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Original Article

Impact of Iron-Deficiency Management on Quality of Life in Patients with Cancer: A Prospective Cohort Study (CAMARA Study)

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Abstract

Background: Iron deficiency (ID) is very common in patients with solid tumors and may cause symptoms such as fatigue. However, its impact on clinical outcomes is poorly described. The aim of this prospective monocentric cohort study was to evaluate the evolution of quality of life (QoL) of these patients after iron supplementation.

Methods: We included patients treated for a solid tumor, which were diagnosed with a functional (ferritin <800 ng/mL) or absolute (ferritin <300 ng/mL) ID (transferrin saturation coefficient <20%). The primary endpoint was patients' QoL evolution between baseline and intermediate visit, 15-30 days after initial intravenous iron supplementation, assessed by the Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale. Secondary endpoints were the same assessment between baseline, intermediate, and final visit at 6 months and the evolution of functional capacities.

Results: From 02/2014 to 12/2016, 248 patients were enrolled, of whom 186 were included in the analyses, including 140/186 (75.3%) with absolute ID. Anemia was detected in 141/174 (81.0%) patients at baseline. The FACT-An scores improved significantly between inclusion and intermediate visit ($P = .001$) and also between the 3 times of evaluation ($P < .001$). The most improved dimensions were those assessing physical, emotional well-being, and fatigue. Patients who performed the functional tests in all 3 phases had a significant improvement in performance on the majority of tests.

Conclusion: The supplementation of ID was associated with an improvement of the QoL and functional capacities in patients with cancer. A randomized control trial is necessary to confirm our results. Our findings underline the importance of supportive care, including screening for ID, in oncology.

Clinical trial registration number: NCT03625661.

Key words: iron deficiency; quality of life; anemia; supportive care; cancer patients; FACT-An scale

Implications for Practice

Screening for iron deficiency must be done routinely in solid oncology. Its supplementation was associated with an improvement of quality of life in the short and long term, specifically regarding the physical and functional well-being, fatigue, and anemia-related symptoms. It was also associated with an improvement of functional capacities, explored by objective assessment using conventional functional and geriatric tests performed by a physiotherapist at 3 and 6 months.

Introduction

Anemia is a frequent condition among oncology patients, concerning 39.3% of them according to the European Cancer Anaemia Survey study[1] and up to 63.4% at diagnosis in others studies depending on the threshold chosen.[2,3] It is often multi-causal, related to chronic disease inflammation, bone marrow invasion, side effect of the treatments, or nutritional deficiencies.[4]

Prevalence of iron deficiency (ID) also seems to be high in these patients, from 42.6%[5] to 50%-60%[6] depending on the tumor location, stage, and the threshold retained. It could be a functional or absolute ID,[7] the first one defined as a lack of biologically available iron: inflammation, mostly by the way of hepcidin,[8] inhibits enteral iron absorption, blocks iron release of the intracellular stock and does not allow it to be used properly. Absolute ID reflects an important decrease of

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iron stock, related to blood loss, impaired iron absorption, or inadequate incoming iron. Iron deficiency could be symptomatic even in the absence of anemia, with cognitive impairment, fatigue, and reduced exercise performance.[9,10]

Anemia could be treated with erythropoiesis-stimulating agents (ESAs), transfusion, and iron supplementation depending on the presence of an associated ID.[11]

Oral or intravenous (i.v.) supplementation could be used and recent guidelines enhance the advantage of i.v. iron preparation in oncology patients with related anemia. It has been shown that iron supplementation enhances the effect of ESAs and could reduce transfusion rates.[12,13]

Several studies have shown the interest of an iron supplementation in non-anemic iron-deficient patients, with an effect on fatigue, mental quality of life (QoL), cognitive function in healthy premenopausal woman but also athletes and heart failure patients.[14] However, its impact on clinical outcomes is poorly described in oncology.

Therefore, we investigated the evolution of QoL of these patients after iron supplementation.

Methods

We performed a prospective monocentric cohort study to evaluate the impact of iron supplementation on the QoL of patients with cancer.

Eligibility criteria were as follows: patients treated for a solid tumor in the day unit of ICO, who were diagnosed with an ID (transferrin saturation coefficient <20%). This could be a functional (ferritin <800 ng/mL) or absolute deficit (ferritin <300ng/mL), associated or not with anemia (hemoglobin <12 g/dL). Patients had to be over ≥18 years old, and could receive any specific oncologic treatment (chemotherapy, targeted therapy, immunotherapy, hormonotherapy, radiotherapy, or surgery). Patients were ineligible if they were in palliative care, suffering for hematologic malignancy, pregnant, or presenting contraindication to iron supplementation.

