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Treatment patterns and outcomes in the management of anaemia in cancer patients in Europe: Findings from the Anaemia Cancer Treatment (ACT) study ☆

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ABSTRACT

Objectives: To examine anaemia management in cancer patients treated with erythropoiesis-stimulating agents (ESAs) in Europe.
Methods: Retrospective pharmacoepidemiologic study of 2192 patients from 307 centres. Minimum of 3 visits over 8–10 weeks with ESA treatment initiated at visit 1.
Results: Most patients were treated per guidelines, except for low iron supplementation rates. Mean Hb rose from 9.54 ± 0.95 g/dl to 10.88 ± 1.49 g/dl at visit 3, without concomitant rise in WHO/ECOG score. Response rates were 65.0% (Hb increase ↑ ⩾ 1 g/dl); 54.3% (Hb increase ↑ ⩾ 1 g/dl in 8 weeks); 38.9% (haematopoietic response); 33.7% (Hb increase ↑ ⩾ 2 g/dl) and 18.8% (Hb between12.0 and 12.9 g/dl)
Conclusions: Treatment patterns were guideline congruent, except for (intravenous) iron supplementation. Hb increased by 1.34 g/dl. A net erythropoiesis boost of Hb ⩾ 1 g/dl is attainable in two-thirds of patients and should be condensed to 8 weeks on an individual patient basis. Anaemia management in Europe has improved significantly. The general effectiveness and relative safety of judicious ESA treatment are evident.

1. Introduction

Anaemia is among the most prevalent side-effects of cancer and cancer treatment,[1,2] is associated with poor prognosis and outcomes[3–5] and significantly impacts quality of life.[6] According to the European Cancer Anaemia Survey (ECAS),[2] in 2001 67.9% of cancer patients had haemoglobin [Hb] levels ⩽ 12 g/dl during a 6-month period. Only 38.9% of them

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were treated: 17.4% received an erythropoiesis-stimulating agent (ESA) (either alone or in combination with blood transfusion or iron supplementation), 14.9% were given blood transfusion (alone or in combination with iron) and 6.5% were treated with iron alone. In a recent French survey, physicians reported to treat 64% of patients with Hb $\leqslant$ 12 g/dl with ESAs, yet 22% of patients did not receive any anaemia treatment at all.[7]

Given the benefits of ESAs but also the variability in treatment and outcomes, evidence-based guidelines have been proposed.[8–12] These guidelines and the ECAS findings may explain the recent attention to anaemia in cancer patients. Whether this has translated into improved outcomes remains unknown.

ECAS was an epidemiological study of the epidemiology and treatment of anaemia in cancer patients. The Anaemia Cancer and Treatment (ACT) study[13] focused on anaemic cancer patients treated with any ESA, treatment patterns, outcomes and response rates. ACT used the EORTC-recommended definition of anaemia of <11 g/dl, whereas in ECAS the threshold was <12 g/dl.

2. Methods

The background and methodology of ACT have been described in a separate background and methodology paper.[13] Key points and deviations from the original methodology are reviewed below.

2.1. Design

Designed as a retrospective, multi-centre, multi-level, longitudinal pharmacoepidemiologic study using medical records, ACT was an international study with 316 participating centres in 16 countries in Europe, Asia and Latin America enrolling a total of 2807 patients. The majority of centres (97.2%) and patients (95.9%) were from 13 European countries. The data reported here are for the European subsample.

For logistical reasons, the French part of the study was conducted in June and July 2006 using a paper-based case record form (CRF). Retrospective data for the entire study were collected from visits occurring between 1st June 2005 and 5th December 2007. Local start dates were determined by compliance with local laws and regulations. The German affiliate chose to use paper CRFs and engaged a contract research organisation (CRO) to enter the data into the electronic CRFs.

2.2. Sample

Records eligible for inclusion were those of patients aged $\geqslant$ 18 diagnosed with a solid (breast, bladder, cervix, colorectal, head/neck, lung, ovary or prostate) or haematological malignancy (myeloma or lymphoma), regardless of stage. Concomitant chemotherapy was not a requirement. Patients had to be anaemic according to the then prevailing EORTC guidelines[10] (Hb $\leqslant$ 11 g/dl) and treated with any approved ESA. ESA treatment should have been initiated within 12 and 3 months preceding the start of the study. Data were required for a minimum of 3 (and optional up to 5) clinic visits over an 8–10 week period. ESA treatment for 8–10 weeks was not required, only that ESA treatment was initiated at visit 1. Centres were asked to recruit a maximum of 20 consecutive patients per site, there were no other specifications given on how patients have to be selected for the chart review.

Per power calculations, required sample size estimates for Europe ranged from 2091 to 2327 recruited from a minimum of 177 centres (before buffering for patient and centre attrition).[13] A data review at the end of October 2007 revealed that the status quo of 2192 evaluable patients of 2286 patients recruited from 307 centres in Europe was amply sufficient for the per-protocol analyses. The study was terminated early on 31st December 2007.

2.3. Data model

Centre-level data included type, patient mix, patient volume, use of anaemia management protocols/guidelines and in-service or continuing medical education programming on anaemia. In addition to demographics, cancer and anaemia history and comorbidities, patient-level data also included selected anthropometric, clinical and laboratory variables. For each patient, treatments for cancer and anaemia (ESA, iron supplementation and blood transfusion) were recorded. Outcomes included Hb and performance status (WHO/ECOG or Karnovsky converted to WHO/ECOG).[13]

An entry of the data from France were entered by local third party in a separate dataset and merged with the electronic ACT dataset by Matrix45. During the programming phase of the electronic data capture system, it was decided to collect some variables at each time point that were collected in the French part of the study only at visit 1: cancer treatments, performance status, selected laboratory values and iron supplementation.

