Cancer Patients' Morbidity (II):
Anemia-related Quality of Life in Relation to Personality

Tsuyoshi Shigehisa[1] and Hiroshi Honda[2]

Department of Surgery, Saiseikai Kurihashi Hospital, Saitama, Japan

Abstract

Background Recent improvement in treatment of patients with cancer caused longer survival but also an increase in the number of patients at risk of developing anemia and impaired quality of life (QOL). Previous studies found that personality confers an increased risk of cancer morbidity related to immunological status, unless patients receive psychological care or intervention.

Method This study examined anemia-related morbidity by comparing patients' subjective reports of QOL using the QOL-20 subscales (correlated with hemoglobin levels before and after surgery or chemotherapy) among 16 personality types on the Eysenck Personality Questionnaire, the EPQ-25.

Results Differences were accounted for by the trait of neuroticism (N+) in conjunction with introversion (E-), vulnerability or softmindedness (P-) and lack of repression or social-naivety (L-), providing evidence for three personality types, intolerant (E-N+P-), melancholic (E-N+) and high-anxious (N+L-), as potential risk factors of developing anemia-related morbidity or QOL deficits. These personality types were predictive of anemia-related cancer morbidity, independent of tumor site, TNM stage, age and sex. Sensitivity for the prediction was 90.6% (intolerant type), 87.2% (melancholic type) or 62.2% (high-anxious type).

Coclusion The evidence of these personality types provides insight into the strategy for the patient selection and stratification for prophylactic treatment, of debility or anemia and related morbidity, by preoperative patient care and support or intervention as well as recombinant human erythropoietin, improving the QOL and anemia-related morbidity.

Keywords cancer morbidity, anemia-related quality of life, personality, quality of life

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Introduction

Recent improvement in treatment of patients with cancer by surgery and myelosuppressive chemotherapy caused longer survival but also an increase in the number of patients at risk of developing anemia, anemia-related morbidity and impaired quality of life (QOL). Anemia is defined by the World Health Organization as hemoglobin (Hb) levels of < or =12 g/dl. Impaired QOL, or anemia-specific QOL deficit, includes reduced energy level, fatigue, debilitating tiredness, inability to carry out normal daily functions or activities, mood deterioration, poor feeling, dyspnoea (suffocating), lack of interest in social relations (social interaction deficit), etc.[1-9].

Although it is common in cancer patients, reported in 20% to more than 90% depending on malignancy of disease and treatment regimen[9], anemia is still overlooked and seriously under-treated. A number of factors have been investigated which may influence anemia, anemia-related morbidity and related complications, including type of tumor, stage, pre-treatment Hb level, response to chemotherapy (type, status), treatment for anemia (blood transfusion and recombinant human erythropoietin or rHuEPO), related Hb level, erythropoietin (EPO) level status, etc. However, most of these factors were examined individually or in separate studies, and there is no universally accepted guidelines for the patient selection or reliable single prognostic indicator for the treatment of anemia, anemia-related complications or QOL deterioration[5,8,10,11].

Hence, patients with cancer will benefit most by appropriate recognition and management of these factors, before the treatment, which will influence severity of the disease, related complications and impaired QOL. It is essential, therefore, to delineate patient characteristics underlying these factors associated with this morbidity, and develop models predicting which patients are at most risk for anemia and associated morbidity, and more likely to respond better to specific treatment such as

1) Tokyo Kasei Gakuin University, Medical Psychology
2) *Correspondence to*: Dr. Hiroshi Honda, Department of Surgery, Saiseikai Kurihashi Hospital, 714-6 Gotanda, Kurihashi, Kitakatsushika, Saitama, 349-1105, Japan.
Tel: 0480-52-3611; Fax: 0480-52-0954; e-mail: hondahiro @ aol. com

rHuEPO therapy, immunoenhancing nutritional support, pharmacological nutrition, etc.[12].

Significant differences have been noted among cancer patients in the relationships between rHuEPO dosing schedule and improvement of the level of EPO, Hb and QOL. In about 50% of the patients, rHuEPO was effective in enhancing the levels of Hb and QOL, when dose was increased[5,13]. These studies suggested that patient characteristics are important parameters involved in the management of anemia and QOL deterioration. One of the reasons for lack of appropriate recognition and management of anemia and related complications in cancer patients may be related to the fact that patient characteristics associated with anemia and response to the therapy are surprisingly unknown. These characteristics, however, could be examined by psychometric measures of personality, genetic variance in which could be contributed by specific genes[14-17], associated with anemia-specific QOL deficits, commonly seen in patients with cancer receiving myelosuppressive chemotherapy.

Four major personality traits of cancer patients have been found to predict global QOL deficits, which included anemia-related QOL items [18,19]. In fact, anemia concerns function of virtually every organ and tissue, including the central nervous system, cognitive function, mood, exertion, bodily strength, tachycardia, dyspnoea, weakness, loss of libido, immune deficiency, malnutrition, etc.[10,20,21]. It is noted that personality traits relate this function to QOL; in that personality traits, such as neuroticism (N), extraversion (E), psychoticism (P) and lie/social desirability or dissimulation (L), may influence various aspects of illness perception, symptom reporting and health-relevant emotional and cognitive processes. Neuroticism is associated with increased emotional distress and poor stress coping, i.e. poor QOL[22-24], and individuals high in neuroticism or negative affectivity report themselves to be in poor health than those low in this dimension[25,26]. Extraversion represents sociability (better QOL) excitement-seeking and high activity levels, psychoticism (a blend of low agreeableness and conscientiousness) is associated primarily with sensation (novelty)-seeking or vulnerability to stress, and social naivety (as opposed to social desirability or dissimulation) represents low defensiveness or repression[24-28].

