those who did receive some antidepressant, the average dosage decreased to 45.1 (SD = 64.7) mg/day. All in all about 74% (70/84) of patients were prescribed no or inadequate drug doses, i.e. less than 75 mg/day. At maintenance phase immediately before relapse, 41% (12/29) were on no antidepressant drug. Among those who did receive some antidepressant, the average dosage was 42.0 (SD = 74.7) mg/day. Again 83% (24/29) were prescribed no or inadequate doses. Patients' refusal was the most common reason for not using antidepressant. None of the patients were administered systematic psychotherapy including cognitive-behaviour therapy or interpersonal therapy.

Discussion

We once reported on the treatment received by patients with depression for the acute phase treatment, and noted their undertreatment (Furukawa *et al.*, 2000b). The current study followed the same cohort and examined the adequacy of the treatment during continuation and maintenance phases. Again we had to note the gross undertreatment as over 80% of the cohort did not receive antidepressants at or above the recommended dose levels, including more than half the subjects who received no medication, during continuation and maintenance phases.

A number of available studies in the literature appear to agree on the quasi-universal inadequacy of continuation and maintenance treatment of major depression. In Finland, of some 200 patients who initiated treatment for their unipolar major depression, about half (49%) terminated treatment prematurely and did not go on to receive continuation treatment (Melartin *et al.*, 2005). The figure was very similar in the United States, as 42% discontinued antidepressant therapy during the first 30 days and only 28% continued antidepressant therapy for more than three months (Olfson *et al.*, 2006). In yet another study, only 32 of 99 patients (32%) received adequate continuation treatment (Kobak *et al.*, 2002). Ramana *et al.* (1999) in UK found that about 80% of patients were prescribed adequate dose of drugs, more than 125 mg/day, and this figure declined slowly but by 18 months approximately 43% were still being prescribed adequately and 40% received no antidepressant. In the Netherlands, 24% of antidepressant prescription for depression were shorter than a month, while 21% were longer than six months. Seventy-eight percent of these prescriptions were below the recommended effective dosage (van Weel-Baumgarten *et al.*, 2000).

Various factors have been found to be associated with inadequate continuation and maintenance treatments. Low education and low income predicted earlier termination, whereas poor pretreatment health status, treatment with new generation antidepressants and psychotherapy were associated with longer continuation treatment (Olfson *et al.*, 1996) History of antidepressant treatment and severer index episode predicted longer treatment (Melartin *et al.*, 2005). Physicians' failure to explicitly advise patients to continue on medication and patients' reluctance to discuss adverse effects with their physicians also predicted earlier discontinuation (Bull *et al.*, 2002).

The advice concerning the duration of treatment contained in the 1985 Consensus Development Conference Statement is probably still appropriate: Duration of the treatment must be determined on an individual basis depending on the previous pattern of episodes, degree of impairment produced, the adverse consequences of a new recurrence and the patient's ability to tolerate the drug. The National Institute of Mental Health consensus panel concluded that stronger the indications for initiating preventive treatment, the longer its duration should be.

Possible weaknesses of the present study may include our failure to collect information regarding several important factors in determining the adequacy of antidepressant treatment, including duration of antidepressant prescription and emergence of side effects. If we take the duration of antidepressant prescription into account, the proportion of patients receiving adequate antidepressant treatment would be even lower. Secondly, treatment was not controlled in this naturalistic study and therefore the level of treatment can be seen as either a cause or an effect. For instance, high levels of treatment are associated with a worse outcome or sicker subjects get more treatment. Thirdly, although the participating centres represented various treatment settings from all over Japan, it is safe to assume that they represent relatively motivated practitioners. The actual practices in less motivated clinical settings could be even more dismaying. Lastly, our findings relate mainly to the situation more than 10 years ago and to tricyclic antidepressants. The present day situation could be different, with more acceptable drugs and with stronger evidence of effectiveness of long-term continuation/maintenance treatments (Geddes *et al.*, 2003).

On the other hand, strengths of this study would include the following. The 23 study settings of the current study were fairly representative of psychiatric practices in Japan and the study sample was a random subset of all hospital admissions to these hospitals. Longitudinal interviewing for each month aided more accurate identification of onset and offset of periods of depression and subsyndromal symptomatology.