2.4. Definitions of response to ESA treatment

Five definitions of ESA treatment response were used. All assume the absence of any blood transfusions in the preceding 28 days:

- Achieving Hb between 12 and 12.9 g/dl (then prevailing EORTC guideline).
- Increase in Hb $\geqslant$ 2 g/dl.
- Increase in Hb $\geqslant$ 2 g/dl and/or attaining an Hb $\geqslant$ 12 g/dl (haematopoietic response).
- Increase in Hb $\geqslant$ 1 g/dl in maximum 8 weeks.
- Increase in Hb $\geqslant$ 1 g/dl.

2.5. Statistical analysis

Per protocol, data from visits 1 through 3 constituted the primary analysis set. Descriptive statistics were used for patient and centre characteristics, treatment patterns and outcomes. Chi-squared-based statistics were applied to test for statistical significance involving discrete variables; and the independent samples *t*-test for two-group comparisons and *F*-test for comparisons of >3 groups for continuous variables; all with

applicable multiplicity corrections. Changes in Hb over time were examined using repeated measures ANOVA with, as applicable, between-subjects in addition to within-subjects effects. Changes in performance status were tested with the Friedman test. Factorial ANOVA was applied to examine Hb level by performance status. Pearson's correlation quantified the association between Hb and performance score. For comparisons with ECAS findings, ECAS results were set as the hypothesised value to compare ACT data using the one-sample test of proportions (discrete variables) and one-sample *t*-test (continuous variables). The significance level was set at 0.05, and all tests were two-tailed.

2.6. Ethics

The study protocol was reviewed in each participating centre, and approval was obtained in accordance with the applicable laws and regulations in each country. Not all countries required patient informed consent for retrospective chart review studies. Informed consent was obtained if mandated by country-specific laws and regulations; and optional or at a centre's discretion if not mandated.

3. Results

3.1. Patients

A total of 2807 patients were enrolled in the study and constituted the enrolment sample. To be considered evaluable, patients had to be of age 18 or older, with a type of cancer specified in the inclusion criteria, and ESA initiation at Hb $\leqslant$ 11 g/dl. Only those with valid Hb values at visits 1 through 3 were retained in the analysis sample (see Fig. 1). Data reported here are for the European analysis subsample (N = 2192).

Table 1 presents patient demographics and clinical status at enrolment. The majority of patients were from Western Europe (79.2%). France contributed the most patients (37.4%) followed by Germany (20.9%). The remaining countries added between 7.7% (Poland) and 0.8% (Croatia) of the sample. The selection of cancer types (including breast [21.4%], ovarian [8.6%] and cervical [1.8%]) resulted in a slight preponderance of female patients (57.1%). Haematological malignancies were diagnosed in 28.8% of the sample, and the remaining 71.2% had solid tumours. Other notable proportions include lung (17.5%) and colorectal cancers (12.6%). Though not recorded in the French subsample, comorbidities such as active infection (2.4%), inflammatory disease (2.7%) and cardiopulmonary disease (7.7%) were observed in very few patients. Staging, disease status and disease burden, as available, suggest that the majority of patients had advanced disease. In terms of treatment, 95.2% were on concomitant chemotherapy, mainly standard dose (92.9%) and non-platinum (59.5%). The median length of the cancer treatment at the time of initiation of ESA treatment was 2.04 months.

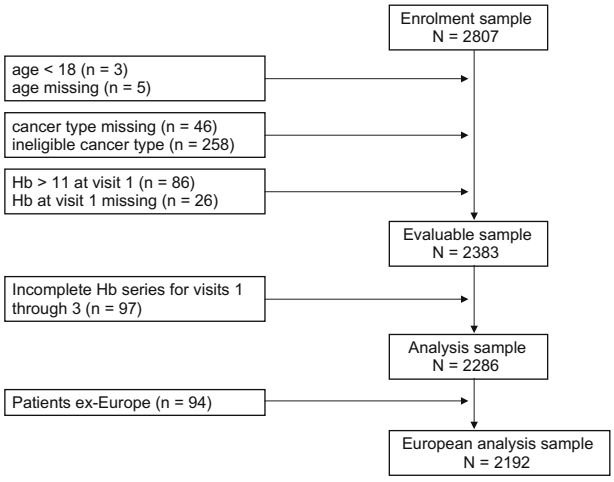

Fig. 1 – Disposition of patients and derivation of the European analysis sample (Hb: haemoglobin).

At enrolment, mean Hb was 9.54 ± 0.95 g/dl (range: 5.0–11.0 g/dl) and mean performance status was 0.96 ± 0.77 (0–4 scale). A small proportion of patients (241 or 11.0%) had received a blood transfusion prior to the initiation of ESA treatment. The mean number of transfusions was 1.13 ± 0.41 per transfused patient, the mean number units per transfusion was 2.19 ± 0.93 per transfused patient and the mean total number of units received across all transfusions was 2.42 ± 1.13 per transfused patient. Though not available for France, mean pre- and post-transfusion Hb levels were 8.02 ± 1.21 g/dl and 10.25 ± 1.62 g/dl, respectively. Only 608 patients (27.7%) received iron supplementation at visit 1, most of which was oral (81.8%). Serum ferritin and transferrin saturation (TSAT) levels at enrolment were available for 531 (24.4%) and 237 (10.9%) patients, respectively; too censored to achieve mature statistical results as to central tendency and dispersion.

There were no significant differences in key patient characteristics, treatment patterns (with the exception of a lower iron supplementation rate) and treatment outcomes between the French and the remaining patients.