Recent studies reported findings of these personality traits as independent predictors of general (global) QOL and physical, psychological and social domain scores on the QOL-20, in postoperative patients with gastric, colorectal or breast cancer, receiving chemotherapy[18,19,29]. An increased risk for QOL was accounted for by the personality traits of neuroticism (N+) in conjunction with introversion (E-), softmindedness (P-) or vulnerability, and social naivety (L-) or non-repression, on the Eysenck Personality Questionnaire (EPQ)[30] or the EPQ-25[20,21], after controlling for the effects of tumor site, TNM stage,

time after surgery, age and sex, despite appropriate treatment or disease-free survival. Among three personality types, one type was found to be predictor of poor global QOL, while another type was found to be predictor of better QOL[31]. The former was identified as intolerant type (or brooder), high N, low E and P scorers, who are more likely intolerant of sensory or negative emotional stimuli (or stress); and the latter was identified as tolerant type (or hedonist), low N, high E and P scorers who are likely to be tolerant of such stimuli or stress, in interpersonal situations, such as doctor/nurse-patient interactions [21], etc. The rest of the patients, neither intolerant nor tolerant type, were more likely to have median global QOL. These cancer patients' personality-QOL relationships, on the QOL-20 and the EPQ-25, are consistent with healthy individuals' relationships of neuroticism and extraversion with self-assessed (subjectively reported) health and disease related cognition, on the European questionnaire and personality inventory of NEO[30,32,33], which are psychometrically similar to the Japanese questionnaires, the QOL-20 and EPQ-25.[18,20,31].

Findings in these studies of cancer patients provided a model predicting which patients are at risk for anemia-related morbidity (Table 1). The model describes that chronic emotional distress stable across time, in terms of negative affectivity (N+P-) and social inhibition (E-L-), confers an increased risk of poor outcome of cancer therapies, anemia-proneness, related morbidity and impaired QOL. In other words, trait of neuroticism (N+) in conjunction with softmindedness or vulnerability (P-), introversion (E-) and social-naivety or lack of repression (L-) constitute debilitating anemia-prone personality.

Although the evidence of these personality types is essential, in order to provide insight into the strategy for the patient selection and stratification, for prophylactic treatment of debility or anemia and related morbidity, by preoperative patient care and support or intervention, improving the QOL; yet relationships of the patient characteristics, in terms of four major personality traits yielding these personality types, to generic QOL impairment and anemia-related QOL deficits have not been studied typologically in different types of malignancy or stages of cancer, in comparison with healthy controls. In this circumstance, the present study, second in a series of three[20,21], examines sensitivity and specificity of 16 personality types (every possible combinations of these traits) as predictors of cancer morbidity, in terms of patients' subjective reports of cancer-related, chemotherapy-induced anemia or anemia-specific QOL.

Method

Subjects:

Patient variables are shown in Table 2. Informed consent was obtained in the form of mutual agreement from

Table 1 A model predicting which patient is at risk for anemia-related morbidity

Definition:	Neuroticism, in conjunction with Introversion, Weakmindedness, Vulnerability, Social-naivety, Lack of repression. N+, E-, P-, L-
Clinical picture:	Chronic emotional distress across time or situations, Tend to worry, Inhibit behaviors, Pessimistic, Closed, Reserved.
Diagnosis:	EPQ-25 E, N, P, L scales (median split)
Prognosis:	Anemia-prone personality (risk factor of anemia-related morbidity) by unique configurations of E-, N+, P-, and L- (Intolerant E-N+P-, Melancholic E-N+, High-anxious N+L-)
	Anemia-resistant personality (protective factor of anemia-related morbidity) by unique configurations of E+, N-, P+, and L+ (Tolerant E+N-P+, Sanguine E+N-, Repressor N-L+)

Table 2 Summary statistics of the cancer patients

	Gastric (n=84)	Colorectal (n=42)	Breast (n=41)	All (n=167)
Age, mean (SD)	60.6 (12.2)	62.6 (9.1)	55.6 (9.0)	59.5 (10.1)
range	29–80	41–80	40–74	29–80
Sex %				
Male	58.3	71.4	0.0	43.2
Female	41.7	28.6	100.0	56.8
TNM stage %				
I	63.3	28.7	31.6	41.2
II	21.5	35.0	29.9	28.8
III	15.2	36.3	38.5	30.0
Days after surgery				
median	1066	612	1239	972
range	30–2485	61–3005	33–3284	30–3284

each patient with no evidence of other chronic diseases. The patients had received surgery and adjuvant chemotherapy in a general hospital and showed no evidence of recurrence or complications at the time of the study. Surgery included total or subtotal resection, and chemotherapy regimen included 5FU or equivalent up to 1-12 months. The study was conducted when the patients had their post-surgery follow-up consultations. Time after surgery was variable, but this factor did not affect the QOL in its relationship to personality., consistent with the previous studies[18,31]. Healthy controls who participated in the study were parents of university students, 73 (43.3%) males and 97 (56.7%) females, reported to be free from serious diseases in the past and not receiving any medical care or medication at the time of the study. Their ages ranged from 42 to 69 years (mean 57.2, SD 9.9). These ages and sex distribution are comparable to those of cancer patients. The subjects with missing values equal to or less than 3 for the questionnaire responses were used for statistical analysis. The complete statistical analysis was performed by using SPSS software package, Version 9.0 (SPSS Inc, Chicago, Ill., USA, 1999).

Questionnaire:

Eysenck Personality Questionnaire (EPQ). The EPQ[30] comprises E (extraversion), N (neuroticism), P (psychoticism) and L (lie/social desirability or dissimulation) scales or dimensions. The 16 personality types[31,34-36] constructed using the EPQ are shown in Tables 3 and 4. The present questionnaire (EPQ-25)[18,20,37] was adapted from the English original for quick and sensitive evaluation of the cancer patients, with appropriate psychometric properties. It comprises 25 items (7 for E, 7 for N, 6 for P, and 5 for L) rated on a 4-point Likert type item format scale[38]. It is a brief sound measure that allows rapid screening of cancer patients, non-cancer patients and healthy individuals[18,19,29,31,37,39,40]. By test-retest correlation, over a 1-week period, the correlation

coefficients for the E, N, P, and L are 0.81, 0.72, 0.68 and 0.70, respectively. Cronbach's alpha coefficients for these dimensions are E 0.82, N 0.83, P 0.69, and L 0.75. Correlation coefficients between this scale and original scale of 90 questions for the dimensions of E, N, P, and L are 0.80, 0.84, 0.72 and 0.78, respectively, indicating appropriate construct validity of the EPQ-25. Correlation between the EPQ-25 (E, N and P) and the NEO Five Factor Inventory[33] (E, N and C) are 0.77, 0.68 and -0.49.