Conclusions

We confirmed that Japan was no exception to other industrialized countries in its provision of continuation and maintenance treatment to major depression. Although the majority of the patients diagnosed with major depression were administered some antidepressant, its dosage was very often below the recommended effective range even 1–6 months after commencement of the treatment. Newer drugs including SSRIs and SNRIs are now available. A further study of actually provided treatments in present day Japan would be of interest.

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References

Anderson I M, Nutt D J, Deakin J F (2000) Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. British Association for Psychopharmacology. J Psychopharmacol *14*: 3–20

Original Article

Plasma Interleukin-6 and Fatigue in Terminally Ill Cancer Patients

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Abstract

Fatigue is one of the most distressing symptoms among terminally ill cancer patients. However, no effective intervention has been established. Several studies have suggested the role of cytokines in fatigue in cancer patients receiving anti-cancer treatment, patients with metastatic cancer, and cancer survivors, but not in terminally ill cancer patients. In the present study, the potential association between fatigue and plasma interleukin-6 (IL-6) was examined in 46 terminally ill cancer patients (median survival: 64.5 days) who received neither steroids nor nonsteroidal anti-inflammatory drugs. Fatigue was evaluated by the Cancer Fatigue Scale (CFS), which consists of multiple dimensions of fatigue, such as Physical, Affective, and Cognitive subscales. Plasma IL-6 levels were measured using an enzyme-linked immunosorbent assay and were compared between patients with and without "clinical fatigue" as defined by the total score of the CFS. Additionally, associations between each of the CFS scores and IL-6 levels were examined. As a result, the IL-6 level in patients with clinical fatigue (n = 27 [59%]; mean, SD, median, and range: 37.1, 46.4, 17.1, and 3.7–182.5 pg/ml, respectively) was significantly higher than those without clinical fatigue (n = 19 [41%]; mean, SD, median, range: 14.3, 12.2, 8.0, and 2.8–45.0 pg/ml, respectively) (P = 0.02). The IL-6 level significantly correlated with the Physical subscale score (r = 0.35, P = 0.02), but not with other subscale scores. In conclusion, IL-6 may play a role in fatigue, especially in the physical dimension, in terminally ill cancer patients. The results of the present study provide information to develop a new treatment

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Key Words
Fatigue, terminally ill, cancer, interleukin-6

Introduction

Fatigue is reported by more than 50–70% of patients with advanced cancer[1] as one of their most frequent and debilitating symptoms.[2] Severe fatigue is more common in patients receiving inpatient palliative care (78%) compared to recently diagnosed cancer patients (16%).[3] As shown by the fact that cancer fatigue in terminally ill patients is one of the reasons for desiring early death,[4] the influence of fatigue on patients' quality of life is quite significant. However, no effective standard intervention strategy has been established.[5]

Cancer fatigue is a multidimensional syndrome. It has physical, affective, and cognitive dimensions, which are hypothesized to be caused by a number of physical and psychosocial mechanisms.[6,7] Many contributing factors, such as tumor by-products, cytokine-mediated cachexia, muscle loss, and deconditioning, have been postulated.[8] To investigate the biological mechanisms of cancer fatigue, we have developed a multidimensional assessment tool, which consists of subscales of physical, affective, and cognitive dimensions of fatigue.[7]

A basic research study has shown that proinflammatory cytokines, such as interleukin-1, interleukin-6 (IL-6), and tumor necrosis factor alpha, can signal the central nervous system to induce sickness behavior including fatigue.[9] In addition, cytokines cause energy expenditure and loss of muscle,[10] suggesting an association between cytokines and fatigue. In patients receiving cancer therapy, those with metastatic cancer, and cancer survivors, some studies,[11–17] but not all,[18–21] indicate associations between fatigue and cytokines. Taking the higher expression of cytokines from, and by, host reaction to advanced cancer, we hypothesized that cytokines may play a role in fatigue in terminally ill cancer patients. A newly developed IL-6 receptor antibody[22,23] may become one of the candidates for new intervention strategies for fatigue in terminally ill cancer patients. However, the role of IL-6 in fatigue in terminally ill cancer patients has not yet been examined. In the present study, we investigated associations between plasma IL-6 levels and fatigue in terminally ill cancer patients.