3.2. Centres

The 307 participating centres were located mainly in Western Europe (87.0%), with France and Germany accounting for most (71.1%) (Table 2). Half the centres (50.2%) were part of an academic health system. 46.9% of centres were oncology or radio-oncology, 15.0% haematology and 6.2% combined oncology–haematology units. A minority of centres were disease-specific with 3.3% specialising in gynaecology and 2.3% in pulmonary cancer. In addition, 24.1% provided insufficient or no data to be classified. The median number of oncology patients seen in 2005 was 500.

The majority of centres (87.9%) provided data on up to 10 patients. Twelve (3.9%) centres exceeded the 20 patients limit, but statistical control analyses did not detect any associated bias. On average, centres contributed 7.2 ± 6.6 patients (Q1 = 4, Mdn = 5, Q3 = 7).

Most centres had formal anaemia management protocols in place (91.9%), of which 35.8% were, or included, those developed by the ASH/ASCO[8] and/or the EORTC.[10] When asked to provide treatment trigger levels as general practice, centres reported initiating blood transfusions at Hb levels between 5.0 and 11.0 g/dl (M ± SD = 8.15 ± 0.75) and ESA treat-

Table 1 – Patient Demographics and Clinical Status at Enrolment (available N listed; valid% reported except where noted).

Number of patients	2192			
Geographic distribution	*N*	*%*		
By region				
Western Europe	1736	79.2		
Central/Eastern Europe	456	20.8		
By country				
Belgium	106	4.8		
Croatia	18	0.8		
France	820	37.4		
Germany	459	20.9		
Greece	73	3.3		
Hungary	103	4.7		
Ireland	63	2.9		
Italy	105	4.8		
Netherlands	59	2.7		
Poland	168	7.7		
Portugal	51	2.3		
Romania	118	5.4		
Slovakia	49	2.2		
Demographics	*N*	Range	*M ± SD*	*95%CI*
Age	2192	18–94	61.5 ± 12.7	60.9–62.0
Gender		*N*	*%*	
Male		941	42.9	
Female		1251	57.1	
Clinical status				
Height (cm)*	1307	140–198	166.2 ± 8.8	165.7–166.6
Weight (kg)	2140	36–150	68.3 ± 13.6	67.7–68.9
	Missing	*N*	*%*	
Active infection*	867	32	2.4	
Cardiopulmonary disease*	866	102	7.7	
Inflammatory disease*	866	36	2.7	
Cancer status	*N*	*%*		
Cancer type				
Bladder	30	1.4		
Breast	470	21.4		
Cervix	40	1.8		
Colorectal	276	12.6		
Head & neck	65	3.0		
Lung	383	17.5		
Lymphoma	324	14.8		
Myeloma	306	14.0		
Ovarian	189	8.6		
Prostate	109	5.0		
General staging*				
I	86	6.7		
II	232	18.2		
III	397	31.1		
IV	560	43.9		
Missing	917			
Disease status (France only)				
Stable	222	28.8		
Progression	468	60.8		
Remission	80	10.4		
Disease burden*				
High	930	71.5		
Low	370	28.5		
Missing	892			

Table 1 – (*continued*)

Cancer treatment	N	Range	M ± SD	95%CI
Months on cancer treatment at baseline	1748	0.0–131.9	3.7 ± 7.4	3.3–4.0
		Missing	N	%
Receiving cancer treatment		54	1962	91.8
Chemotherapy		197	1900	95.2
of which ...	Standard dose	693	1393	92.9
	High dose		106	7.1
and of which ...	Platinum	503	684	40.5
	Non-platinum		1005	59.5
Radiotherapy		207	119	6.0
Hormonal therapy		207	66	3.3
Targeted treatment		208	237	11.9
Other treatment		206	124	6.2

* – Data not collected in France.

Table 2 – Participating centres.

	N	%
Geographic distribution		
By region		
Western Europe	267	87.0
Central/Eastern Europe	40	13.0
By country		
Belgium	15	4.9
Croatia	1	0.3
France	173	56.4
Germany	45	14.7
Greece	5	1.6
Hungary	13	4.2
Ireland	8	2.6
Italy	8	2.6
Netherlands	8	2.6
Poland	18	5.9
Portugal	5	1.6
Romania	4	1.3
Slovakia	4	1.3
Centre characteristics		
Type of centre		
Academic	154	50.2
Non-academic/private	50	16.3
Non-academic/non-private	95	30.9
Missing	8	2.6
Specialty		
Oncology/radio-oncology	144	46.9
Gynaecology	10	3.3
Haematology	46	15.0
Haematology/oncology	19	6.2
Pulmonology/pneumo-oncology	7	2.3
Other	74	24.1
Missing	7	2.3
Protocols and Guidelines Regarding Anaemia Management		
Centres with formal protocols		
Yes	282	91.9
No	14	4.6
Missing	11	3.6

(*continued on next page*)

Table 2 – (continued)

	N		%
Anaemia guidelines used in centres			
ASH/ASCO (2002)	27		8.8
EORTC (2004)	56		18.2
National guidelines	68		22.1
Guidelines developed at centre	68		22.1
ASH/ASCO & EORTC	19		6.2
EORTC & National guidelines	5		1.6
ASCO & Other guidelines	3		1.0
Other guidelines	36		11.7
Missing	25		8.1
	Range	M ± SD	95%CI
Hb level at which ESA treatment is initiated (g/dl) (missing = 13)	7.5–12.0	10.39 ± 0.88	10.28–10.49
Hb level at which blood transfusion is initiated (g/dl) (missing = 13)	5.0–11.0	8.15 ± 0.75	8.06–8.23
Patient case mix			
Number of oncology patients seen in 2005	20–15,000	1507 ± 2424	1220–1794
*Of all patients seen in last full clinic day**			
Proportion who were anaemic	0–100%	36.4 ± 30.6%	30.8–41.9
Proportion which were treated**	0–100%	68.3 ± 32.0%	62.2–74.3
With ESA	0–100%	62.2 ± 34.4%	55.3–69.1
Blood transfusion	0–100%	32.2 ± 33.4%	25.4–39.0
Iron supplementation	0–100%	37.3 ± 37.8%	29.5–45.1