Quality of life questionnaire. QOL scores were obtained using the QOL-20, which measures generic QOL in cancer patients and healthy individuals[31,41]. It comprises 20 items rated on a 3-point scale[18,39] yielding global score (composite unweighted sum of the 20 items), scores for physical (8 items), psychological (8 items) and social (4 items) domains[18], anemia-specific domain score (composite unweighted sum of the 6 items: energy (item 1), fatigue (item 2), activity (item 4), mood (item 3), dyspnoea (item 12) and interest in social relations (item 18)), and scores for energy, fatigue and activity[39]. Each of these measures is scaled with low scores indicating poor QOL and high scores indicating good QOL, thus low anemia-specific QOL score indicates patients reporting more clinical symptoms related to anemia, comparable to low Hb level. The QOL-20 global score ranges from 20 to 60, and the anemia-specific QOL score ranges from 6 to 18. Over a 1-week period, the correlation coefficients between the global QOL scores, and the anemia-specific QOL scores, are 0.70 and 0.74, respectively. Alpha values are 0.78 and 0.76. Correlation between the QOL-20 and the EORTC QLQ-C30[42] global scores is 0.51, indicating appropriate construct validity of the QOL-20[41].

Results

Table 5 summarizes the EPQ-25 and QOL-20 scores for cancer patients as a whole and healthy controls. Although the EPQ P score is lower, the L score and all

Table 3 The 16 personality types

Type	E	N	P	L
Tolerant (hedonist)	High	Low	High	
Impulsive	High	High	High	
Spectator	Low	Low	High	
Insecure	Low	High	High	
Entrepreneur	High	Low	Low	
Complicated	High	High	Low	
Sceptic	Low	Low	Low	
Intolerant (brooder)	Low	High	Low	
Sanguine	High	Low		
Choleric	High	High		
Phlegmatic	Low	Low		
Melancholic	Low	High		
Repressor		Low		High
Defensive high-anxious (DHA)		High		High
Low-anxious		Low		Low
High-anxious		High		Low

Types were distinguished based on median splits of the EPQ-25 scores of E, N, P or L.

Median scores were E 17, N 18, P 13 and L 17. Subjects were divided into low E (7 to 16), high E (17 to 28), low N (2 to 17), high N (18 to 27), low P (5 to 12), high P (13 to 23), low L (10 to 16), or high L (17 to 20). A crossing of the 3 factors (E, N and P) yielded 8 personality groups or types (Tolerant to Intolerant), and 2 factors (E and N, or N and L) yielded further 8 groups or types (Sanguine to Melancholic, Repressor to High-anxious).

Table 4 Personality types and mean (SD) scores of the EPQ-25.

Type	E	N	P	L
Tolerant	20.0 (2.0)	15.5 (2.0)	14.4 (1.4)	15.6 (1.8)
Impulsive	20.9 (2.3)	21.1 (2.2)	14.4 (1.9)	15.1 (2.4)
Spectator	14.5 (2.3)	15.7 (2.0)	14.2 (1.7)	15.7 (1.9)
Insecure	14.8 (2.1)	20.8 (1.6)	13.8 (1.1)	15.2 (2.2)
Entrepreneur	19.6 (1.4)	15.8 (1.7)	11.3 (0.9)	15.4 (2.7)
Complicated	20.0 (2.7)	21.7 (2.0)	11.1 (1.3)	15.8 (1.8)
Sceptic	14.4 (2.2)	15.9 (3.0)	11.2 (1.9)	15.5 (2.1)
Intolerant	14.7 (2.0)	21.5 (2.0)	10.5 (1.5)	16.1 (2.1)
Sangine	19.9 (1.9)	15.6 (1.9)	13.1 (1.9)	15.5 (2.1)
Choleric	20.6 (2.2)	21.4 (2.1)	12.7 (2.2)	15.4 (2.1)
Phlegmatic	14.4 (2.3)	15.8 (2.5)	12.8 (2.2)	15.6 (2.0)
Melancholic	14.7 (2.0)	21.2 (1.9)	12.3 (2.1)	15.7 (2.2)
Repressor	17.1 (3.8)	15.3 (2.2)	12.9 (1.9)	17.7 (0.9)
DHA	17.0 (3.8)	21.0 (2.1)	12.0 (2.2)	17.8 (1.0)
Low-anxious	16.8 (3.1)	15.8 (2.3)	12.9 (2.3)	14.0 (1.4)
High-anxious	17.7 (3.3)	21.4 (2.0)	12.6 (2.2)	14.1 (1.5)

QOL domain (except energy) scores are higher for cancer patients compared to healthy controls.

Table 6 shows standard regression coefficients for personality traits as predictors of QOL in cancer patients. Personality traits accounted for about 22% (global) and about 13% (anemia-related) of the total variation in QOL, after controlling for the effects of tumor site, TNM stage, time after surgery, age and sex. Anemia-related QOL is predicted by E, N and P, indicating that intolerants (low E, high N and low P scorers) and melancholics (low E and high N scorers) are more likely to have a greater anemia-related QOL deficit or more clinical symptoms of anemia. Although it is not significant, anemia-related QOL is also predicted by L, suggesting

Table 5 Mean (SD, range) scores of the EPQ-25 and QOL-20

	Patients (n=167)	Controls (n=170)	t
EPQ-25			
E	17.1 (2.5, 7-25)	17.2 (2.6, 7-28)	0.44
N	18.6 (2.2, 7-27)	18.4 (2.3, 2-27)	0.61
P	12.4 (1.9, 6-23)	13.0 (2.0, 5-20)	2.36[*]
L	16.1 (2.1, 11-20)	15.0 (2.0, 10-20)	4.95[***]
QOL-20			
Global	47.2 (4.9, 32-59)	44.7 (6.3, 26-59)	3.92[***]
Physical	19.5 (2.4, 14-24)	18.5 (2.9, 9-24)	3.03[**]
Psychological	17.6 (2.4, 9-24)	16.6 (2.9, 8-24)	3.47[***]
Social	10.0 (1.6, 6-12)	9.4 (1.7, 4-12)	3.31[***]
Anemia-related	8.0 (1.6, 6-15)	7.3 (1.6, 6-13)	2.63[**]
Energy	1.3 (0.4, 1-3)	1.2 (0.4, 1-3)	1.59
Fatigue	1.0 (0.3, 1-3)	0.7 (0.2, 1-3)	3.71[***]
Activity	1.2 (0.3, 1-3)	1.0 (0.3, 1-3)	2.17[*]

Global, sum of 20 items (8 physical, 8 psychological, 4 social).
Anemia-related, sum of 6 items (energy, fatigue, activity, mood, dyspnoea, interest in social relation).
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, (2-tailed).

