Anemia Affects the Quality of Life of Japanese Cancer Patients

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The Functional Assessment of Cancer Therapy-Anemia (FACT-An) was developed to measure the effect of anemia on quality of life (QOL) in cancer patients. We have previously validated the Japanese version of the FACT-An in Japanese cancer patients receiving chemotherapy, hormone therapy, or radiation therapy. That analysis was limited to evaluating the relationship between QOL scores and hemoglobin (Hb) levels. In this study, the data were further analyzed in order to identify factors that affect QOL. The mean Hb level of the patients was unchanged over three months. Patient age, Eastern Oncology Group Performance Status (ECOG-PS) score, Hb level, and the type of treatment method received were each predictive factors of a patient's FACT-An score at baseline, while the patient's Hb level at three months and whether the patient had received a blood transfusion were both predictive factors of a patient's FACT-An score at three months. Anemia consistently negatively affected the QOL of cancer patients measured over a three-month period. These results confirm the clinical effectiveness of the FACT-An as a tool to assess anemia-related QOL in Japanese cancer patients.

Key words: anemia, quality of life, FACT-An, cancer, chemotherapy

INTRODUCTION

Toxic responses or the side effects of cancer therapy often affect a patient's quality of life (QOL). However, mild toxic responses that do not interfere with cancer treatment are often neglected. For instance, anemic conditions that do not require blood transfusions are often perceived to be of little clinical importance. Studies have shown that continuous anemia can cause tachycardia, palpitations, fatigue, respiratory disorders, and other symptoms [1]. These symptoms may also affect a patient's QOL. Therefore, anemia management for cancer patients is clinically important even when survival is the primary treatment goal.

The Functional Assessment of Cancer Treatment-Anemia (FACT-An) is a disease-specific scale that has been widely used to measure the effect of anemia on the QOL of cancer patients [2]. The scale has been proven to be reliable and valid in both Western [3] and Japanese populations [4]. Crawford *et al.* [5] reported a non-linear relationship between hemoglobin (Hb) levels and FACT-An scores. Our previous study indicated that this scale is clinically valid for differentiating anemia among patients with a variety of cancers [6]. However, the effects of factors other than anemia on the validity of the scale were not fully examined in the previous study. The current paper reports the findings of an exploratory study to examine the factors that affect QOL in patients with a variety of cancers who received various treatments using the FACT-An.

PATIENTS AND METHODS

From October 2003 to May 2004, cancer patients from nine institutions in Japan were enrolled in this study. The patients were either receiving or about to receive some form of cancer treatment, including chemotherapy, hormone therapy, or radiation therapy. Patients who received surgical treatment alone were

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not included; however, patients who received adjuvant treatment three months after surgery were included. Other factors required for inclusion were: age greater than 20 years; Eastern Cooperative Oncology Groups Performance Status (ECOG-PS) score of 0 to 2; creatinine level ≤ 2.0 mg/dL; and a survival expectation of at least three months. Patients with hemorrhagic lesions or anemia not related to treatment were excluded. Patients with unfavorable health conditions, as determined by their physicians, were also excluded. Demographic, disease, and treatment data were gathered from the patients' clinical records. Disease complications were categorized into 65 types. All patients provided written informed consent after receiving a thorough verbal explanation of the study protocol. The study conformed to the principles set forward in the Declaration of Helsinki and was approved by the ethics committees of each institution.

The FACT-An questionnaire survey was conducted both at baseline and at three months. The Hb levels were measured at baseline and at three months. At baseline, data including each patient's demographic background, ECOG-PS score, type of cancer treatment received, and whether the patient received any type of supportive care for anemia, such as blood transfusions, were collected at the central data center. At three months, the current status of each patient's cancer therapy and anemia treatment were reported. FACT-An questionnaires were considered to be complete if answers for all of the domains and subscales were included.

Statistical analysis

Data collection, management, and monitoring were coordinated by the Comprehensive Support Project for Oncological Research (CSPOR) data center of the Japan Clinical Research Support Unit (J-CRSU). Pearson's correlation coefficients, Mann-Whitney U test, scatter plots, and box-and-whisker plots were used to assess the strengths of the relationships between the FACT-An scores and the Hb levels. A multiple regression analysis was used to identify factors that affect QOL, using the FACT-An scores as the dependent variable. Anemia was defined as an Hb level < 11 g/dL. Treatment was classified as either platinum-based chemotherapy or non-platinum-based chemotherapy. The least squares mean (LS mean) was used to estimate the differences in FACT-An scores between the two groups. All analyses were performed with SAS Version 8.02. $P < 0.05$ was considered significant.