Methods

Subjects

The present study was approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center, Japan, and was performed after obtaining written informed consent from the patients. Cancer patients who registered with the Palliative Care Unit (PCU) of the National Cancer Center Hospital East, Japan, between October 1997 and November 1999 were prospectively and consecutively recruited to participate in research on distress symptoms, such as fatigue and psychiatric disorders, in terminally ill cancer patients. Reports based on information contained in this database and regarding the prevalence of psychiatric disorders and suicidal ideation in terminally ill cancer patients have already been published.[24–27] The eligibility criteria for enrollment were 1) age 18 years or older; 2) newly registered with the PCU and having visited our outpatient clinic at least once after registration with the PCU; 3) not receiving or currently undergoing curative anticancer treatment; 4) informed of their cancer diagnosis; 5) not too ill to complete questionnaires and to participate in an interview; 6) not exhibiting cognitive impairment; and 7) able to verbally communicate in Japanese. In the present study, we checked the survival status of the participants at least six months after the assessment, and only analyzed the data of patients whose death was confirmed to have occurred within six months of our assessment, to avoid including long-term survivors in the current analyses. Patients taking any nonsteroidal anti-inflammatory drugs (NSAIDs) and/or

steroids were excluded from the analysis of the present study because of their potential influences on IL-6, and those who could not provide blood samples because of refusal and/or technical difficulties were also excluded.

Procedure

After obtaining the participants' written informed consent, eligible patients participated in an interview, including the Structured Clinical Interview for DSM-IV Axis I Disorder, Clinician Version,[28] and completed questionnaires, including the Cancer Fatigue Scale (CFS),[7] as described below, while in the outpatient clinic on their next visit after their registration with the PCU. Blood collection was performed by venipuncture into blood collection tubes between 10:30 AM to 5:30 PM on the same day as the interview was conducted and the questionnaires were administered. The blood was immediately centrifuged (4°C, 3000 rpm, 10 minutes) to separate the plasma from the whole blood; the plasma was stored at −80°C until the IL-6 assay. Subjects underwent the same investigations, including the interview, questionnaires, and blood sampling, at the time of their admission to the PCU, but data from the second investigation were not used in the current study because blood samples were not available for many of the subjects and because several patients were taking NSAIDs and/or steroids at that time.

Fatigue

Subjects' fatigue was assessed using the CFS.[7] The CFS is a 15-item self-rating scale for assessing cancer-related fatigue, which was designed specifically to reflect the nature of the fatigue. The reliability and validity of this scale have been established by a previous study. The optimal cutoff point for "clinical fatigue," defined as any fatigue that interferes with daily activities such as walking ability, sleep, normal work, mood, relations with other people, enjoyment of life, or general life activities, was 18/19.[29] The sensitivity and specificity calculated in 117 cancer patients were 71.3% and 74.0%, respectively. The CFS consists of three subscales—Physical, Affective, and Cognitive—which are generated by factor analysis. The physical aspect of fatigue includes being easily tired, an urge to lie down, exhaustion, a heavy and tired feeling, being fed up, reluctance, and not knowing what to do with oneself. The affective aspects of fatigue are lack of energy, lack of interest, lack of concentration, and not encouraging oneself to do anything. The cognitive aspects of fatigue are forgetfulness, errors while speaking, slower thinking, and carelessness. Each item is rated on a scale of 1 (not at all) to 5 (very much), and patients are asked to circle the number that describes their current state. The possible responses for each subscale range from 0 to 28 for Physical, 0 to 16 for Affective, and 0 to 16 for Cognitive. The maximum total score is 60. Higher scores reveal more severe fatigue. A visual analog scale (VAS) for evaluating fatigue was also used as a reference.