Table 6 Standard regression coefficients for personality traits as predictors of quality of life in cancer patients (n=167).

Predictor	Global QOL	Anemia-related QOL
E	0.295[***]	0.209[**]
N	-0.172[*]	-0.174[*]
P	0.176[*]	0.182[*]
L	0.168[*]	0.116
Tumor site	0.078	0.051
TNM stage	-0.029	-0.046
Time	0.061	0.038
Age	0.090	0.050
Sex	0.107	0.106
Adj. R2	21.5	12.9
F	6.07[***]	4.48[***]

Tumor site, (gastric=2, colorectal or breast=1).
Time, days after surgery.
Sex, (male=2, female=1).
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

that high-anxious patients (high N and low L scorers) are likely to have a greater anemia-related QOL deficit.

Based on these results, typological analyses were carried out. Table 7 shows lower generic QOL scores (global and each of the 3 domains) for intolerants, melancholics and high-anxious patients, whereas higher scores for tolerants, sanguines and repressors, compared with other 7 or 3 types of patients. Anemia-related QOL scores for intolerants, melancholics and high-anxious patients are 7.0, 7.1 and 7.3 which represent deficits of 1.0, 0.9 and 0.7 (12.5%, 11.3%, and 8.8%), respectively. Anemia-specific QOL scores for tolerants, sanguines and repressors are 9.7, 8.9 and 8.5, which represent advantage of 1.7, 0.9 and 0.5 (21.3%, 11.3% and 6.3%), respectively.

Patients (disease-free survivors, after surgery and chemotherapy) who were tolerants or sanguines scored higher on global QOL and anemia-related QOL, compared with healthy controls (with no history of specified

Table 7 Personality types and mean (SD) scores of the quality of life in cancer patients

	Tolerant E+N-P+	Impulsive E+N+P+	Spectator E-N-P+	Insecure E-N+P+	Entrepreneur E+N-P-	Complicated E+N+P-	Sceptic E-N-P-	Intolerant E-N+P-	F
(n)	20	14	25	15	18	26	17	32	
Global	52.1 (4.8) a,c	49.7 (3.6) a	47.4 (4.5)	44.6 (5.2)	48.2(4.5)	46.5(5.5)	45.3(3.5)	44.1(4.0)b,c	9.56***
Physical	21.5 (2.0) a,c	20.4 (2.1)	20.0 (2.1)	18.4 (2.8)	19.2(2.6)	18.9(2.3)	18.6(2.6)	18.4(2.2)b	5.48***
Psychological	19.6 (2.7) a.c	18,8 (1.7)	17.7 (2.4)	16.5 (2.6)	18.5(1.9)	17.3(2.8)	17.1(1.0)	16.5(2.0)b,c	7.94***
Social	11.0 (1.2) a,c	10.6 (1.7)	9.8 (1.5)	9.7 (1.7)	10.6(1.5)	10.2(1.7)	9.7(1.4)	9.3(1.3)b	7.25***
Anemia-related	9.7 (2.1) a,c	9.3 (1.4) a	8.3 (1.4)	7.4 (1.8)	7.8(1.5)	7.6(1.5)	7.6(1.4)	7.0(0.9)b	6.02***
Energy	1.7 (0.7) a,c	1.6 (0.6) a	1.3 (0.4)	1.2 (0.4)	1.2(0.3)	1.2(0.3)	1.2(0.3)	1.0(0.1)b	3.70***
Fatigue	1.3 (0.5) a	1.3 (0.4)	1.2 (0.3)	0.8 (0.3)	0.9(0.3)	1.0(0.3)	0.8(0.2)	0.8(0.2)b	3.46***
Activity	1.4 (0.4) a,c	1.4 (0.5)	1.2 (0.3)	1.2 (0.4)	1.2(0.4)	1.0(0.3)	1.2(0.3)	0.9(0.2)b	2.61*

	Sanguine E+N-	Choleric E+N+	Phlegmatic E-N-	Melancholic E-N+	F	Repressor N-L+	DHA N+L+	Low-anxious N-L-	High-anxious N+L-	F	All
(n)	38	40	42	47		35	46	45	41		167
Global	50.2 (5.0) a,c	47.6 (5.1)	46.6 (4.3)	44.2 (4.4) b,c	19.47***	49.4 (5.2) a	46.8 (5.3)	47.3 (4.6)	44.6 (4.2) b	8.69***	47.2 (4.9) c
Physical	20.4 (2.6) a	19.4 (2.3)	19.5 (2.4)	18.4 (2.4) b	8.36***	20.5 (2.4)a	19.1 (2.4)	19.4 (2.5)	18.7 (2.4)b	2.97*	19.5 (2.4)c
Psychological	19.1 (2.3) a,c	17.9 (2.5)	17.5 (2.0)	16.5 (2.2) b,c	15.56***	18.7 (2.4) a	17.7 (2.4)	17.8 (2.2)	16.4 (2.3)b	9.59***	17.6 (2.4) c
Social	10.8 (1.3) a	10.3 (1.7)	9.7 (1.5)	9.4 (1.5) b,c	17.59***	10.3 (1.6)	10.1 (1.6)	10.1 (1.4)	9.5 (1.6) b	6.20***	10.0 (1.6) c
Anemia-related	8.9 (2.2) a,c	8.1 (1.6)	8.0 (1.4)	7.1 (1.2) b	8.88***	8.5 (1.7) a	7.8 (1.4)	8.0 (1.6)	7.3 (1.4) b	2.73*	8.0 (1.6) c
Energy	1.5 (0.5) a	1.3 (0.4)	1.3 (0.4)	1.1 (0.2) b	4.23**	1.4 (0.4)	1.2 (0.3)	1.3 (0.4)	1.2 (0.3)	1.30	1.3 (0.4)
Fatigue	1.1 (0.4)	1.1 (0.3)	1.1 (0.3)	0.8 (0.2) b	3.84**	1.1 (0.3)	1.0 (0.3)	1.1 (0.3)	0.9 (0.2)	1.73	1.0 (0.3) c
Activity	1.3 (0.4) a	1.2 (0.4)	1.2 (0.3)	1.0 (0.3) b	4.97**	1.2 (0.4)	1.1 (0.3)	1.2 (0.4)	1.0 (0.3)	0.89	1.2 (0.3) c