ASH: American Society of Hematology; ASCO: American Society of Clinical Oncology; EORTC: European Organisation for Research and Treatment in Cancer; ESA: erythropoiesis-stimulating agent; Hb: haemoglobin.
* Data not collected in France.
** Treatment categories not mutually exclusive.

ment at Hb levels between 7.5 and 12.0 g/dl (M ± SD = 10.39 ± 0.88). Centres were also requested to review the clinical records of the last full clinic day and to record, of the patients seen that day, the percentages with anaemia and the percentages treated with epoetin, blood transfusions and iron supplementation. Of all patients reported to have been seen in the last full clinic day, on average 36.4 ± 30.6% were anaemic. Of these, on average 68.3 ± 32.0% were treated; mainly with ESAs (M ± SD = 62.2 ± 34.4%) but not infrequently with blood transfusions (M ± SD = 32.2 ± 33.4%) and iron supplementation (M ± SD = 37.3 ± 37.8%), alone or in various combinations. There was a statistically significant variation between countries in terms of the proportion of anaemic patients seen on the last full clinical day ($p < 0.001$) and, of these, the proportions treated ($p = 0.013$). While there were between-country differences in the proportions of ESA treatment and iron supplementation (both $p < 0.001$), countries did not differ significantly in the proportions of patients who received a blood transfusion (p = n.s.).

3.3. *Anaemia and anaemia treatment patterns*

Anaemia was attributed to chemotherapy in 77.7% of patients and/or chronic disease in 45.3%, with other causes being minimally present (causes were not mutually exclusive; Table 3). Time between diagnosis and start of ESA treatment ranged from 0 to 22.9 months with 79.1% of patients started on ESA treatment within 3 weeks of anaemia diagnosis. Initial ESA treatment included epoetin alfa (20.7% of patients), beta (42.6%), darbepoetin alfa (36.4%) and other ESAs (0.3%), mainly on a fixed dose (96.7%) and once-weekly regimen (65.7%). These proportions did not change significantly across the three visits for patients treated; however, at visit 2 ESA treatment had been discontinued in 139 (6.3%) and at visit 3 in 503 (22.9%) patients. Standardised to IU/week, the median starting dose was 30,000 IU/week. Blood transfusions and iron supplementation decreased slightly across the three visits, but not significantly so. Though the proportions of patients treated with intravenous (i.v.) iron increased, this trend was not statistically significant. Actual patients thus treated declined from 108 at visit 1 to 72 at visit 3.

In addition to their ESA treatment, 19.4% (95% confidence interval (CI) = 17.8–20.0) of patients were transfused and 32.8% (95%CI = 30.9–34.7) received supplemental iron any time from visit 1 to and including visit 3. In terms of treatment regimens, 53.8% (95%CI = 51.8–55.8; $n = 1179$) were treated exclusively with an ESA, whereas 13.4% (95%CI = 12.0–14.8; $n = 294$) were also transfused, 26.8% (95%CI = 25.0–28.6; $n = 587$) were additionally prescribed iron and 6.0% (95%CI = 5.0–7.0; $n = 132$) received the triple combination of ESA, blood transfusion and iron supplementation.

At visit 1, mean ESA doses were statistically not different across Hb levels (Table 4). However, at visits 2 ($p < 0.001$) and 3 ($p = 0.002$) there was a trend of mean ESA doses declining as Hb levels increased. Across visits, the mean ESA doses increased from visit 1 to visit 3 in patients with Hb < 9.0 g/dl and with Hb = 11.0–11.9 g/dl (both $p = 0.012$), but not in the Hb strata of 9.0–9.9 g/dl and 10.0–10.9 g/dl (both p = n.s.). Eighteen (0.8%) patients had their dose doubled over the study period, including 7 in the Hb < 9.0 g/dl, 8 in the Hb = 9.0–9.9 g/dl and 3 in the Hb = 10.0–10.9 g/dl strata (p = n.s.).

Table 3 – Anaemia and anaemia treatment patterns: initial status and evolution from visit 1 to visit 3.

Cause(s) of anaemia	Missing	N	Actual %
Anaemia status at visit 1			
Chemotherapy-induced	51	1703	77.7
Anaemia of chronic disease	60	993	45.3
Radiotherapy-induced*	882	84	3.8
Blood loss due to surgery*	883	58	2.6
Nutritional deficits*	884	80	3.6
Iron deficiency*	884	111	5.1
Other*	883	88	4.0

ESA treatment	Visit 1			Visit 2			Visit 3		
	Missing	N	%	Missing	N	%	Missing	N	%
Type	0			200			518		
Epoetin alfa		453	20.7		399	20.0		340	20.3
Epoetin beta		934	42.6		866	43.5		765	45.7
Darbepoetin alfa		798	36.4		719	36.1		559	33.4
Other		7	0.3		8	0.4		10	0.6
ESA discontinued				0	139	6.3	0	503	22.9
Weekly dose in IU	Min	Max	Median	Min	Max	Median	Min	Max	Median
Epoetin alfa	10,000	60,000	40,000	3333	80,000	40,000	10,000	80,000	40,000
Epoetin beta	1000	60,000	30,000	1000	60,000	30,000	1000	90,000	30,000
Darbepoetin alfa	10,000	100,000	33,333	6250	100,000	33,333	6667	100,000	33,333
Other	30,000	33,333	33,333	30,000	33,333	33,333	30,000	33,333	33,333
Missing	0			207			530		
	Missing	N	%	Missing	N	%	Missing	N	%
Frequency	0			200			539		
3x/weekly		173	7.9		155	7.8		135	8.2
2x/weekly		12	0.5		28	1.4		18	1.1
1x/weekly		1440	65.7		1291	64.8		1104	66.8
Q10days		0	0		0	0.0		1	0.1
Q2W		93	4.2		83	4.2		60	3.6
Q3W		460	21		423	21.2		328	19.8
Q4W		11	0.5		10	0.5		6	0.4
Q5W		0	0		2	0.1		0	0
Q6W		3	0.1		0	0		1	0.1
Dosing	934			1015			1161		
Weight-based		41	3.3		46	3.9		28	2.7
Fixed		1217	96.7		1131	96.1		1003	97.3