Interleukin-6

Plasma IL-6 levels were measured with an enzyme-linked immunosorbent assay using sets of paired monoclonal antibodies for capture and detection, as suggested by the manufacturer's protocol (Quantikine, Human IL-6 Immunoassay kit, R&D Systems Inc., MN, USA). Samples were assayed in triplicate, and IL-6 levels were derived from a standard curve comprising serial dilutions (3.12−300 pg/ml) of purified recombinant human IL-6. Assay sensitivity was less than 0.70 pg/ml. The mean inter- and intraassay coefficients of variation were 7.4% and 5.6%, respectively.

Biomedical-Psychological Factors

A structured interview was conducted to identify demographic factors. Medical factors were collected by chart review and were double-checked by two independent raters. Laboratory data, including hematological and biochemical data (see Table 1), were also measured as part of routine clinical examinations conducted at the same time as the interviews and questionnaires; these data were subsequently collected by chart review. Among the data, we entered factors previously reported as being associated with fatigue and/or cachexia to describe in detail the association of factors other than IL-6 with regard to the analyses of the current study, such as hematological data (including blood cell count and hemoglobin concentration), hepatic metabolism, renal function, and electrolytes. The Structured Clinical Interview for DSM-IV Axis I Disorder,

Table 1
Background and Medical Factors of Patients ($n = 46$)

	All Patients ($n = 46$)	Clinically Fatigued ($n = 27$)	Not Fatigued ($n = 19$)	Statistic Value	P
Age (years)[a]	58.4 ± 10.5	56.9 ± 11.0	60.4 ± 9.5	$t = 1.10$	0.27
Gender: female[b,d]	18 (39)	14	4	$\chi^2 = 4.40$	0.04
Height (cm)[a]	160.6 ± 7.5	159.3 ± 6.5	162.3 ± 8.7	$t = 1.30$	0.20
Weight (kg)[a]	52.9 ± 10.1	49.6 ± 7.9	57.7 ± 11.1	$t = 2.90$	0.006
Body temperature (degree)[a]	36.5 ± 0.5	36.5 ± 0.5	36.6 ± 0.5	$t = 0.04$	0.97
Cancer site[b,d]				$\chi^2 = 16.0$	0.53
Lung	11 (24)	9	2		
Gastric	9 (20)	3	6		
Colon	8 (17)	3	5		
Breast	5 (11)	4	1		
Liver	3 (7)	2	1		
Pancreas	2 (4)	1	1		
Other	8 (179)	5	3		
Cancer metastasis[b]					
Brain	4 (9)	2	2	$\chi^2 = 0.14$	0.55
Bone	6 (13)	5	1	$\chi^2 = 1.73$	0.20
Liver	14 (30)	8	6	$\chi^2 = 0.02$	1.00
Lung	10 (22)	7	3	$\chi^2 = 0.67$	0.33
Previous treatment[b]					
Surgery	24 (52)	12	12	$\chi^2 = 1.57$	0.25
Chemotherapy	27 (29)	17	10	$\chi^2 = 0.49$	0.55
Radiation[e]	12 (26)	9	3	$\chi^2 = 1.78$	0.16
Immunological	1 (2)	1	0	$\chi^2 = 0.72$	0.59
Blood laboratory data[a]					
WBC (10^2/dl)[d]	68.7 ± 30.2	72.7 ± 36.8	62.9 ± 16.3	$t = 1.08$	0.29
RBC (10^4/μl)	379.4 ± 97.3	366.3 ± 98.4	398.1 ± 95.2	$t = 1.09$	0.28
Hemoglobin (%)[e]	11.2 ± 2.3	10.7 ± 2.1	11.8 ± 2.6	$t = 1.52$	0.14
Cholesterol (mg/dl)	196.3 ± 76.7	192.9 ± 77.5	201.1 ± 77.3	$t = 0.35$	0.73
Triglyceride (mg/dl)	117.8 ± 67.2	110.8 ± 56.2	126.9 ± 81.5	$t = 0.56$	0.58
Albumin (g/dl)[e]	3.5 ± 0.5	3.4 ± 0.5	3.6 ± 0.6	$t = 1.32$	0.20
GOT (IU/l)	56.6 ± 50.9	50.0 ± 49.4	58.7 ± 53.9	$t = 0.57$	0.57
GPT (IU/l)	37.9 ± 43.4	30.3 ± 28.8	48.7 ± 57.3	$t = 1.44$	0.16
GTP (IU/l)	246.8 ± 436.9	250.0 ± 487.6	242.5 ± 372.9	$t = 0.06$	0.96
BUN (mg/dl)	19.7 ± 13.0	20.6 ± 16.4	18.4 ± 5.5	$t = 0.58$	0.57
Na (mEq/l)	136.1 ± 4.0	135.7 ± 4.1	136.6 ± 3.9	$t = 0.73$	0.47
Cl (mEq/l)	99.2 ± 4.9	99.3 ± 5.9	99.0 ± 90.0	$t = 0.20$	0.84
K (mEq/l)	4.4 ± 0.4	4.4 ± 0.4	4.5 ± 0.5	$t = 1.21$	0.24
Ca (mEq/l)	8.8 ± 0.8	8.7 ± 1.0	9.0 ± 0.6	$t = 1.11$	0.27
Major depression[b]	5 (11)	5	0	$\chi^2 = 3.95$	0.06
ECOG PS[c,e]	1 (0–3)	2 (1–3)	1 (0–3)	$U = 79.0$	<0.001
Survival time (day)[c,d]	61.5 (2–164)	46.0 (22–142)	89.0 (2–164)	$U = 148.5$	0.02