This study was approved by an independent ethics committee and all patients were informed. The study was registered with ClinicalTrials.gov (NCT03625661) databases. All patients gave written informed consent before participating in the trial.

At the inclusion, patients received an iron supplementation, using an i.v. iron preparation of ferric carboxymaltose according to ESMO Guidelines.[11]

Patients' QoL was assessed by the Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale, which is a specific variation of the Functional Assessment of Cancer Therapy-General (FACT-G) scale related to anemia.[15]

The primary endpoint was its evolution at the intermediate visit, 15-30 days after initial intravenous iron supplementation.

Secondary endpoints included on one hand the evolution of this same assessment between baseline, intermediate, and final visit at 6 months, calculated among the patient that complete the entire survey.

On the other hand, the evolution of functional performance measured by conventional functional and geriatric tests between the 3 times of evaluation calculated among the patients who completed all the test at all the evaluation time. These tests, performed by a physiotherapist, consist in "Tinetti", "Berg", "6-minute walk" test",[16] "timed up and go," [17] and measure of the number of sit/stand action in 1 min[18,19]).

All statistical analyses were computed using R software version 3.5.0 (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.) Quantitative data at inclusion were summarized by mean and standard deviation. Categorical and binary data at inclusion were summarized using counts, percentage, and missing data were indicated. Characteristics of patients answering or not the FACT-An questionnaire and undergoing or not the

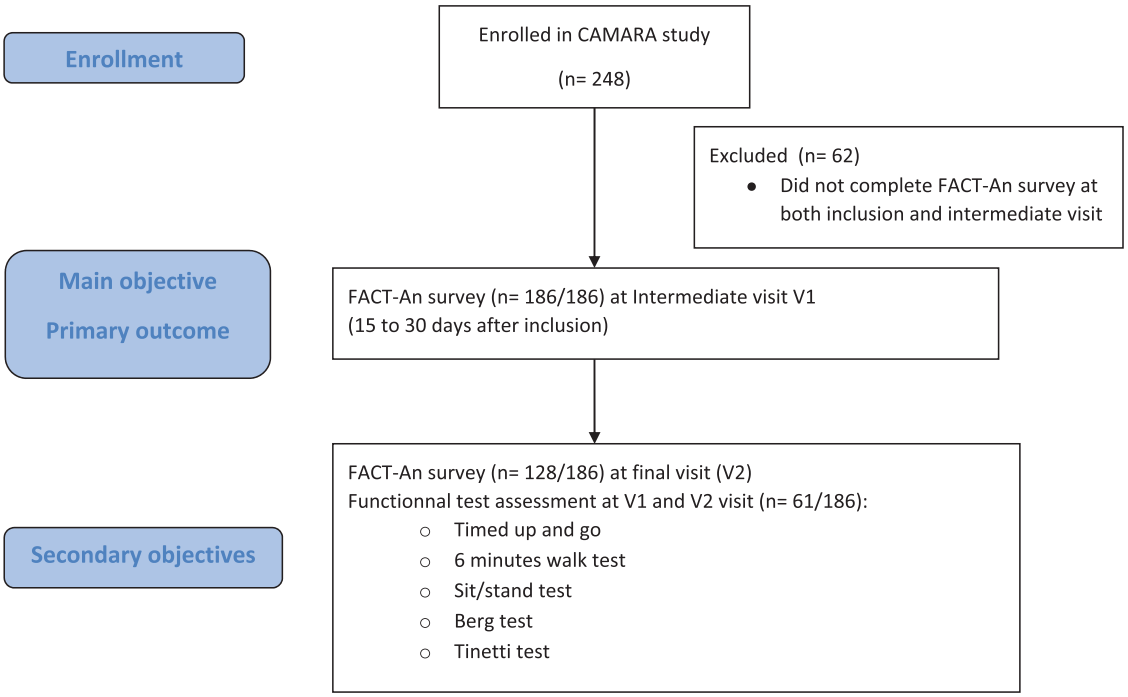

Figure 1. Flow chart.

functional tests at the 3 times of the study were compared using Student *t* test and chi-square tests as appropriate.

FACT-An questionnaire were self-administered by patients.