RESULTS

The patients' baseline demographic and clinical data are shown in Table 1. A broad spectrum of cancer types was seen, with lung cancer being the most frequent. Approximately 30% of the patients had comorbidities, with hypertension and diabetes being the most common. Most subjects (223/227, 98%) were ambulatory at baseline. The response rate at baseline, in terms of the percentage of patients who completed the questionnaire at baseline, was very high (225/227, 99%). At three months, 18 patients had dropped out of the study. The reasons for dropping out included: the patient's voluntary decision (n = 2); transfer to another hospital (n = 2); death (n = 10); or unknown (n = 4). According to the FACT Scoring Manual, the total FACT score was not calculated in three patients because the number of items to which they responded was insufficient. Over the three months, the patients' mean Hb level did not change from the baseline level (11.4 g/dL).

Univariate analyses showed weak correlations between the FACT-An score and Hb level at baseline and at three months; Pearson's correlation coefficients were 0.24(p = 0.0002) at baseline and 0.24(p = 0.0007) at three months after enrollment (Fig. 1). The patients were divided into 2 groups: anemia group (Hb < 11 g/dL) or non-anemia group (Hb ≥ 11 g/dL). The baseline FACT-An scores of the anemia (mean ± SD; 120.2 ± 24.9, n = 91) and non-anemia (130.5 ± 24.3, n = 134) groups were significantly different (Mann-Whitney U test P = 0.004) (Fig. 2 (a)). At three months, the FACT-An scores of the anemia (120.1 ± 25.2, n = 72) and non-anemia (128 ± 26.9, n = 132) groups were also significantly different (P = 0.017) (Fig. 2 (b)).

Multiple regression analyses showed that patient age, ECOG-PS score, Hb level, and the type of treatment method received (either chemotherapy with platinum or other treatments) were each predictive of a patient's baseline FACT-An score (Table 2). At three months, the patient's Hb level and whether the patient had received a blood transfusion were each predictive of the patient's FACT-An score. When measuring changes over three months, the patient's age at baseline and the change in the patient's Hb level were each predictive of the change in the patient's FACT-An score. The goodness of fit of these models was confirmed. Appropriate regression diagnostics, including examination of residuals and testing multicollinearity were performed to confirm the validity these models.

A patient's Hb level both at baseline and at three months consistently showed a predictive positive correlation with the patient's FACT-An score at each time point, while the change in the patient's Hb level was also predictive of a change in the patient's FACT-An score in the same direction. This result indicates that subjects with higher Hb levels had higher FACT-An scores, even when adjusted for other factors.

DISCUSSION

In the present study, patient age, ECOG-PS score, Hb level, and the type of treatment method received each significantly affected QOL as measured by FACT-An scores in patients with malignancy. A patient's Hb level consistently showed an effect on the patient's QOL score measured both at baseline and at three months. Additionally, the change in a patient's Hb level over three months corresponded to the change in the patient's QOL score, showing a positive correlation. The subjects who were anemic (Hb < 11.0 g/dL) consistently had lower FACT-An scores than subjects who were non-anemic (Hb ≥ 11.0 g/dL) when adjusted for other confounding factors. These results indicate that anemia is a significant factor that affects cancer patients' QOL.

Age is another factor that affected QOL in the present study. The baseline FACT-An was better in elderly patients than in younger patients. Aapro *et al.* reported

Table 1 Patients' baseline demographic and clinical characteristics (N = 227)

Characteristic	Mean ± SD (range)	Patients No	Patients %
Age (years)	59.0 ± 12.1 (27–84)	–	–
Sex		–	–
Male		126	55.3
Female		102	44.7
Cancer type		–	–
Lung		98	43.2
Breast		60	26.4
Stomach		3	1.3
Colon		4	1.8
Liver, bile, pancreas		3	1.3
Lymphoma		32	14.1
Leukemia		24	10.6
Others		3	1.3
Comorbidity		–	–
Yes		77	33.9
No		150	66.1
Performance status (ECOG)		–	–
0 (fully ambulatory without physical symptoms)		137	60.1
1 (ambulatory with symptoms)		86	37.7
2 (requiring bed rest during waking day)		5	2.2
Blood infusion		–	–
Yes		2	0.9
No		225	99.1
Treatment method		–	–
Chemotherapy (non-platinum)		141	62.1
Chemotherapy (platinum)		63	27.8
No chemotherapy		23	10.1
Hemoglobin levels (g/dL)	11.4 ± 1.8 (4.5–15.6)	–	–
< 11.0		92	40.5
< 8		13	5.7
8–9		6	2.6
9–10		25	11.0
10–11		48	21.1
> 11.0		135	59.5
11–12		38	16.7
12–13		60	26.4
> 13		37	16.3