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Table 3 – (*continued*)

Blood transfusions	Prior to visit 1			Between visit 1 and visit 2			Between visit 2 and visit 3		
	N	%		*N*	%		*N*	%	
Patients transfused during period	241	11.0		186	8.5		143	6.5	
	Range	M ± SD	95%CI	Range	M ± SD	95%CI	Range	M ± SD	95%CI
Total number of transfusions received	1–3	1.13 ± .41	1.08–1.18	1–4	1.11 ± 0.39	1.05–1.16	1–4	1.15 ± 0.49	1.07–1.23
Total number of units transfused	1–9	2.42 ± 1.13	2.28–2.57	1–8	2.20 ± 0.93	2.07–2.34	1–8	2.34 ± 1.06	2.17–2.52
Average number of units per transfusion	1–9	2.19 ± 0.93	2.08–2.31	1–8	2.03 ± 0.69	1.93–2.13	1–4	2.08 ± 0.60	1.98–2.18
Hb prior to first transfusion (g/dl)*	3.3–11.0	8.02 ± 1.21	7.81–8.23	5.0–11.8	8.19 ± 1.07	8.01–8.37	5.1–11.9	8.25 ± 1.15	8.01–8.49
Hb after last transfusion (g/dl)*	8–17.2	10.25 ± 1.62	9.95–10.55	7.4–14.0	10.44 ± 1.28	10.20–10.68	7–13.1	10.36 ± 1.21	10.09–10.64
Iron supplementation	Visit 1			Visit 2			Visit 3		
	Missing	*N*	%	Missing	*N*	%	Missing	*N*	%
Percent of patients receiving iron	1	608	27.7	821	287	20.9	823	276	20.2
Route of administration	16			1			2		
Oral		484	81.8		204	71.3		202	73.7
Intravenous		108	18.2		82	28.7		72	26.3
	Min	Max	Median	Min	Max	Median	Min	Max	Median
Number of weeks on iron**	0	12	0	0	9	3	0	10	4

ESA: erythropoiesis-stimulating agent; Q10days: every 10 days; Q*x*W: every *x* weeks.

* – Data not collected for France.

** – Considering missing data reported above and as recorded.

Table 4 – Number of ESA dose and patients treated by Hb level across visits.

ESA dose by Hb level (g/dl)	Visit 1 M ± SD	Visit 2 M ± SD	Visit 3 M ± SD	p^{*}
<9	31,682 ± 10,151	34,244 ± 11,987	34,454 ± 13,695	0.012
9–9.9	32,456 ± 9690	34,528 ± 12,182	34,792 ± 11,599	n.s.
10–10.9	32,063 ± 8781	33,052 ± 10,738	33,337 ± 12,104	n.s.
11–11.9	30,344 ± 8646	31,653 ± 7428	33,183 ± 10,055	0.012
12–12.9		31,641 ± 10,731	31,820 ± 10,336	
⩾13		29,485 ± 9151	29,475 ± 9364	
p^{**}	0.240	<0.001	0.002	
Patients treated by Hb level (g/dl)	N	N	N	p^{*}
<9	536	277	157	<0.001
9–9.9	837	453	278	<0.001
10–10.9	761	710	455	<0.001
11–11.9	58	432	509	<0.001
12–12.9		137	210	<0.001
⩾13		44	80	0.001
p^{**}	<0.001	<0.001	<0.001	
p^{***}	<0.001			

ESA: erythropoiesis-stimulating agent; Hb: haemoglobin.
* p value for tests within Hb level and across visits.
** p value for tests across Hb levels and within visit.
*** p value for omnibus contingency analysis.

3.4. *Outcomes of and response to anaemia treatment*

In this sample of 2192 ESA-treated patients, mean Hb rose from 9.54 ± 0.95 g/dl at the initiation of ESA treatment to 10.34 ± 1.29 g/dl at visit 2 to 10.88 ± 1.49 g/dl at visit 3 ($p < 0.001$; Table 5), along with a widening of the dispersion of Hb values (Fig. 2). There were no statistically significant differences in mean Hb levels at each visit and across the three-visit study period between patients who received platinum versus non-platinum chemotherapy (all p = n.s.). Changes in performance status (WHO/ECOG) were not statistically significant (missing $n = 223$). Contingency analysis of patients treated across Hb categories and visits yielded a statistically significant omnibus result ($p < 0.001$), indicating an overall shift of patients across Hb categories and across visits: proportionately more patients migrated to higher Hb categories over time (for all rows and columns, $p < 0.001$) (Table 4).

We examined for differences in mean Hb levels at each and across the three visits between the four ESA-centric treatment regimens observed in this study: ESA only, ESA and transfusion, ESA and iron and the triple combination of ESA, blood transfusion and iron supplementation (Table 5). Cross-sectionally, mean Hb levels differed significantly across ESA regimens at each time point (all $p < 0.001$). Longitudinally, both omnibus within-subjects and between-subjects main effects were observed (both $p < 0.001$), indicating that mean Hb levels tended to improve over time but differentially so across treatment regimens. The test for interaction effect was not statistically significant (p = n.s.).