Differences among the personality types were examined by comparing each type to the average of the other 7 or 3 types.

a, Significantly higher than the other types (p<0.05)

b, Significantly lower than the other types (p<0.05)

c, Significantly higher than the healthy controls (p<0.05)

* p<0.05; ** p<0.01; *** p<0.001

illnesses) who were equally tolerants or sanguines. In contrast, patients who were intolerants or melancholics scored higher on global QOL, but not anemia-related QOL, compared with healthy controls who were equally intolerants or melancholics. These results suggest that intolerant or melancholic patients suffer from anemia-related QOL deficits but not necessarily generic QOL deterioration. On the contrary, high -anxious patients are more likely to suffer from both anemia-related QOL deficits and generic QOL deterioration.

These results (Tables 6 and 7) provide evidence for the model (Table 1), predicting which patients are at most risk for anemia; in that chronic emotional distress, in terms of negative affectivity (N+P-) and social inhibition (E-L-), confers an increased risk of poor outcome, anemia-related morbidity. In other words, trait of neuroticism in conjunction with softmindedness (vulnerability), introversion and social-naivety (lack of repression) constitutes the proneness to cancer morbidity associated with anemia or reported anemia symptoms. This model is instrumental in providing, each personality type, sensitivity and specificity for predicting which patient is at risk for cancer morbidity, anemia-specific QOL deficit (Table 8). Correlations of anemia-specific QOL score (range: 6-15) with Hb levels (g/dl) before and after surgery (range: 9.8-15.1; 8.9-15.0) were positive (r=0.20, 0.22; df=89, 88; p=0.060, 0.037; 2-tailed, with effects of age and sex removed), indicating that 6 clinical symp-

Table 8 Sensitivity and specificity of personality types for predicting which patient is at risk for anemia-related quality of life deficit.

Personality Type	Cut-off value	n of patients	Sensitivity
Intolerant	<8.0	29/32	90.6%
Tolerant	<8.0	7/20	35.0%
Melancholic	<8.0	41/47	87.2%
Sanguine	<8.0	18/38	46.9%
High-anxious	<8.0	26/41	62.2%
Repressor	<8.0	19/35	54.3%

Cut-off value	n of patients	Inverse sensitivity	X2
≥8.0	3/32	9.4%	21.12***
≥8.0	13/20	65.0%	1.80
≥8.0	6/47	12.8%	26.06***
≥8.0	20/38	53.1%	0.11
≥8.0	15/41	37.8%	2.38
≥8.0	16/35	45.7%	0.11

Cut-off value, mean anemia-related QOL score.

*** p<0.001

toms of anemia are negatively related to the Hb levels after surgery.

Discussion

Although applicability of the findings is limited by small sample sizes, non-longitudinal design and analysis of the data from limited tumor sites; theory-based and statistically significant differences found in anemia-

related QOL scores among 16 personality types have important implications for the (patient individuality-based) tailor-made strategies for cancer research and therapy. Outcome research in cancer patients' morbidity and QOL has focused largely on the biomedical treatment regimen, however, it is time now to account for not only biomedical but also psychological and social risk or protective factors of patient as a whole contributing to the morbidity, treatment effectiveness and survival. The typological analysis to identify patients' characteristics, receiving major surgery or chemotherapy, who experience chronic emotional distress and need immediate attention, psychological care or support, may lead to more accurate risk estimate in clinical practice, leading to appropriate recognition and management of their morbidity and QOL. Pre-treatment patients' condition, Hb level, anemia-proneness or debility as well as immunological or nutritional status[3,10,12,13,20,21] may influence survival or relapsing in certain types of tumor[5,43,45], and such an influence and the proneness to specific morbidity could be predicted by the personality types, such as intolerant, melancholic or high-anxious, which were found to be directly associated with anemia-related QOL deficits (Tables 6 and 7).

On the contrary, opposite types of patients, tolerants, sanguines or repressors, might have enjoyed better anemia-associated QOL without debility or clinical symptoms of anemia, compared to healthy controls with no history of specified illnesses, suggesting that these types of patients are resistant to anemia-related morbidity or debility. This evidence provides insight into the relationships between QOL and factors of resilience[46-48], which appear to promote self-efficacy (confidence and motivation to fight against the disease)[49] and fighting spirit[56] as a result of cancer experience, and enhance inoculation effect of stress (stress of being ill with cancer)[23,34,50,56,57], in patients with these personality types. Resilience refers to effective coping and flexible adaptation, although faced with adversity (truth-telling about cancer diagnosis, prognosis or survival), and resistance to or denial (not acceptance) of strain associated with illness experiences [46,57]. Hence, it is expected that resilient patients, such as tolerants, sanguines or repressors, bounce back from stressful cancer illness experiences more quickly and effectively compared to non-resilient patients, such as intolerants, melancholics or truly-anxious patients. A potent resilience factor for cancer-related QOL may be the induction and maintenance of positive emotions, confidence and motivation, which might undo the aftereffects of negative emotions and immunosuppressive illness distress experiences[23,34] (Table 1). The present personality questionnaire, the EPQ-25, allows rapid screening and early assessment of such cancer patients, predicting which patient is at potential risk for cancer morbidity associated with anemia and which patient is resilient hence resistant to such a morbidity or debility.