that age was not significantly correlated with Short-Form 36 (SF-36) and FACT-An scores [7]. We consider that age alone may not always necessarily be a poor indicator of a patient's QOL. Anemia is common among the hospitalized elderly [7]. The number of elderly cancer patients is rapidly increasing in Japan, and many of these patients are able to receive chemotherapy. Earle *et al.* showed, in a large retrospective study, that chemotherapy itself did not diminish survival outcomes in elderly cancer patients [8]. Langer *et al.* reported that platinum-based chemotherapy-induced hematological toxicity was found to be more severe in elderly patients (> 70 years of age), even though these patients had a similar survival outcome [9]. Future studies to examine chemotherapy-associated anemia and QOL in this specific population are necessary.

Toxic responses to chemotherapy include anorexia, nausea, vomiting, and bone marrow dysfunction. An ideal approach for the treatment of cancer would be to maximize the effectiveness of treatment while controlling the toxic responses. The present results showed that platinum-based chemotherapy decreased QOL. Patients undergoing platinum-based chemotherapy easily become anemic [9]. An inverse correlation between accumulated doses of cisplatin and Hb levels has been reported [10]. This anemic condition is primarily caused by poor erythropoiesis and excessive synthesis of cytokines [11]. Reports have shown the incidence of anemia to be especially high among patients with lymphoma, lung cancer, and gynecologic cancer [12, 13]. Platinum-based chemotherapy has become the treatment strategy of choice for lung cancer because it has been shown to significantly reduce the risk of death when combined with other therapies [14].

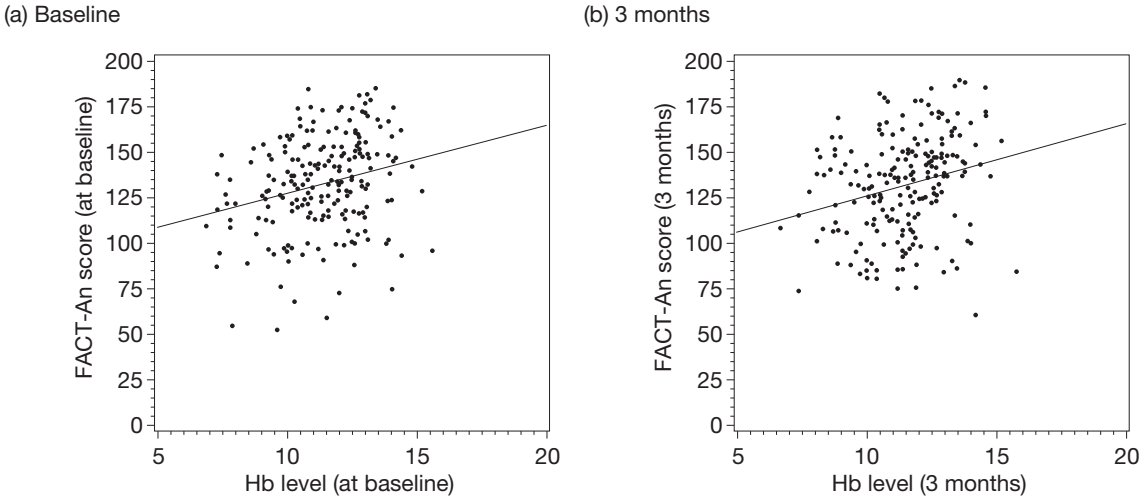

Fig. 1 Scatter plots of FACT-An scores vs. Hb levels (g/dL), measured at baseline (the left panel) and three months after enrollment (the right panel).