Table 6 reviews the percentage of patients who showed a response to treatment according to the five definitions used and the median number of weeks needed to achieve this response. Fig. 3 depicts the five treatment response rates for all patients and for tumour types with more than 200 evaluable patients (visits 1–3). Only 18.8% of patients with data for at least three visits achieved the EORTC criterion of Hb 12–12.9 g/dl, yet 65.0% of patients did show a rise in Hb ⩾ 1 g/dl. The three other criteria classified between 33.7% and 54.3% of patients as responders. The median time to response ranged from 4.7 weeks (increase in Hb ⩾ 1 g/dl) to 6.1 weeks (Hb 12–12.9 g/dl). Response rates were higher in patients with 5 data points because of the additional time to reach the targets (Table 6).

3.5. *Comparison to ECAS results*

With the caveats that the ECAS and ACT studies had different objectives, that ECAS results may have included non-anaemic patients and that different anaemia thresholds applied (<12 g/dl in ECAS versus <11 g/dl in ACT), some comparisons between both the studies are possible (Table 7). Though at enrolment the ECAS sample had proportionately more patients with WHO/ECOG score of 0 than ACT (35.7% versus 27.7%), the inverse applies to the score of 1 (43.5% versus 52.5%), yet this was not statistically significant. ECAS reported a correlation of –0.24 between Hb and performance status at enrolment compared to –0.19 in the ACT study (p = n.s.). Hb levels by performance status (0–1 versus 2–4) at enrolment were statistically significant within both studies ($p < 0.001$) but not between them.

4. Discussion

ECAS[2] raised awareness about the issue of anaemia in cancer patients. Coupled with the subsequent publication of evidence-based guidelines[8–12], there seems to have been an impact on 'real world' clinical practice in cancer in Europe. The low ESA treatment rate in 2001 (17.4%) increased almost

Table 5 – Haemoglobin and performance status: evolution over time.

	Visit 1				Visit 2				Visit 3			
	N	Range	M ± SD	95%CI	*N*	Range	M ± SD	95%CI	*N*	Range	M ± SD	95%CI
Haemoglobin												
All patients	2192	5.0–11.0	9.54 ± 0.95	9.50–9.58	0	5.0–16.4	10.34 ± 1.29	10.29–10.40	0	4.1–17.3	10.88 ± 1.49	10.82–10.94
ESA only	1179	6.1–11.0	9.72 ± 0.83	9.67–9.77	1179	6.7–16.4	10.58 ± 1.19	10.51–10.65	1179	6.1–17.3	11.11 ± 1.36	11.03–11.19
ESA + transfusion	294	5.4–11.0	8.89 ± 1.06	8.77–9.01	294	5.9–14.0	9.67 ± 1.45	9.50–9.83	294	5.7–15.5	10.15 ± 1.62	9.96–10.33
ESA + iron	587	6.1–11.0	9.68 ± 0.84	9.61–9.78	587	6.2–13.6	10.45 ± 1.15	10.35–10.54	587	4.1–15.1	11.01 ± 1.39	10.90–11.13
ESA + transfusion + iron	132	5.0–11.0	8.72 ± 1.07	8.54–8.91	132	5.0–13.2	9.32 ± 1.38	9.08–9.56	132	5.5–15.3	9.88 ± 1.76	9.57–10.18
Performance status	1969	0–4	0.96 ± 0.77	0.92–0.99	1173	0–4	0.81 ± 0.71	0.77–0.85	1341	0–4	0.80 ± 0.75	0.76–0.84

ESA: erythropoiesis-stimulating agent; CI: confidence interval.

fourfold (62.2%) over 4–6 years; though with the caveat that these rates were calculated at the patient level in ECAS but at the centre level in ACT. This article is the first report of treatment patterns involving ESAs, transfusions and iron supplementation. Further, this is the first evidence of how these treatment patterns are associated with clinical effectiveness and treatment response.

ACT offers evidence that, despite significant variability in treatment patterns in ESA-centric regimens, mean haemoglobin levels rose by a net 1.34 g/dl or 14% over 8–10 weeks. Importantly, this is a net increase: Hb levels are known to drop by about 1 g/dl after the initiation of chemotherapy and the total rise in Hb in most of these ESA-treated patients may have been in excess of 2 g/dl. Though we did not report detailed data for visits 4 and 5 as these visits were optional and the data censored, mean Hb rose to 11.19 g/dl (SD = 1.53) at visit 4 and 11.42 g/dl (SD = 1.55) at visit 5. Depending on the definition, between 18.8% (reaching Hb between 12 and 12.9 g/dl) and 65.0% of patients (reaching Hb $\geqslant$ 1 g/dl) responded to treatment with an ESA by visit 3; and rates were higher in the censored datasets of patients with 4 and 5 visits (see Table 6). Note that the EORTC criterion of reaching Hb between 12 and 12.9 g/dl no longer applies today due to the change in label in Europe.

The observed treatment response rates are lower than the efficacy rates observed in RCTs. This may be due to the treatment duration in ACT not being standardised and being shorter than in RCTs. Also, 95.2% of patients were being treated with chemotherapy concomitantly, which is known to suppress Hb levels.