It would be helpful, to the strategies for cancer research and therapy, to identify likely responders and non-responders to available therapy before initiating treatment regimens. Clinically useful prediction of response to a certain therapy may be possible by these personality types using the EPQ-25, because of good sensitivity and specificity for predicting anemia-related cancer morbidity associated with QOL deterioration (Table 8). There is a growing recognition that clinical personality assessment requires refined and broadened patient information having a strong biological underpinning[22,27,51]. The EPQ has a number of important advantages over other systems of personality description and measurement. Unlike other systems derived solely from the statistical analysis, the biological system of the EPQ was derived from the differences observed between clinically meaningful criterion groups[24,28,52,56,57]. Hence, discrepant predictive power of EPO level and Hb increases, for responsiveness of the patient to prophylactic treatment of anemia and related morbidity by nutritional or pharmacological support or rHuEPO[8,10,12] could be understood in terms of differences in these personality types using the EPQ-25.

Standard rHuEPO doses increased Hb levels in 2/3 of patients with chemotherapy-induced anemia[53], i.e., 1/3 of patients did not respond to such doses. This figure, 1/3 of patients, corresponds roughly to 28.1% of patients (47 melancholics, in the present study) showing relatively severe anemia-specific QOL deficits or score of 7.1 which represents 11.3% deficit (Table 7). It would benefit patients if their personality types could be elucidated (before initiating the therapy) to help identify potential responders to rHuEPO therapy at specific doses.

The rHuEPO (epoetin alfa) treatment of anemic cancer patients (anemia of chronic disease, ACD) receiving cytotoxic/myelosuppressive chemotherapy leads to significant increases in Hb levels and reduction in transfusion utilization, effects associated with both statistically and clinically significant improvements in chemotherapy-induced, cancer-related QOL[5,6,10,54,58]. The present study suggest a potential benefit associated with rHuEPO therapy in certain specific types (not all types) of patients on psychometric measures of personality. Although it is not known whether this effect could be due to the correction of anemia-related morbidity or whether rHuEPO may have an intrinsic effect on QOL or function of related organs and tissues. Analysis of previous studies of rHuEPO[5,13,55] noted that the largest incremental gains in QOL occurred when Hb levels were increased from 11 to 12 g/dl. That is when patients were experiencing mild-to-moderate anemia, not when patients were severely anemic. In the present study, mild-to-moderate anemia-specific QOL deficits were observed in the following 9 personality types: spectator, insecure, entrepreneur, complicated, sceptic, choleric, phlegmatic, defensive high-

anxious (DHA), and low-anxious (Table 7). Hence, it is very likely that treatment of anemia by such an agent as rHuEPO[55] or specific nutritional support therapy[12, 21] will result in the largest incremental gains in the levels of Hb and QOL in these types of patients, who are more likely to experience mild-to-moderate anemia, the related-morbidity or Hb levels of 11-12 g/dl. This remains to be examined, however, with direct measures of baseline and post-treatment Hb levels, EPO levels and nutritional status (subjective or biochemical) and also rHuEPO dosages and nutritional support regimens[5,12,21].

The present results suggest that intolerants (brooders), melancholics (pessimists) and high-anxious (truly neurotic) patients, having relatively severe anemia-specific QOL deficits, are very likely to have a more severe clinical symptoms of anemia, or Hb levels <11 g/dl, and expected to respond less to standard rHuEPO therapy or nutritional support therapies (showing <1 g/dl increase in Hb). In contrast, tolerants (hedonists), sanguines (optimists) and repressors (dissimulators or deniers), having no anemia-specific QOL deficits (or having Hb levels >12 g/dl), are unlikely to suffer from anemia and expected to be non-responders to rHuEPO or similar dietary supplement therapies, enteral, parenteral, etc. The remaining types of patients (except for impulsive type) in Table 7, having a relatively moderate anemia-specific QOL deficits, are likely to have a moderate anemia or related morbidity and expected to respond to these therapies at specified doses and regimens, resulting in incremental gains in QOL.

When cancer patients were divided into 2 groups by Hb levels, patients with Hb levels greater than 12 g/dl reported significantly less QOL deficits (physical, psychological or global) and showed fewer clinical symptoms of anemia[2]. Hence, it seems likely that cancer patients who are hedonists, optimists or dissimulators have higher Hb levels and no anemia-related QOL deficits, compared to brooders, pessimists or truly-neurotic patients reporting greater anemia-related QOL deficits. This provides avenues for maximizing the benefits of prophylactic treatment of debility or anemia-related QOL deficits, after surgery and chemotherapy, in remaining types (the 9 personality types) of patients (cf. Table 7).

The greatest improvement in QOL occur when Hb values increase from 11 to 12 g/dl, suggesting that a Hb level at or below 11 g/dl may be an appropriate trigger point to prevent QOL deterioration in patients whose symptoms or morbidity have not already necessitated prophylactic intervention[13]. As some patients, not all patients, experience the effects of anemia, related morbidity or QOL deterioration before their Hb decreases below 11 g/dl[5], it seems unlikely that using a standard or average Hb level as a trigger point, regardless of personality, will identify all patients who could benefit from the prophylactic treatment of anemia or anemia-related morbidity.

The personality types identified in the present study will provide avenues of predicting not only which patient is at risk for anemia-related morbidity, but also which patient will respond better to the (preoperative) prophylactic treatment of this morbidity. The test of these personality types approached 80% to 90% levels of sensitivity (Table 8) for predicting anemia-specific QOL deficits, which were significantly correlated (p=0.037) with postoperative Hb level. These levels of sensitivity are generally regarded as appropriate for clinically useful predictive tests[8]. Two personality types benefited from sufficient specificity (p<0.001), less than 10% or 13% of patients went on to inverse sensitivity (negative prediction) (Table 8). The validation and precision of these personality types will be examined further in order to establish reliable prediction criteria for patient selection and patient stratification, for (otherwise costly, time-consuming) prophylactic treatment of cancer morbidity.

References

1) Demetri, D.G., Kris, M., Wade, J., Degos, L. and Cella, D.: for the Procrit Study Group. (1998) Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. J.Clin. Oncol. 16: 3412-3425.

