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## Introduction

Cancer(-therapy)-related anemia is one of the most common side effects of malignant diseases and can significantly impact on patients' quality of life (QoL). Treatment strategies recommended by current guidelines include erythropoiesis-stimulating agents (ESAs), and iron supplementation either alone or in combination with ESAs [1]. If no causal therapy is indicated, red blood cell transfusions (RBCTx) can be considered in patients with symptomatic anemia and hemoglobin (Hb) levels below 8g/dl or upon the appearance of symptoms potentially indicating anemic hypoxia (so called physiological triggers, e.g. tachycardia or hypotension) accompanied with an Hb level between 8-10g/dl [2].

## Methods

The TAR was an open, prospective, multicenter, longitudinal study investigating routine anti-anemic treatment and its effectiveness in cancer patients in Germany (ClinicalTrials.gov NCT01795690). From March 2012 to September 2013 a total of 88 study sites recruited 1018 patients at the start of anti-anemic treatment with Hb levels <11g/dl (females) or <12g/dl (males). Additional inclusion criteria were ≥18 years of age, diagnosed cancer, ECOG performance status of 0-3 and a life expectancy >16 weeks. Patients with myelodysplastic syndrome or an experimental anti-anemic therapy as part of a clinical trial were excluded. Study sites were encouraged to enroll patients consecutively to ensure unselected recruitment. Patients were treated according to physicians' choice based on patients' individual needs. During an observation period of 12 weeks patient characteristics, laboratory parameters and data on anti-anemic treatment were collected from patients' medical files and documented in a secure web-based electronic case report form. To determine QoL, patients completed the Functional Assessment of Cancer Therapy Anemia (FACT-An) questionnaire at enrollment and 6 and 12 weeks later. 984 patients matched inclusion criteria and were included into the final analysis. Hereafter data on the 4 most common initial anti-anemic therapies are shown (n=962, 97%).

Table 1 Characteristics of patients receiving anti-anemic treatments in German routine practice

		Operable solid tumor (n=207)				Inoperable solid tumor (n=606)				Hematological malignancy (n=149)					
Day-1-treatment		Trans-fusion	ESA	IV iron	ESA + IV iron	Trans-fusion	ESA	IV iron	ESA + IV iron	Trans-fusion	ESA	IV iron	ESA + IV iron	Total	
Number of patients [n]		114	51	30	12	362	108	102	34	95	37	10	7	962	
Sex	Male [%]	36.8	27.5	40.0	50.0	50.0	43.5	52.9	58.8	57.9	51.4	80.0	57.1	48.0	
Age at start of therapy	Mean ± StD	66.0 ±12.8	64.2 ±12.5	66.2 ±9.5	66.4 ±8.8	66.6 ±10.6	64.4 ±9.7	66.8 ±10.6	69.1 ±9.2	69.2 ±11.5	64.8 ±17.0	67.7 ±14.3	67.4 ±10.4	66.5 ±11.3	
CCI <sup>a</sup> [0-36]	Mean ± StD	0.6 ±1.6	0.5 ±0.9	0.5 ±0.9	0.8 ±1.1	0.8 ±1.3	0.6 ±1.2	0.6 ±1.1	0.6 ±1.0	0.5 ±0.9	0.8 ±1.3	0.3 ±0.7	1.4 ±2.9	0.7 ±1.2	
Karnofsky Index [0-100]	Mean ± StD	81.6 ±11.5	82.2 ±9.2	87.7 ±8.2	86.7 ±4.9	78.7 ±12.8	82.5 ±8.8	78.8 ±12.0	80.6 ±10.7	82.6 ±12.5	82.2 ±10.0	77.0 ±14.9	88.6 ±6.9	80.7 ±11.8	
Most frequent solid cancers [%]	Breast	16.7	41.2	16.7	8.3	14.1	25.0	11.8	14.7	-	-	-	-	14.7	
	Colorectal	15.8	13.7	30.0	33.3	9.1	5.6	20.6	2.9	-	-	-	-	10.3	
	Lung (NSCLC)	10.5	11.8	3.3	16.7	10.8	15.7	3.9	5.9	-	-	-	-	8.6	
Tumor therapy [%]	No therapy	6.1	-	3.3	-	2.5	0.9	2.0	-	6.3	5.4	20.0	-	3.1	
	Chemotherapy	92.1	98.0	93.3	100.0	88.1	95.4	86.3	94.1	76.8	81.1	40.0	85.7	88.4	
	Other	1.8	2.0	3.4	-	9.4	3.7	11.8	5.9	16.9	13.5	40.0	14.3	8.5	
Baseline Hb	Median [g/dl]	8.7	9.3	9.6	9.6	8.6	9.5	9.6	9.4	8.5	9.2	9.6	10.8	8.9	