QoL scores were calculated using FACT-COG Scoring recommendations and "FACTscorer" package [Ray Baser (2015). FACTscorer: Scores the FACT and FACIT Family of Patient-Reported Outcome Measures. R package version 0.1.0. https://CRAN.R-project.org/package=FACTscorer]. No imputation of missing data was performed. For each FACT-An dimension and for functional measures, quantitative scores were compared between inclusion and intermediate visit (primary endpoint) using a Mann-Whitney test. Comparison between the 3 times of evaluation was done using a Friedman test. A change of 5 points or more was considered as clinically relevant on the overall FACT-An score.

Results

From February 2014 to December 2016, 248 patients treated for a solid tumor in the day unit of ICO were enrolled in the CAMARAs study of whom 186 were assessable for the primary endpoint and included in the analyses (Fig. 1).

Patients' characteristics at baseline are described in Table 1. The median age was 63.1 years, there were 27.4% (51/186) of men. Regarding the oncologic status, 48.9% (91/186) of patients were metastatic, 50.5% (94/186) were suffering from gynecologic neoplasia, 18.9% (35/186) from digestive neoplasia, 15.1% (28/186) from urologic neoplasia, 2.7% (5/186) from head and neck cancer and 2.2% (4/186) from pulmonary cancer. Regarding the treatment, 82.8% (154/186) were under chemotherapy, 16.7% (31/186) targeted therapy, 11.8% (22/186) radiotherapy, 5.9% (11/186) hormonotherapy, and 3.2% (6/186) immunotherapy (Table 1).

Table 1. Baseline characteristics and treatment at the inclusion (n = 186).

Characteristic	Overall cohort, *n* (%)
Median age ± SD, years	63.1 ± 14.6
Gender	
Male	51 (27.4%)
Performance status	
0	29 (15.6%)
1	92 (49.5%)
≥2	23 (12.3%)
n/a	42 (22.6%)
Type of cancer	
Gynecologic	94 (50.5%)
Digestive	35 (18.9%)
Urologic	28 (15.1%)
Head and neck	5 (2.7%)
Pulmonary	4 (2.2%)
Other	20 (10.8%)
Metastatic sites (more than 1 possible)	91 (48.9%)
Lymph nodes	35 (18.8%)
Peritoneal	25 (13.4%)
Lung	26 (14.0%)
Bone	23 (12.4%)
Hepatic	30 (16.1%)
Other	11 (5.9%)
Specific treatment (more than 1 possible)	
Chemotherapy	154 (82.8%)
Targeted therapy	31 (16.7%)
Immunotherapy	6 (3.2%)
Radiotherapy	22 (11.8%)
Hormonotherapy	11 (5.9%)
Surgery	9 (4.8%)

At the inclusion all patients had ID, among whom 75.7% (140/186) were suffering from absolute ID. Anemia was detected in 81.0% (141/174) patients and was symptomatic for 22.4% (39/174) of them.

At the intermediate and final visit, 57.4% (93/162) and 40.6% (43/106) of the patients, respectively, were still anemics.

Iron was assessable for only 30 and 17 patients at intermediate and final visit, of whom 1 and 4 patients had absolute ID and 8 and 10 patients had a functional one, respectively.

All the patients were evaluated on the Fact-An scale at intermediate visit, and 128 patients were assessed at the 3 times of analysis.

The patients who did not answer the questionnaire at the final time of analyses seems older (66.2 vs 61.8 years (P = .058)), even if not statistically significant and in a worse general condition with a higher proportion of patients having a performance status ≥2 (P = .001) but they were not more or less anemic (P = .914). They were also more likely to be metastatic (65.5% vs 41.4%; P = .004).

The FACT-An scale scores improved significantly between inclusion and intermediate visit in the 186 evaluable patients (P < .001), with a median of 116.2 to 124.9. More specifically the physical well-being (P < .001), the emotional well-being (P = .004), and the specific scale regarding anemia (P < .001) were improved (Table 2). Focusing on the 128 patients who complete the 3 times of evaluation, Total Fact-An score was statistically improved between V0, V1, and V2 (P < .001). More specifically the physical well-being (P < .001), the emotional well-being (P = .015), the functional well-being (P = .021), and the specific scale regarding anemia (P < .001) were improved (Fig. 2).

At the3 times of evaluation, 61 patients underwent all the functional tests. Patients who did not complete these tests were significantly older (66.1 vs 57.1; P = <.001) but were not different regarding performance status at V0, V1, or V2 (P = .138, .094, .114). Even if baseline was similar, they were more likely to be anemic at V1 (66.1% vs 38.0% (P = .002)) and V2 (52.4% vs 23.3% (P = .005)). The functional tests assessed among the patients, who underwent the 3 times of evaluation, were significantly better after iron supplementation between initial, intermediate, and final analysis. Patients significantly improved their time of "timed up and go" test (P < .001), the number of actions on the "sit/stand" test (P = .001) and their "6 minutes' walk" test (P = .003). Tinetti test (P = .081) and Berg test (P = 0.084) were not improved (Table 3).