Importantly, ACT provides further insights in how anaemia is managed in cancer patients and whether this is congruent with the EORTC guidelines. Blood transfusions tended to be given when Hb levels were below 9 g/dl, consistent with the EORTC guidelines. Transfusion rates did not decline significantly over time, and there were no differences in rates between individual countries and when Central and Eastern European (CEE) countries were compared to Western Europe. The transfusion rates reported by centres on all cancer patients seen in the last full clinic day were high at an average of 32.2% of patients. This stands in contrast to the 11% of patients in the study who had received a transfusion prior to being started on an ESA. Thus, transfusions may be used rather frequently in anaemia management in general, perhaps as a generalised if not at times indiscriminate response to safety issues that have been attributed to ESAs over the last few years. The rather high general transfusion rates may also be affected by the mere increase in awareness about anaemia in cancer patients following the ECAS study and the development of guidelines. A similar pattern of rather high iron supplementation rates at the centre level (37.3% on average) but lower (intravenous) iron treatment among patients in the study sample was observed. Greater awareness about anaemia in cancer patients may explain this result in part. However, whereas the EORTC guidelines are rather explicit in regards to blood transfusions, they are less so where iron supplementation is concerned. The relatively low iron treatment rates may reflect the need for more scientific evidence to strengthen the corresponding EORTC guideline.

That the type of ESA-centric regimen was associated with differential Hb outcomes across the three visits offers novel

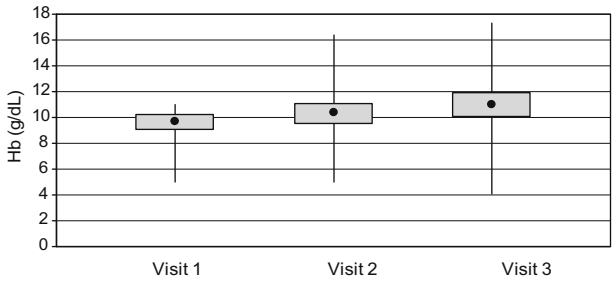

Fig. 2 – Haemoglobin (Hb) evolution across 3 ACT visits. In plots, box represents 25th to 75th percentiles; dot specifies median; and whiskers extend to minimum and maximum values observed.

insights in the relationship between treatment patterns and outcomes. Recall that these regimens were defined as '(n)ever-over-time' at any of the three visits: in addition to ESA treatment, was the patient ever transfused, ever prescribed supplemental iron or ever treated with both. As can be seen from Table 5, mean Hb levels for the regimens that included blood transfusion were consistently between 0.9 and 1.3 g/dl lower than those for the ESA only and the ESA and iron supplementation regimens (which differed by at most a negligible 0.1 g/dl). Transfusions were added if patients tended to have a low Hb (especially Hb < 9.0 g/dl) and/or responded slower than expected to erythropoietic stimulation. This would be in accordance with EORTC guidelines, though less careful transfusion practices cannot be excluded and should remain of concern given the known disadvantages of allogeneic blood transfusions. Further, mean Hb levels for patients in the ESA only and the ESA-plus-iron regimens were virtually identical, suggesting that clinicians may decide iron supplementation on a case-by-case basis – which would be in the spirit of the EORTC guidelines. However, to be compliant with the EORTC guidelines, the main decision criterion should be whether patients have absolute or functional iron deficiency; in which case intravenous iron is recommended.[12] Though the ACT data were too censored to permit mature statistical results, a cursory review (data not reported) revealed that serum ferritin and TSAT values were not available for, respectively, 75.6% and 88.4% of patients in the ESA + iron regimen and, respectively, 68.2% and 81.8% of those receiving the triple regimen of ESA, blood transfusion and iron supplementation. Possibly, investigators may have failed to report these data, and others may have prescribed iron per internal centre protocol. Yet the pervasive absence of such basic clinical

Table 6 – Percentage of patients with response to erythropoiesis-stimulating agent (ESA) treatment and time to response by various criteria of treatment response for visits 1–3 (a); percentage of patients with response to ESA treatment and time to response by various criteria of treatment response for all valid visits (up to 5) (b).

EORTC: Hb 12–12.9 g/dl		Hb ↑ ⩾ 2 g/dl		Hb ↑ ⩾ 2 g/dl or Hb ⩾ 12 g/dl		Hb ↑ ⩾ 1 g/dl in 8 weeks		Hb ↑ ⩾ 1 g/dl	
% of pts	Mdn Δt	% of pts	Mdn Δt	% of pts	Mdn Δt	% of pts	Mdn Δt	% of pts	Mdn Δt
(a)									
18.8	6.1	33.7	6.0	38.9	6.0	54.3	N/A	65.0	4.7
(b)									
33.0	8.7	49.6	8.0	56.0	7.7	56.3	N/A	75.7	5.4

EORTC: European Organisation for Research and Treatment in Cancer; Hb: haemoglobin; Mdn Δt: median time to response; N/A: not applicable as 8 week time limit is specified.

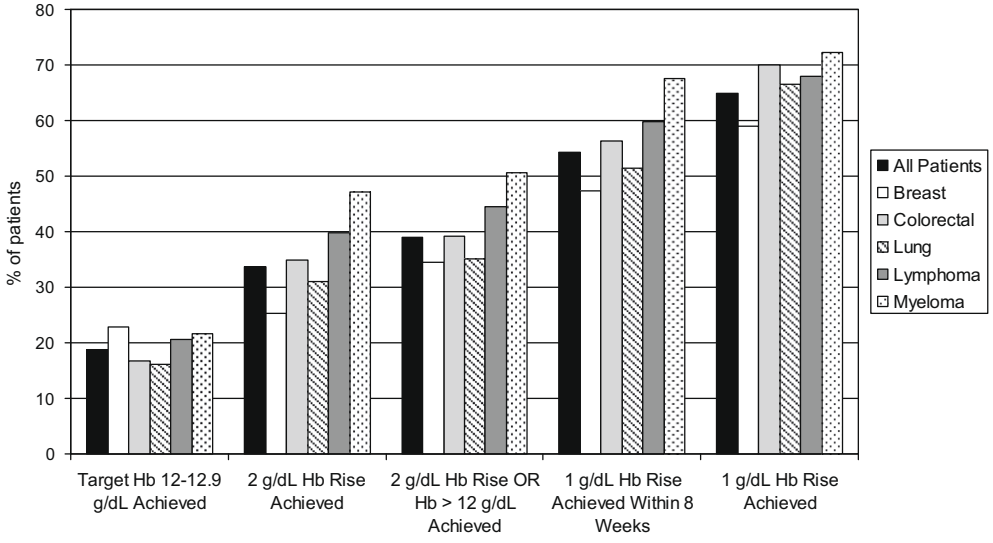

Fig. 3 – Response by selected cancer types (Hb: haemoglobin).

