode, months		
Mean (SD)	7.4 (3.4)	5.3 (2.4)
Median (range)	7.3 (2.9–12.8)	4.5 (1.1–13.1)
Duration between diagnosis of cancer and last anaemia episode, months		
Mean (SD)	27.0 (45.6)	27.3 (37.2)
Median (range)	4.6 (0–266)	8.7 (0–232)
First anaemia episode, *n* (%)	22 (44)	134 (59)
Hb level at anaemia diagnosis, g/dL		
Mean (SD)	9.3 (1.4)	9.8 (1.1)
Median (range)	9.5 (6.1–11.8)	10.0 (4.6–11.9)
Hb level classes in g/dL, *n* (%)		
<8	8 (16)	13 (6)
[8–10]	24 (48)	96 (43)
⩾10	18 (36)	117 (52)
Cause of anaemia, *n* (%)		
Chemotherapy	23 (47)	156 (70)
Surgery	2 (4)	9 (4)
Surgery + radiotherapy	0	1 (0.4)
Surgery + chemotherapy	0	2 (1)
Radiotherapy	0	3 (1)
Radiotherapy + chemotherapy	0	17 (8)
Unknown	24 (49)	36 (16)
Not reported	1	2
Biological tests for anaemia diagnosis,[a] *n* (%)		
Complete blood count alone	37 (74)	183 (81)
Complete blood count with at least one biological test of iron metabolism[b]	13 (26)[c]	43 (19)[d]

[a] Not taking into account CRP dosage.
[b] Serum ferritin, serum iron, transferrin saturation.
[c] Ferritin alone, 18%; serum iron plus ferritin, 4%; at least three biological tests of iron metabolism, 4%.
[d] Ferritin alone, 0.4%; serum iron alone, 0.4%; serum iron plus ferritin, 3%; at least three biological tests of iron metabolism, 15%.

Table 3 – Treatment of the last anaemia episode.

	Haematological malignancies N = 50	Solid tumours N = 226
Treatment of last anaemia episode, *n* (%)		
Erythropoietin stimulating agents (ESA)	49 (98)	201 (89)
Blood transfusion	35 (70)	104 (46)
Iron	7 (14)	96 (42)
Oral	6 (12)	39 (17)
Intravenous	1 (2)	57 (25)
Strategy of treatment, *n* (%)		
ESA alone	13 (26)	75 (33)
Iron alone	0	7 (3)
Transfusion alone	1 (2)	13 (6)
ESA + transfusion	29 (58)	42 (19)
Transfusion + iron	0	5 (2)
ESA + iron	2 (4)	40 (18)
ESA + iron + transfusion	5 (10)	44 (20)

$\geqslant$8 g/dL ($p = 0.004$). In patients with haematological malignancies, these percentages were 100% (8/8) for Hb <8 g/dL and 64% (27/42) for Hb $\geqslant$8 g/dL, respectively.

4. Discussion

Comparisons of data reported by studies on anaemia in European cancer patients evidence a marked decrease of patients untreated for anaemia: 61% in the 2001 ECAS study and 17% in the 2006 F-ACT study. This decrease is clearly related to a marked increase of ESA use during the last years.[2,8,21,22] Even though these studies are not strictly comparable (e.g. study design, Hb level for anaemia definition, inclusion criteria), our data recorded in a more recent period (2009–2010) confirm this increased tendency with a very frequent prescription of ESA in cancer patients: 91% of cancer patients treated for anaemia received ESA (associated or not to other treatment of anaemia).

These data on ESA use in cancer patients are not in line with the recent updated ASCO guidelines, which recommend restricting ESA to patients with chemotherapy-induced anaemia with Hb <10 g/dL.[23] Indeed, in our study, chemotherapy was reported as the cause of anaemia in 47% of patients with haematological malignancies and 70% of patients with solid tumours and 36% and 52% had Hb $\geqslant$10 g/dL at anaemia diagnosis, respectively. Despite the recent recommendations on ESA use, up to 98% of patients with haematological malignancies and 89% with solid tumours received ESA for treatment of last anaemia episode, respectively.

Another concern pointed out in our study is the low level of iron prescription with ESA in cancer patients. In contrast with chronic kidney disease patients who receive generally iron supplementation, ESA was prescribed with iron in only 14%