<sup>a</sup> Charlson Comorbidity Index

Table 2 Effectiveness of anti-anemic treatments in German routine practice

		Operable solid tumor (n=207)				Inoperable solid tumor (n=606)				Hematological malignancy (n=149)					
Day-1-treatment		Trans-fusion	ESA	IV iron	ESA + IV iron	Trans-fusion	ESA	IV iron	ESA + IV iron	Trans-fusion	ESA	IV iron	ESA + IV iron	Total	
ΔHb(max) <sup>b</sup> [g/dl]	n <sup>a</sup>	78	41	18	11	257	79	71	27	67	34	7	5	962	
	Median	2.9	2.7	2.0	2.6	2.7	2.6	2.0	2.3	2.6	2.6	2.0	2.9		
	Mean ± StD	3.1±1.5	3.0±1.4	2.3±1.2	2.8±1.3	2.8±1.8	2.8±1.5	2.0±1.6	2.5±1.3	2.6±1.5	2.5±1.9	2.6±1.5	2.8±1.5		
ΔHb(final) <sup>c</sup> [g/dl]	n <sup>a</sup>	63	40	16	11	223	77	67	26	62	32	7	5	962	
	Median	1.6	2.0	1.6	1.7	1.5	1.9	1.1	1.8	1.2	2.1	2.0	2.3		
	Mean ± StD	2.0±1.8	2.1±1.2	1.7±1.5	2.1±1.3	1.6±1.5	2.1±1.7	1.3±1.5	1.9±1.5	1.6±1.8	1.9±2.0	2.4±1.6	2.2±1.9		
Responders <sup>d</sup>	n <sup>a</sup>	63	40	16	11	223	77	67	26	62	32	7	5	962	
	%	50.8	72.5	62.5	63.6	41.3	55.8	43.3	57.7	35.5	59.4	57.1	80.0		
Patients receiving transfusions	n <sup>a</sup>	114	51	30	12	362	108	102	34	95	37	10	7	962	
	Week 1 - 4 [%]	100.0	25.5	13.3	8.3	100.0	26.9	16.7	17.6	100.0	29.7	10.0	-		
	Week 5 - 8 [%]	24.6	5.9	6.7	-	31.5	14.8	9.8	2.9	44.2	10.8	10.0	14.3		
	Week 9 - 12 [%]	17.5	3.9	3.3	-	26.2	8.3	7.8	5.9	33.7	21.6	20.0	-		

<sup>a</sup>Number of patients for whom variable is documented or could be calculated.

<sup>b</sup> The difference between the baseline Hb and the highest Hb documented.

<sup>c</sup> The difference between the baseline Hb and the last Hb documented within the 12 weeks observation period, but at least 4 weeks after the start of treatment.

<sup>d</sup> A responder is defined as a patient with a final Hb >11g/dl or with a final Hb of ≥1.5g/dl above baseline, with the final Hb being the last documented Hb within the observation period, but at least 4 weeks after the start of anti-anemic treatment.

## Results

Overall, patients with operable solid tumors (curative situation) were treated less frequently with transfusions than patients with inoperable solid tumors (palliative situation) or patients affected by hematological malignancies. Patients with operable solid tumors received more often ESAs as patients with inoperable solid tumors (Fig. 1).

Patients, who were treated with transfusion initially, had lower Hb values at the start of treatment than patients receiving a causal anti-anemic therapy. Patients treated with ESA were often younger and/or suffering from breast cancer than patients receiving other therapies. Patients with colon carcinoma most frequently received IV iron as anti-anemic treatment (Tab. 1).

Of the 571 patients receiving transfusions, 78% (n=443) had Hb levels ≥8g/dl and 29% (n=165) Hb levels ≥9g/dl at the start of treatment. For 88% and 85% of these patients the presence of anemic symptoms was reported, respectively. Data on the appearance of physiological triggers (see Introduction) were not systematically documented in TAR.

Within 4 weeks before the start of therapy, iron status was determined in approximately 30% of all patients, most frequently by measuring ferritin, serum iron or TSAT (Fig. 2). Iron parameters were measured more often in patients with colorectal cancer than in patients affected by other malignancies (43% vs. 28%).

Overall, anti-anemic treatment was successful in approximately half of all patients ("responders", Tab. 1). The majority of patients receiving causal anti-anemic therapies required no additional transfusions during the observation period (Tab. 1).

The median anemia-specific subscale scores of FACT-An questionnaire showed improvement in all treatment groups within the 12 weeks observation period. Clinically meaningful changes [3] were observed for all patients undergoing causal therapies. These data should be interpreted with caution since patients receiving transfusions had lower Hb values at the start of treatment among other differences, which may also affect QoL. Due to the non-interventional, non-randomized design of the registry causal relations cannot be drawn.