PS = performance status; ECOG = Eastern Cooperative Oncology Group; WBC = white blood cell; RBC = red blood cell; GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase; GTP = γ-glutamyltranspeptitase; BUN = blood urea nitrogen.
[a]Mean ± standard deviation.
[b]Number of subjects (%).
[c]Median (minimum-maximum).
[d]$P < 0.05$ indicate significant association with IL-6 levels.
[e]$P < 0.01$ indicate significant associations with IL-6 levels.

Clinician Version[28] was performed to diagnose psychiatric disorders. We used data regarding the diagnosis of major depression as psychological background information because fatigue is associated with depression.

Statistical Analysis

Between the patients who had clinical fatigue and those who did not, background and medical factors were compared using the Student's t-test, the Mann-Whitney U-test, and the χ^2 test. Associations between IL-6 level and background and medical factors were examined using the Mann-Whitney U-test and the Spearman's correlation test. As a primary analysis, a comparison of the IL-6 levels between patients with and those without clinical fatigue was performed by the Mann-Whitney U-test. Correlations between plasma IL-6 levels and the CFS scores were examined using the

Spearman's rank correlation test. As a secondary analysis, a stepwise logistic regression analysis was performed with background and medical factors significantly associated with clinical fatigue as covariates, except for performance status and factors that can be hypothesized to mediate between IL-6 and fatigue, such as anemia. The reason not to enter these factors as covariates to the model was to avoid over-adjustment. We hypothesized that characteristics explained by performance status were similar to and overlapped by those measured by the CFS. Also, we performed multiple regression analyses with the same factors as covariates to examine associations between logarithm-transformed IL-6 levels and the scores of each dimension of fatigue. *P*-values were set as <0.05 (two-tailed). All statistical procedures were done with SPSS 14.0J for Windows (SPSS, Tokyo, Japan).

Results

A total of 726 incurable cancer patients registered with the PCU during the study entry period, but 253 of them were ineligible (age less than 18, $n=1$; not informed of the cancer diagnosis, 4; too ill, 187; cognitive impairment, 51; and difficulty with verbal communication, 10). Of the remaining 473 patients, 227 did not visit the outpatient clinic (only registration with the PCU without any scheduled visit to the outpatient clinic, $n=114$; death before next visit, 12; admission to an inpatient ward, 60; and unknown reasons, 11) and 37 refused to participate (too busy to participate, $n=5$; too ill, 5; living too far away to come to the hospital, 1; refusal to undergo blood sampling, 1; and unknown reasons, 25). Of the 209 participants in the baseline assessment, 163 patients were excluded from the analysis (survival more than six months, $n=56$; unknown survival, 13; prescribed steroids and/or NSAIDs, 84; and no blood samples, 10) and 46 patients were analyzed. Background and medical factors are shown in Table 1.