Discussion

For the first time, we prospectively demonstrated that iron supplementation was significantly associated with increased QoL in oncology patients with ID, in the short and long term.

The choice of a QoL questionnaire as the main objective is clinically relevant.[20] This was demonstrated through the

Table 2. FACT-An evolution between baseline (V0) and intermediate visit (V1).

	V0	V1	*P*-value
Physical well-being	18.83 (15-22)	20 (16-24)	**<.001**
Social well-being	18.67 (16.3-22.4)	18.67 (16.3-22.17)	.058
Emotional well-being	19 (15-21)	19 (14.55-22)	**.004**
Functional well-being	15 (11-18.92)	15 (11-19)	.680
Anemia-specific part	48.4 (37.78-61.1)	52.47 (42.42-64)	**<.001**
Total FACT-An	116.17 (95.92-140.42)	124.88 (101.12-141.59)	**<.001**

Median, 25th and 75th percentile are presented; *P*-values are calculated using Mann-Whitney tests. Bold values are statistically significant *P*-values ($P < .05$).

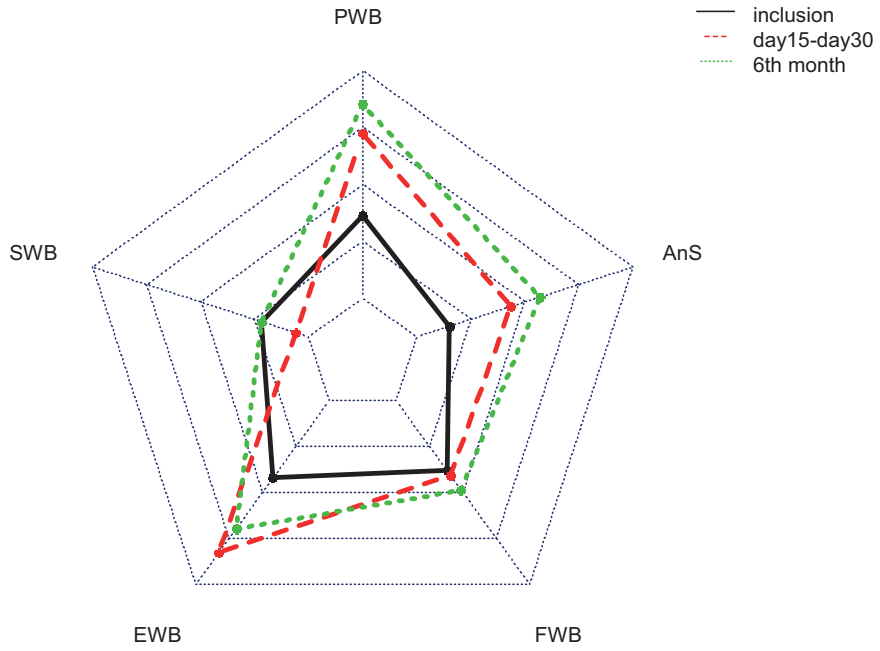

Figure 2. Radar plot representing FACT-An variation from inclusion (V0; black line) to intermediate (V1; red line) and final visit (V2; green line). *P*-values are calculated using non-parametric Friedman test. *P*-value: PWB: <.001; SWB: .239; EWB: .015; FWB: .021; AnS: <.001. PWB: physical well-being; SWB: social well-being; EWB: emotional well-being; FWB: functional well-being; FACT G: Functional Assessment of Cancer Therapy-General (fatigue); AnS: anemia scale.

significant improvement of the median Fact-An score. Physical and emotional welfare as well as anemia and asthenia-related well-being were increased, whereas there was no difference regarding social or functional well-being. However, the ASCO guideline recognizes QoL as one of the most important patient outcomes to evaluate the efficacy of oncological treatment, especially in metastatic disease.[21]

This study also demonstrated an improvement in objective functional capacity up to 6 months after the supplementation. This result was reproductive between the different tests, except for Berg and Tinetti test. This result is explained by the fact that Berg and Tinetti test explore the stability and the risk of fall and were already at the maximum (56 and 28, respectively) at baseline.

These results are not exactly consistent with those found in the healthy population[9,22]: In Houston et al meta-analysis, iron supplementation reduced self-reported fatigue, without significant impact on objective physical capacity. The worst baseline capacity of our patients, linked with their neoplasia probably explains their greater sensitivity to this intervention.