## Conclusions

In conclusion, our data suggest that diagnostics for possible causes and causal therapies of anemia are underused in routine clinical practice in German oncology centers. The large proportion of patients treated with transfusions, especially with Hb values ≥8g/dl, highlights the need for systematic studies into the benefits of diagnostic-led treatment decision making and for an European guideline on anemia management. It urgently needs to be discussed whether thorough anemia diagnostics and earlier intervention can decrease the need for transfusions, at least in subsets of patients.

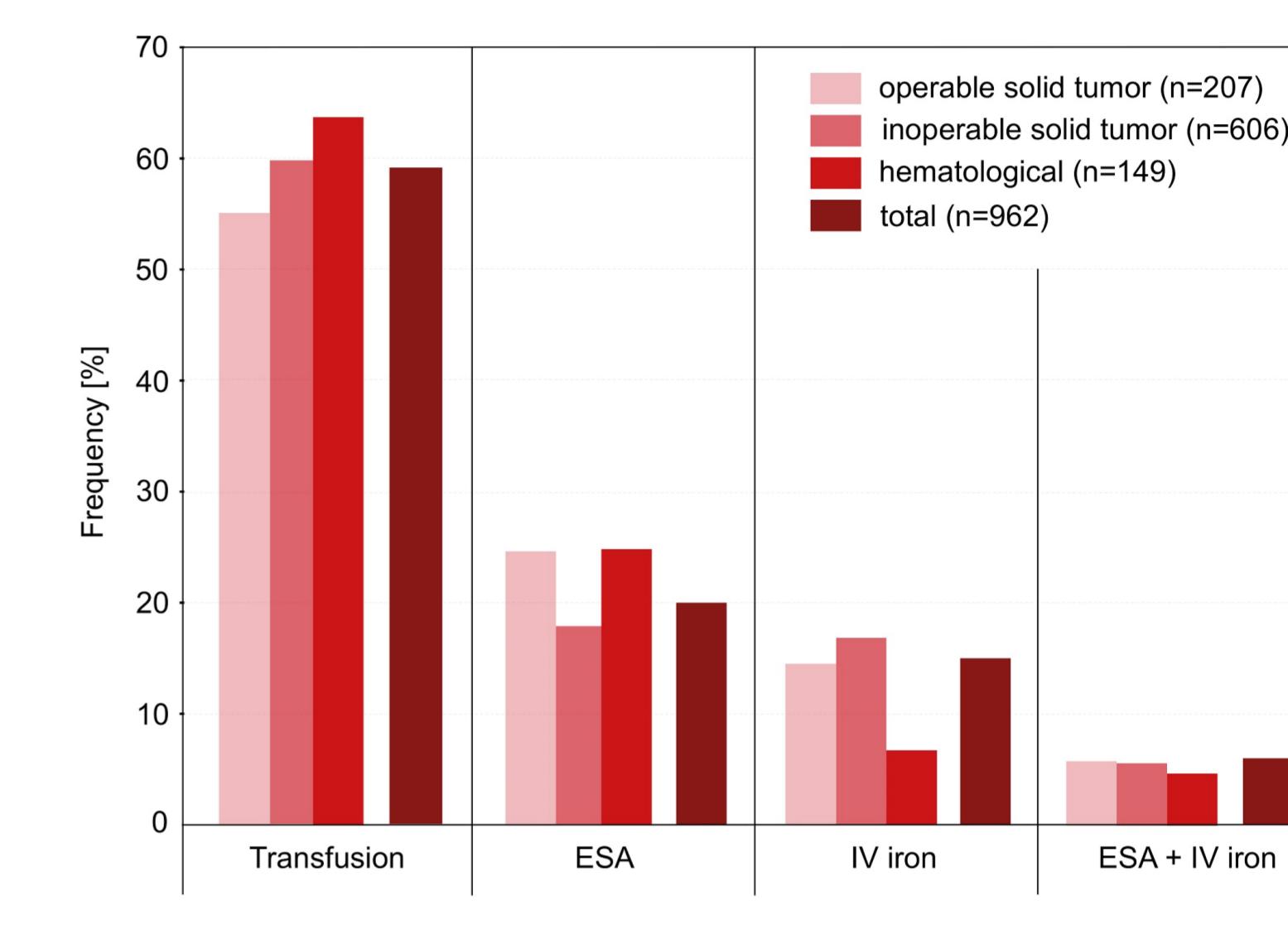


Figure 1  
Frequency of anti-anemic day-1-treatments by type of disease