2) Cella, D. (1997) The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: A new tool for the assessment of outcomes in cancer anemia and fatigue. Semin. Hematol. 34: 13-19.

3) Cella, D., Zagari, M.J., Vandoros, C., Gagnon, D.D., Hurtz, H-J. and Nortier, J.W.R. (2003) Epoetin alfa treatment results in clinically significant improvements in quality of life in anemic cancer patients when referenced to the general population. J. Clin. Oncol. 21: 366-373.

4) Cella, D., Dobrez, D., and Glaspy, J. (2003) Control of cancer-related anemia with erythropoietic agents: a review of evidence for improved quality of life and clinical outcomes. Ann. Oncol. 14: 511-519.

5) Demetri, G.D. (2001) Anemia and its functional consequences in cancer patients: current challenges in management and prospects for improving therapy. Br. J. Cancer. 84 (Suppl 1): 31-37.

6) Littlewood, T.J., Bajetta, E., Nortier, J.W.R., Vercammen, B. and Rapoport, B.: Epoetin Alfa Study Group (2001) Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving non-platinum chemotherapy: Results of a randomized, double-blind, placebo-controlled trial. J. Clin. Oncol. 19: 2865-2874.

7) Littlewood, T.J., Nortier, J., Rapoport, B., Pawlicki, M., deWasch, G., Vercammen, E., Schnette, W., Wils, J. and Freund, M.: Epoetin Alfa Study Group (2003) Epoetin alfa corrects anemia and improved quality of life in patients with hematologic malignancies receiving non-platinum chemotherapy. Hematol. Oncol. 21: 169-180

8) Littlewood, T.J., Zagari, M., Pallister, C. and Perkins, A. (2003) Baseline and early treatment factors are not clinically useful for predicting individual response to erythropoietin in anemic cancer patients. Oncologist, 8: 99-107.

9) Groopman, J.E. and Itri, L.M. (1999) Chemotherapy-induced anemia in adults: incidence and treatment. J. Nat. Cancer Inst. 91: 1616-1634.

10) Ludwig, H., Rai, K., Blade, J., Dammacco, F., Degos, L., Itri, L., Kyle, R., Liso, V., Littlewood, T.J., Mandelli, F., Meloni, G., Molica, S., Osterborg, A., Pangalis, G.A., San Miguel, J., Schmitt, B. and Voliotis, D. (2002) Management of disease-related anemia in patients with multiple myeloma or chronic lymphocytic leukemia: epoetin treatment recommendations. Hematol. J. 3: 121-130.

11) Soignet, S. (2000) Management of cancer-related anemia: epoetin

alfa and quality of life. Semin. Hematol. 37 (4 suppl. 6): 9-13.

12) Nitenberg, G, and Raynard, B. (2000) Nutritional support of the cancer patients: issues and dilemmas. Crit. Rev. Oncol. Hematol. 34: 137-168.

13) Cleeland, C.S., Demetri, G.D., Glaspy, J., Cella, D.F., Portenoy, R.K., Cremieux, P.Y. and Itri, L. (1999) Identifying hemoglobin level for optimal quality of life: results of an incremental analysis. Proc. Am. Soc. Clin. Oncol. 18: 574a (abst 2215).

14) Cloninger, C., Adolfsson, R. and Surakic, N. (1996) Mapping genes for human personality. Nature Genet. 12: 3-4.

15) Ebstein, R., Novick, O., Umansky, R., Priel, B., Osher, Y., Blaine, D., Bennett, E., Nemanov, L., Katz, M., and Belmaker, R. (1996) Dopamine D4 receptor (D4DR) exon III polymorphism association with human personality trait of novelty-seeking. Nature Genet. 12: 78-80.

16) Benjamin, J., Li, L., Patterson, C., Greenberg, B., Murphy, D. and Hamer, D. (1996) Population and familial associations between the D4 dopamine receptor gene and measures of novelty-seeking. Nature Genet. 121: 81-84.

17) Lesch, K-P., Bengel, D., Heils, A., Sabol, S.Z., Greenberg, B.D., Petri, S., Benjamin, J., Miller, C.R., Hamer, D.H., and Murphy, D.L. (1996) Association of anxiety-related traits with a polymorphism in the serotonin regulatory region. Science, 274: 1527-1531.

18) Shigehisa, T. (2002) Eysenckian personality traits and health-related quality of life in patients with stomach, colorectal or breast cancer. Jpn. Health Psychol. 10: 19-32.

19) Honda, H. and Shigehisa, T. (2001) Influence of four major personality traits on cancer patients' response to the QOL-20 questionnaire. 16th QOL Res. Soc. Meet. (in Japanese)

20) Shigehisa, T. and Honda, H. (2006) Cancer patients'morbidity (I): Immunological status varies with psychological intervention in relation to personality. Ann. Cancer Res. Ther. 14: 28-38.

21) Shigehisa, T. and Honda, H. (2006) Cancer patients' morbidity (III): Malnutrition in relation to doctors', nurses' and patients' personality. Ann. Cancer Res. Ther. (submitted).

22) Eysenck, H.J. (1967) The biological basis of personality. Springfield, Ill.: Thomas.

23) Eysenck, H.J. (1981) A model for personality. New York: Springer.

24) Eysenck, H.J. and Eysenck, M.W. (1985) Personality and individual differences: A natural science approach. New York: Plenum.

25) Costa, P.T. and McCrae, R.R. (1987) Neuroticism, somatic complaints, and disease: Is the bark worse than the bite? J. Pers. 55: 299-331.

26) Watson, D. and Pennebaker, J. (1989) Health complaints, stress and distress: exploring the central role of negative affectivity. Psychol. Rev. 96: 234-254.

27) Eysenck, H.J. (1992) A reply to Costa and McCrae: P or A and C-the role of theory. Person. Individ. Diff. 13: 867-868.

28) Zuckerman, M. (1989) Personality in the third dimension: A psychological approach. Person. Individ. Diff. 10: 391-418.

29) Shigehisa, T., Yamaoka, K. and Honda, H. (2002) The relation between personality traits and health-related quality of life in patients with stomach, colorectal or breast cancer. Int. J. Behav. Med. 9 (suppl 1): 246-247.