The number (%) of patients who exhibited clinical fatigue was 27 (59%). Mean, SD, median, and range of total score of the CFS were 21.2, 9.5, 20, and 6–42, respectively. Among the background and medical factors, female, reduced weight, and poor performance status were significantly associated with clinical fatigue (Table 1). Mean, SD, median, and range of the VAS score of fatigue were 31.5, 24.7, 30.0, and 0–92.0, respectively. The VAS score of fatigue was significantly different between cancer patients with (mean [SD]: 43.6 [23.8]) and without clinical fatigue (mean [SD]: 31.5 [24.7]) ($t=4.60$, $P<0.001$), and significantly correlated with the total score of the CFS ($r=0.71$, $P<0.01$).

Mean, SD, median, and range of plasma IL-6 levels were 27.7, 37.8, 14.2, and 2.8–182.5 pg/ml, respectively. The IL-6 level in men was significantly higher than that in women (mean, SD, median, and range in men: 36.8, 45.8, 22.1, and 2.8–182.5 pg/ml, respectively; in women: 13.6, 10.2, 10.4, and 2.8–39.6 pg/ml, respectively; $U=160.5$, $P=0.04$). Also, cancer site, a history of radiation therapy, performance status, the number of white blood cells, and percentage of hemoglobin were significantly associated with IL-6 levels (Table 1). Among the cancer sites, lung cancer ($n=11$; mean, SD, median, and range: 49.6, 64.7, 13.6, and 2.8–182.5 pg/ml, respectively), pancreas cancer ($n=2$; mean, SD, median, and range: 32.3, 0.4, 32.3, and 32.0–32.6 pg/ml, respectively), and colon cancer ($n=8$; mean, SD, median, and range: 30.7, 37.3, 17.3, and 6.7–117.9 pg/ml, respectively) showed relatively higher levels of IL-6 compared to other cancer sites.

As a result of our primary analysis, plasma IL-6 levels in clinically fatigued patients (mean, SD, median, and range: 37.1, 46.4, 17.1, and 3.7–182.5 pg/ml, respectively) were significantly higher than in nonfatigued patients (mean, SD, median, and range: 14.3, 12.2, 8.0, and 2.8–45.0 pg/ml, respectively) ($U=154.5$, $P=0.02$) (Figure 1). The plasma IL-6 concentration was significantly correlated with the Physical subscale score of the CFS, but not with the total, Affective, and Cognitive subscales scores (Table 2 and Figure 2). In a logistic regression analysis with IL-6 level, gender, and weight as independent variables and clinical fatigue as a dependent variable, the IL-6 level was significantly associated with clinical fatigue ($P<0.01$). A multiple regression model with gender, weight, and the logarithmic-transformed IL-6 level as independent variables, and the total score of the CFS as

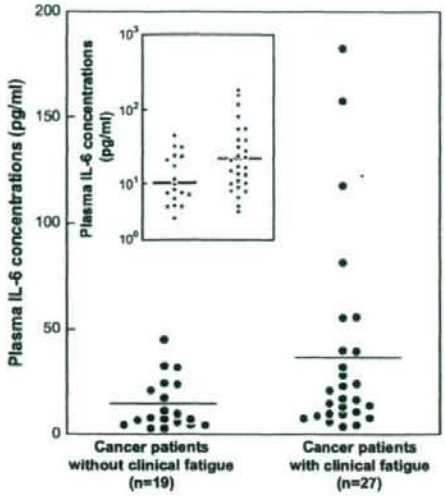

Figure 1. Plasma IL-6 concentrations of terminally ill cancer patients with and without clinical fatigue. Horizontal bars indicate the mean values of IL-6 in cancer patients with and without clinical fatigue. A superimposed scattered image indicates logarithmic-transformed IL-6 in cancer patients with and without clinical fatigue.

a dependent variable indicated a significant association of IL-6 with the total CFS score (standardized $R^2 = 0.27$, standardized beta = 0.38, and $P = <0.01$). In a model using the Physical subscale score of the CFS as a dependent variable, there was a significant association between the logarithmic IL-6 level and the Physical subscale score (standardized $R^2 = 0.32$, standardized beta = 0.44, and $P < 0.01$). Even in a model where the survival time was added as one of independent variables to the regression model, a significant association was observed and confirmed (standardized $R^2 = 0.31$, standardized beta = 0.56, and $P = 0.03$).