Table 7 – Comparisons ECAS–ACT.[a]

	ECAS	ACT	p^*
Performance status at enrolment			n.s.
0	35.7%	27.7%	
1	43.5%	52.5%	
2	16.6%	16.7%	
3	3.7%	2.4%	
4	0.5%	0.6%	
Correlation Hb and performance status at enrolment	–0.24	–0.19	n.s.
	<0.001	<0.001	
Hb level (four levels[b]) by performance status (0–1 versus 2–4) at enrolment	<0.001	<0.001	n.s.

No significant differences: tumour types, gender and age; ECAS: European Cancer Anaemia Survey; ACT: Anaemia Cancer Treatment.

* Statistical significance of ECAS–ACT comparison.

a ECAS estimates include non-anaemic patients.

b Hb levels: <8, 8–9.9, 10–11.9, ⩾12; Hb: haemoglobin.

information may indicate a trend of making treatment decisions involving supplemental iron without the essential variables to determine whether patients have absolute or functional iron deficiency.

Virtually all ESA regimens were started on a fixed dose, and the median starting dose was in accordance with the EORTC guidelines. The trend of increasing mean ESA doses across visits in patients with Hb < 9 g/dl suggests dose escalation; and so may the rise in mean dosing observed in patients with Hb between 11 and 11.9 g/dl (the effect of dose-doubling is virtually nil). This may also reflect an attempt to maintain Hb levels in target range. These practices are consistent with the EORTC guidelines. A large-sample study should be conducted to examine whether practicing in congruence with EORTC guidelines is associated with better Hb outcomes, as a recent study suggests it may.[14]

Both ECAS[2] and RCTs[15–20] have shown an association between higher Hb levels and better performance status. ACT yielded a weak correlation in the same order of magnitude as ECAS (–0.19 versus –0.24); however, the statistically significant rise in Hb from visits 1 to 3 seen in ACT was not paralleled by a similar rise in WHO/ECOG scores (as was the case in ECAS). This might be due to the higher proportion of patients in ACT with a score of 1 rather than 0 (compared to ECAS), the residual range of scores being insufficient to permit detectable variation and/or ECAS including non-anaemic patients. ACT confirmed the statistically significant cross-classification of Hb levels and performance status (0–1 versus 2–4).

Being a retrospective chart review study and not having comparative patient groups, ACT did not collect safety data. The question raised in, for instance, the ECAS report[2] as well as a recent exchange of opinions[21,22] about the risk for serious adverse events associated with improved Hb outcomes merits further investigation. Sampling was not proportionate to either population size or the prevalence of respective types of cancer. Notwithstanding (and to the positive), this permitted an assessment of the natural flow of patients in participating centres rather than targeted recruitment to fulfil quotas. Follow-up was limited to two visits after the initiation of ESA treatment, though there was the option of providing data for up to two additional visits. Still, this may not be long enough a time frame to examine whether Hb thresholds were maintained over time.

The ACT study had limitations yet also revealed several areas of future investigation. The determinants, positive and negative, of Hb levels and treatment response to ESAs need to be elucidated to so better identify modifiable or manageable factors. While ACT showed that some aspects of clinical practice are in accordance with EORTC guidelines, this needs to be investigated in a study designed specifically for that purpose. The ACT study was retrospective, and future studies may benefit from a prospective design. As with any observational study, it must be assumed that not all confounding variables may have been known and thus controlled for. Though offset in part by the large-sample size, sampling procedures may have introduced a selection bias. The use of summary centre data regarding patient volume and treatment practices and rates may be subject to an aggregation bias. The current debate as to the safety of ESAs in general and in specific tumour types needs to be integrated into observational studies. Such studies will enable further safety monitoring. Importantly, such studies will permit the evaluation of safety outcomes as a function of variability in ESA treatment, not just ESA treatment in itself (as in RCTs), and under consideration of many potential determinants and confounds. In light of recent regulatory actions in Europe and the United States (US) with regard to the use of ESAs in cancer patients, a change in treatment patterns and associated outcomes may be observed in the years ahead.

In conclusion, in Europe more anaemic cancer patients are being treated with ESAs as evidenced by the almost fourfold increase in ESA treatment rates. However, there remains room for an improvement in practice patterns and outcomes before the effectiveness of ESAs under 'real world' conditions achieves the results recorded in RCTs. In turn, this will lead to a better differentiation of which patients benefit, why, and how. The ACT study underscores the general effectiveness and relative safety of judicious ESA treatment.

Contributions

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Conflict of interest statement

H.L., M.A., C.B., and P.S. have received compensation from F. Hoffmann-La Roche AG for professional and scientific services. M.T. is an employee of F. Hoffmann-La Roche AG. I.A., K.M., and T.A. are employees of Matrix45. By company policy, they are prohibited from owning equity in client organisations and performing independent duties for client companies. Matrix45 received consulting and research contracts from F. Hoffmann-La Roche AG to conduct the study. Matrix45 provides similar services to other pharmaceutical companies.

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