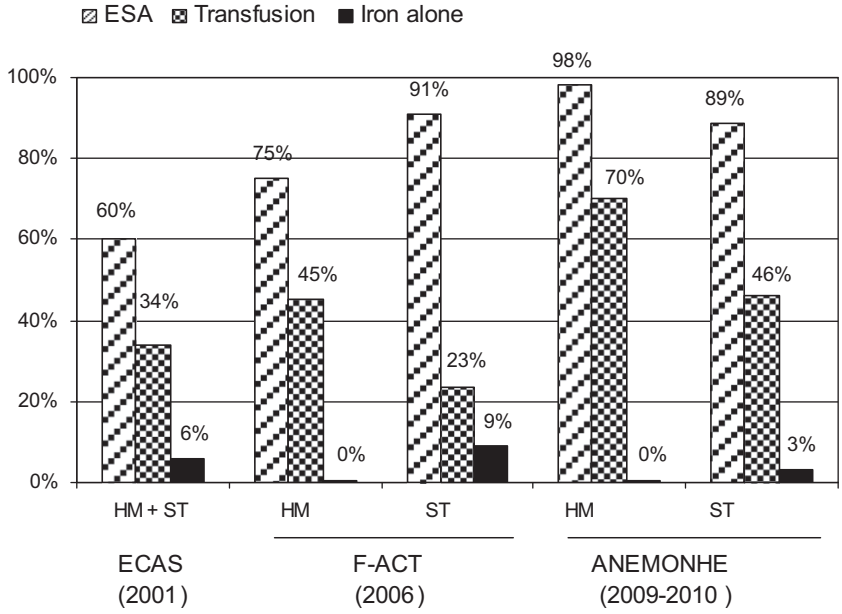

Fig. 1 – Treatment of anaemia in different studies. In the present study [*Anaem*ia in *On*cology–*Hae*matology (AnemOnHe)], the cancer patients were more frequently treated with ESA than in previous studies: 2001 European cancer anaemia survey (ECAS) Study for subgroup of French patients (22) and 2006 French Anemia Cancer Patient (F-ACT) study (21). The rates of blood transfusion were high in AnemOnHe study; in contrast the rates of iron supplementation alone remained low across the studies. Results on the figure are calculated for the 39% and 83% of patients of the ECAS and F-ACT studies who received specific treatment for anaemia, respectively; in the AnemOnHe study, specific treatment for anaemia was a selection criterion. ESA, erythropoiesis-stimulating agent; HM, haematological malignancies; ST, solid tumours.

of patients with haematological malignancies and in 42% of patients with solid tumours; furthermore, these rates of supplementation included only 2% and 25% of intravenous iron, respectively. Indeed, oral iron fails in functional iron deficiency and only intravenous iron is efficient by bypassing intestinal barrier and iron sequestration in macrophages. The guidelines from the National Comprehensive Cancer Network (NCCN) and from the European Organisation for Research and Treatment of Cancer (EORTC) recommend the use of intravenous iron (and not oral iron) for the treatment of functional iron deficiency as seen in cancer patients.[24,25]

Consistent with our findings, Shord et al. reported that biological tests of iron metabolism were not routinely measured in cancer patients of an academic medical centre and very few patients received iron supplementation.[9] In the ACT study, only 20–28% patients with cancer received iron supplementation.[8] Yet, intravenous iron has been demonstrated in randomised controlled studies to enhance ESA effect.[10–15] Moreover, there are important cost savings for intravenous iron administration together with ESA. This has been largely demonstrated not only in chronic kidney disease patients but also in cancer patients. Thus, Hedenus et al. calculated that intravenous administration of iron in patients treated with ESA reduced costs by 11% in comparison with patients receiving ESA alone.[12] We used recently a pharmaco-economic model that suggested that the use of intravenous iron according to recommendations of international guidelines was cost saving, particularly in chemotherapy-induced anaemia in breast cancers.[26]

Therefore, there is a rationale to recommend the use of intravenous iron in cancer patients receiving ESA, especially taking into account the very few clinically relevant adverse events reported with the new formulations of intravenous iron. The number of patients receiving intravenous iron alone was marginal in our study, as observed in the ECAS and F-ACT studies (Fig. 1). It is not clear whether administration of intravenous iron would improve quality of life and anaemia in patients not receiving ESA. An increase of Hb level in response to endogenous erythropoietin could be expected if iron is delivered directly though intravenous route. Further clinical studies are nevertheless needed to address this point.

As suggested by Pedrazzoli et al., the underuse of iron supplementation in cancer patients could be related to the false perception that these patients do not have decreased iron stores (as measured by ferritin) and, therefore, do not need iron supplementation. However, this is only a partial explanation for underuse of iron supplementation since, as previously observed by other authors, a striking finding of our study was the absence of exploration of iron metabolism contrasting with the high ESA prescription.[9] Diagnosis of anaemia was based mainly on Hb level, but the causes of anaemia were not explored; at least one biological iron test was performed in only one case out five. Another hypothesis to the underuse of iron supplementation could be due to the risk of haemochromatosis with concomitant use of iron and transfusion.

The percentage of patients receiving transfusions was high in our study (70% for haematological malignancies and 46% in solid tumours), even in patients with Hb $\geqslant$8 g/dL (64% and 44%, respectively). These rates are higher than those reported in the subgroup of French patients treated for anaemia in the 2001 ECAS study (34%) or in the 2006 F-ACT study (45% for haematological malignancies and 23% for solid tumours) (Fig. 1). The reasons of these high rates of blood transfusion are not clear and a significant proportion of patients received both transfusion and ESA for treatment of the same anaemia episode (68% for haematological malignancies and 38% for solid tumours). Although our study was not designed to answer this question, it could be suggested that the use of both treatments for the same anaemia episode could be a way for clinicians to moderate the use of ESA after the warning on ESA. Allogeneic blood transfusion is, however, a scarce and expensive resource, which is not devoid of safety concerns and is associated with infectious and non-infectious hazards.[27]

In conclusion, although recent guidelines recommend evaluating iron deficiency and correcting anaemia by using intravenous iron, our study in cancer patients evidenced that ESA and blood transfusions are still frequently used as the treatment of anaemia in cancer patients. Iron deficiency is insufficiently assessed (only one patient among five) and as a consequence iron deficiency is most likely insufficiently treated.

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Conflict of interest statement

Dr. L. Mahi is employee of Vifor Pharma.

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