Discussion

This is the first study showing significant associations between fatigue and plasma IL-6 in terminally ill cancer patients, using an assessment tool that can evaluate physical, affective, and cognitive dimensions separately. Only the Physical, but not the Affective and Cognitive subscale scores of the CFS, was significantly associated with the IL-6 level, which may be one of the mediators related to a physical

Table 2
Correlations Between Subscale Scores of the CFS and IL-6 Levels ($n = 46$)

	Mean ± SD	Median (range)	r	P
CFS total score	21.2 ± 9.5	20 (6–42)	0.28	0.06
CFS physical score	7.7 ± 5.9	6.5 (0–20)	0.35	0.02
CFS affective score	9.3 ± 3.5	9 (1–16)	0.01	0.95
CFS cognitive score	4.3 ± 3.3	4 (0–13)	0.22	0.14
VAS	31.5 ± 24.7	30 (0–92)	0.35	0.02

SD = standard deviation; CFS = Cancer Fatigue Scale; VAS = visual analog scale.
Each of analyses was performed using the Spearman's rank correlation test between scores of the CFS, VAS, and plasma IL-6 levels.

dimension of fatigue. Given that cytokines cause energy expenditure and loss of muscle,[10] it may be plausible that IL-6 was associated with the physical dimension of fatigue.

The result of the present study seems to be consistent with the previous studies indicating an association between cytokines and fatigue in cancer patients.[11–17] However, among these studies, many examining IL-6 levels failed to show a significant association between higher IL-6 levels and fatigue,[13–15,17–21] except for one study on breast cancer patients receiving radiotherapy.[16] Maximum IL-6 levels in several studies were lower (<16 pg/dl)[13,15,19,21] than even the mean levels of the present study (28 pg/dl), and changes in the IL-6 levels were small (mean change: 2.2 pg/ml).[17] A relatively lower level and small change in IL-6 may not cause fatigue, and the association observed in the present study may be attributed to the terminally ill conditions with advanced cancer, which may cause the higher level of IL-6. In addition, although circadian IL-6 secretion has been reported,[30] the time of blood sampling was not controlled in these previous studies. This may cause the results of the present study, to be inconsistent with those of the previous studies.

Given a potentially deteriorated physical condition in terminally ill cancer patients, effects of IL-6 may be especially emphasized on the physical dimension of fatigue, suggesting a unique profile of biological effects of IL-6 on multidimensional fatigue in terminally ill cancer patients. As in a previous report demonstrating a therapeutic effect of IL-6 receptor antibody on fatigue in patients with multicentric Castleman disease, whose IL-6 levels were higher (mean [SD]: 34.8 [34.5]) than normal,[22] the present study indicates a basic result that warrants