The link between iron supplementation and QoL is usually attributed to the correction of pre-existing anemia whose impact on patient well-being is widely explored.[23] In our study, an iron effect seems to be independent, with an improvement in the FACT-An score greater than the improvement in anemia, at the intermediate and final visit. The number of missing data and the lack of pre-specified subgroup analysis do not allow us to conclude on that point, but these analyses are a first step for further dedicated studies. The implication of iron in varied enzymatic reactions, including immune and neural system, energy metabolism, and functioning of skeletal muscle could explain this result.[24]

Current ESMO guidelines recommend the use of i.v. iron supplementation alone in case of absolute ID and if ESA's treatment is considered in case of functional ID in anemic patients under chemotherapy.[11] This study may contribute to expend these recommendations to any patient with ID regardless of his anemic status or treatment as 16.7% of our patients underwent targeted therapy, 11.8% radiotherapy, 5.9% hormonotherapy, and 3.2% immunotherapy.

Table 3. Functional tests evolution between baseline (V0), intermediate (V1), and final visit (V2).

	V0	V1	V2	*P*-value
Timed up and go (seconds)	7 (6-9)	7 (5-9)	6 (5-8)	**<.001**
6 minutes walk test (metres)	424 (356-489)	452 (377-514)	458 (405-532)	**.003**
Sit/stand test (number of action)	20 (15-25)	22 (18-27)	23 (19-29)	**.001**
Berg test (score)	56 (54-56)	56 (55-56)	56 (54-56)	.084
Tinettitest (score)	28 (27-28)	28 (28-28)	28 (28-28)	.081

Median, 25th and 75th percentile are presented; *P*-values are calculated using Mann-Whitney tests. Bold values are statistically significant *P*-values ($P < .05$).

There is few data in the field of radiotherapy about the prevalence of ID and the interest of a supplementation despite the fact that anemia seems to be a frequent condition interesting 48% of the patients before treatment and 57% after, with important variations depending on the tumor site.[25]

Regarding iron supplementation, Kim et al have shown the benefit of iron supplementation in patients undergoing concurrent chemoradiotherapy for a cervical carcinoma but without collecting any data about the iron status.[26] In this situation, ID is suspected to be mostly functional, following pro-inflammatory cytokine synthesis in reaction to irradiation exposure, despite the large proportion of anemic patients before the start of the treatment.

In our knowledge, there is no study regarding effect of iron supplementation alone in patients under hormonotherapy, targeted therapy, or immunotherapy, but our results show that it could be interesting to focus more on these specific populations with dedicated studies.

Our study had several limitations. One of its major weaknesses was probably the amount of missing data mostly regarding the iron status, particularly the ID correction, the red blood count and the functional capacity of patients at the evaluation time. This could be explained by the difficulty to have permanent access to a multimodal staff including physiotherapists.

Patients who did not answer the questionnaire at the final time of analyze seems older, even if not statistically relevant and in a worse general condition and we cannot exclude that this selection had an impact on our results. Patients who did not do the functional test at evaluation point were older and were more likely to be anemic at V1 and V2. Statistical analyses were done according to the high rate of missing data since no imputation of missing data was realized. More than, we did not captured information regarding treatment and disease evolution and cannot excluded that the improvement in QoL through the different evaluations could also be linked for a part to natural course of the treatment or disease. However, the large size of the study, the variety of diseases, stages, and oncological treatments could partially limit this bias. Finally, we could also note that our study was monocentric and that it would be exciting to carry out a randomized, multicenter trial to confirm these results.

This study points out the importance of supporting care with a need for a systematic screening of ID that could probably be extended to every oncology patient.

Conclusion

In summary, in the present study the supplementation of a functional or absolute ID, with or without anemia, was associated with an improvement of QoL and functional capacities in the short and long term.

Investigations in patients without anemia or in those who did not correct their hemoglobin level are needed to confirm the action of iron for itself. Moreover, this study even if large and prospective is hypothesis generating and must be controlled by a randomized trial, with further explorations specifically dedicated to the prevalence and the correction of ID in patients under any active therapy.

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Conflict of Interest

The authors indicated no financial relationships.

Author Contributions

Conception/design: V.S., D.C.-F. Provision of study material/patients: D.C.-F. Collection and/or assembly of data: N.P., C.B., H.K., R.D., D.C.-F. Data analysis and interpretation: V.S., C.G., M.d.V.-B/, D.C.-F. Manuscript writing: C.G., M.d.V.-B. Final approval of manuscript: All authors.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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