30) Eysenck, H.J. and Eysenck, S.B.G. (1975) Manual of Eysenck Personality Questionnaire. London: Hodder and Stoughton.

31) Yamaoka, K., Shigehisa, T., Ogoshi, K., Haruyama, M., Watanabe, M., Hayashi, F. and Hayashi, C. (1998). Health-related quality of life varies with personality types: a comparison among cancer patients, non-cancer patients and healthy individuals in a Japanese population. Qual. Life Res. 7: 535-544.

32) Williams, P.G., O'Brien, C.D. and Colder, C.R. (2004) The effects of neuroticism and extraversion on self-assessed health and health-relevant cognition. Person. Individ. Diff. 37: 83-94.

33) Costa, P.T. and McCrae, R.R. (1992) Revised NEO Personality Inventory (NEO-PI-R) and NEO Five Factor Inventory (NEO-FFI): Professional manual. Odessa, Fl.: Psychological Assessment Resources,Inc.

34) Eysenck, H.J. (1994) Cancer, personality and stress: prediction and prevention. Adv. Behav. Res. Ther. 16: 167-215.

35) Vollrath, M and Torgersen, S. (2002) Who takes health risks? A probe into eight personality types. Person. Individ. Diff. 32: 1185-1197.

36) Ruch, W. (1992) Pavlov's types of nervous system, Eysenck's typology and the Hippocrates-Galen temperaments: A empirical examination of the asserted correspondence of three temperament typologies. Person. Individ. Diff. 13: 1259-1271.

37) Shigehisa, T. (2001) Influence of personality on quality of life measurement in cancer patients. W'Waves, 7: 33-37. (in Japanese).

38) Muniz, J., Garcia-Cueto, E. and Lozano, L.M. (2005) Item format and the psychometric properties of the Eysenck Personality Questionnaire. Person. Individ. Diff. 38: 61-69.

39) Shigehisa, T. (2004) Quality of life during chemotherapy: the role of anemia. -Influence of cancer patients' personality. W'Waves, 10: 36-42. (in Japanese with English summary).

40) Shigehisa, T and Fukui, I. (1995) Cancer-prone Type C personality toxic component: Suppression of emorion. Jpn. Health Psychol. 3: 25-39.

41) Yamaoka, K., Takeda, Y., Shigehisa, T., Ogoshi, K., Kobayashi, K., Hayashi, F. and Hayashi, C. (2003) Health-related quality of life in Japanese lung cancer patients as determined by two questionnaires: the HRQOL-20 and the EORTC QLQ-C30. Ann. Cancer Res. Ther. 11: 31-46.

42) Osoba, D., Aaronson, N., Zee, B., Sprangers, M. and teVelde, A. (1997) Modification of the EORTC QLQ-C30 (version 2.0) based on content validity and reliability testing in large samples of patients with cancer. Qual. Life Res. 6: 103-108.

43) Caro, J.J., Salas, M., Ward, A. and Goss, G. (2001) Anemia as an independent prognostic factor for survival in patients with cancer: a systematic, quantitative review. Cancer, 91: 2214-2221.

44) Sengelov, L., Kamby, C., Geertsen, P., Andersen, L.J. and von der Maase, H. (2000) Predictive factors of response to cisplatin-based chemotherapy and the relation of response to survival in patients with metastatic urotherial cancer. Cancer Chemother. Pharmacol. 46: 357-364.

45) Davies, M. (2005) Nutritional screening and assessment in cancer-associated malnutrition. Eur. J. Oncol. Nurs. 9 (suppl 2): S64-S73.

46) Lazarus, R.S. (1993) From psychological stress to the emotions: A history of changing outlooks. Ann. Rev. Psychol. 44: 1-21.

47) Rauch, P., Miny, J., Conroy, T., Neyton, L. and Guillemin, F. (2004) Quality of life among disease-free survivors of rectal cancer. J. Clin. Oncol. 22: 354-360.

48) Wengel, L.B., Donnelly, J.P., Fowler, J.M., Habbal, R., Taylor, T.H., Aziz, N. and Cella, D. (2002) Resilience, reflection and residual stress in ovarian cancer survivorship: a gynecologic oncology group study. Psycho-Oncol. 11: 142-153.

49) Bandura, A. (1992) Self-efficacy mechanism in psychobiologic functioning. In: Schwarzer, R. editor, Self-efficacy: Thought control of action Washington, D.C.: Hemisphere; p.355-394.

50) Eysenck, H.J. (1983) Stress, disease and personality: the "inoculation effect". In: Cooper, C.L. editor, Stress research. New York: Wiley; p.121-146.

51) Van Heck, G.L., Perugini, M., Caprasa, G. and Froger, J. (1994) The big five as tendencies in situations. Person. Individ. Diff. 16: 715-731.

52) Pervin, L.A. (1994) A critical analysis of current trait theory. Psychol. Inquiry 5: 103-113.

53) Gabrilove, J.L., Cleeland, C.S., Livingston, R.B., Sarokhan, B., Winer, E. and Einhorn, L.H. (2001) Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: Improvements in hemoglobin and quality of life are simlar to three-times-weekly dosing. J. Clin. Oncol. 19: 2875-2882.

54) Weiss, M.J. (2003) New insights into erythropoietin and epoetin alfa: Mechanism of action, target tissues and clinical applications. Oncologist, 8(suppl 3): 18-29.

55) Glaspy, J., Bukowski, R., Steinberg, D., Taylor, C., Tchekmedyian, S. and Vadhan-Ray, S. (1997) Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. J. Clin. Oncol. 15: 1218-1234.

56) Pettingale, K.W., Morris, T., Greer, S. and Haybittle, J.L. (1985) Mental attitude to cancer: An additional prognostic factor. Lancet, 1: 750.

57) Shigehisa, T. (1995) Personality and cancer: a cross-cultural perspective. Ann. Cancer Res. Ther. 4: 5-19.

58) Weiss, G. and Goodnough, L.T. (2005) Medical progress: Anemia of chronic disease. New England J.Med. 352: 1011-1023.