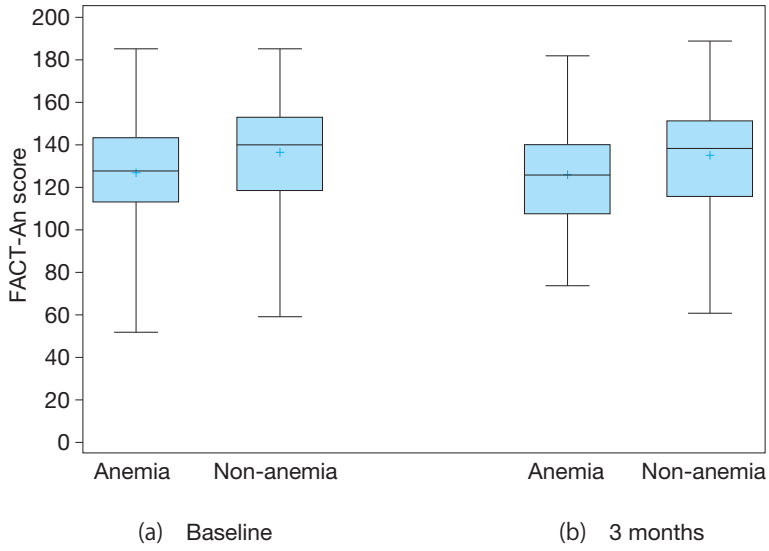

Fig. 2 Box-and-whisker plots of FACT-An scores for anemia and non-anemia patients at baseline and three months. Left two boxes show the FACT-An scores at baseline and the right boxes show the scores at three months among the anemia patients (Hb < 11 mg/dL) and the non-anemia patients (Hb ≥ 11 mg/dL). The box represents the 25th and 75th quartiles; + plots and vertical lines in the boxes represent the mean and the median, respectively. The whiskers extend from the ends of the box to the outermost data point.

In the present study, although a broad spectrum of cancer types was seen, a majority of the patients had lung cancer. These patients had an opportunity to receive platinum-based chemotherapy, and their anemic conditions partly affected their QOL.

In Japan, anemia is treated only with blood infusions, and this treatment method is restricted to renal patients or severely anemic patients. Blood infusions can lead to dangerous outcomes, such as acute lung injury, infection, or other problems [15]. Meanwhile, active intervention to reverse anemia with the use of drugs or growth factors, such as erythropoietin alpha, has provided substantial benefits for cancer patients in other countries [16]. According to a recent meta-analysis, the administration of recombinant human erythropoietins clearly showed benefits, with reduced risk of blood transfusions and improved hematologic responses in cancer patients. Conversely, treatment with these agents has also been reported to increase the risk of thrombo-embolic events, and uncertainties remain as to the influence of these agents on the overall survival of patients [17]. The clinical practice guidelines for the use of erythropoietic factors in cancer patients were revised in ASCO and ASH2007. In Japan, studies supporting the use of such growth factors are also needed. Future well-designed interventional studies to examine the QOL gains that occur with corrected anemia are necessary.

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Table 2 Multiple regression analysis with the FACT-An score as the dependent variable

Variables	Baseline		Three months		Change[a]	
	Coefficient (95%CI)	P-value	Coefficient (95%CI)	P-value	Coefficient (95%CI)	P-value
Age (65 years or over/younger)	10.27 (3.24: 17.30)	**0.004****	1.73 (- 6.56: 10.01)	0.681	- 9.19 (- 15.64: - 2.74)	**0.006****
Sex (female/male)	4.94 (- 2.07: 11.96)	0.166	6.90 (- 1.43: 15.23)	0.104	0.34 (- 6.08: 6.77)	0.916
Cancer type(leukemia/others)	7.45 (- 3.25: 18.14)	0.171	4.81 (- 7.28: 16.9)	0.434	- 2.33 (- 11.72: 7.06)	0.625
Comorbidity (Y/N)	- 1.02 (- 7.81: 5.77)	0.767	- 2.61 (- 10.33: 5.12)	0.504	- 1.17 (- 7.21: 4.86)	0.701
ECOG-PS score (2 or over/0,1)	- 30.25 (- 52.41: -8.08)	**0.008****	- 10.22 (- 40.67: 20.23)	0.509	13.08 (- 10.68: 36.85)	0.279
Blood infusion (Y/N)	13.12 (- 23.07: 49.31)	0.475	22.72 (2.17: 43.26)	**0.030***	1.65 (- 29.57: 32.87)	0.917
Latest treatment (chemo with platinum/others)	- 10.30 (- 18.20: -2.40)	**0.011***	- 1.49 (- 11.11: 8.13)	0.760	3.63 (- 3.69: 10.96)	0.329
Latest Hb level (per + 1 g/dL)	3.32 (1.35: 5.30)	**0.001****	4.69 (2.27: 7.10)	**< 0.001****	0.66 (- 1.38: 2.70)	0.525
Hb level change (per + 1 g/dL)[b]					3.27 (1.09: 5.44)	**0.003****

*P ≤ 0.05; **P ≤ 0.01
a, b: Change in scores over three months.
Abbreviations: ECOG-PS, Eastern Oncology Group Performance Status. Hb, Hemoglobin. CI, confidence interval.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

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