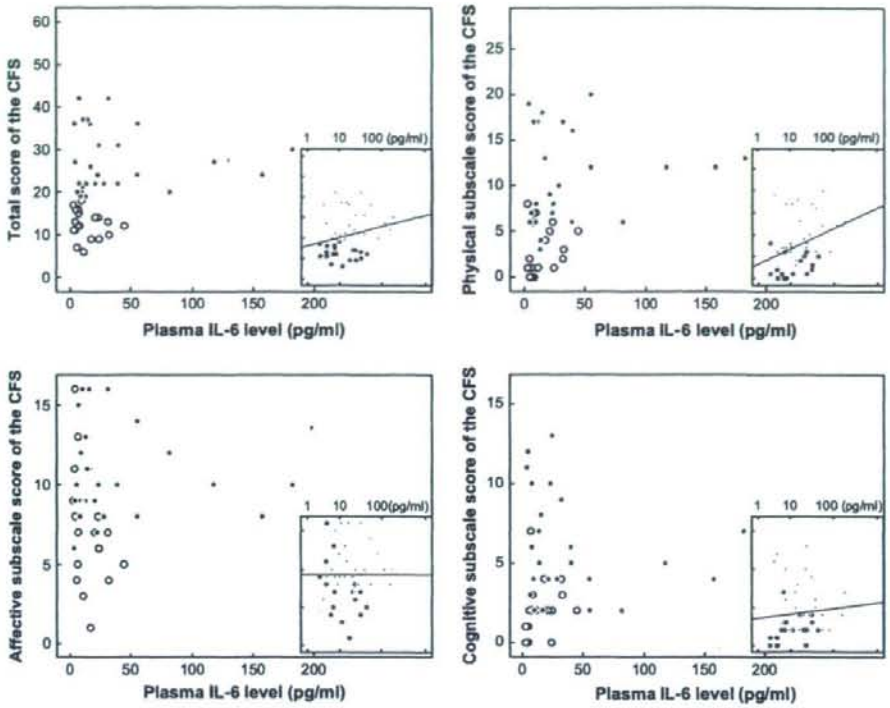

Figure 2. Plasma IL-6 concentrations and each of the subscale scores of the CFS. Solid and open circles indicate the values of patients with and without clinical fatigue, respectively. Superimposed scatter plots display IL-6 levels on logarithmic scales. Lines in the superimposed graphs indicate regression lines between logarithmically transformed IL-6 levels and each of the subscale scores.

further study to examine the possible effect of an IL-6 receptor antibody as a therapeutic agent for fatigue in terminally ill cancer patients, especially for the physical dimension. On the contrary, IL-6 may not have effects on affective and cognitive dimensions of fatigue, suggesting that a multidimensional systemic interventional strategy not only for physical, but also for affective and cognitive dimensions is needed to be developed to treat for all dimensions of fatigue in terminally ill cancer patients.

An advantageous point of the present study was the use of the multidimensional assessment tool for evaluating fatigue. A detailed contribution of IL-6 to each dimension of fatigue could be successfully investigated. In addition, the present study excluded patients receiving NSAIDs and/or steroids. Also, we included only patients whose survival time was less than six months by detecting the date of their death prospectively. These criteria can selectively isolate the fatigue that is specific for patients with terminally ill cancer, excluding any possible error associated with the estimation of survival length and confounding influences of NSAIDs and steroids.

There are several limitations. First, the participant rate was too low to generalize the results of the present study. We might not have investigated gravely ill patients who might demonstrate more severe fatigue. Eighty-four subjects who were excluded from the total eligible subjects because of the absence of blood samples may have been more severely ill, possibly confounding the current results. Second, other cytokines and their receptors should be investigated to elucidate the mechanism of fatigue in detail. Although the physical dimension of fatigue was especially associated with IL-6 among the multiple dimensions of fatigue

evaluated in the present study, the details of the biomedical mechanisms of IL-6 resulting in fatigue remain unclear. The investigation of soluble IL-6 receptors and other factors, such as endocrine function, may be useful for elucidating the mechanisms of fatigue in terminally ill cancer patients. Third, the findings of the current study, which are based on the results of analyses using a database with multiple purposes, should be interpreted with caution. Further study to confirm these results is needed. Fourth, we did not control for background or medical factors. To avoid over-adjustments, we did not include background and medical factors significantly associated with the IL-6 level. These factors might have confounded the results; therefore, the findings of the current study should be interpreted with caution.

In conclusion, plasma IL-6 may play a role, particularly in the physical dimension of fatigue, in terminally ill cancer patients. Although there are tasks to be addressed, the results of the present study encourage further study that could lead to a clinical trial of an IL-6 receptor antibody for fatigue, especially for its physical dimension, in terminally ill cancer patients.

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References

1. Rao A, Cohen HJ. Symptom management in the elderly cancer patient: fatigue, pain, and depression. J Natl Cancer Inst Monogr 2004;32:150–157.

2. Sarna L, Brecht ML. Dimensions of symptom distress in women with advanced lung cancer: a factor analysis. Heart Lung 1997;26(1):23–30.

3. Stone P, Richards M, A'Hern R, Hardy J. A study to investigate the prevalence, severity and correlates of fatigue among patients with cancer in comparison with a control group of volunteers without cancer. Ann Oncol 2000;11(5):561–567.

4. Morita T, Sakaguchi Y, Hirai K, Tsuneto S, Shima Y. Desire for death and requests to hasten death of Japanese terminally ill cancer patients receiving specialized inpatient palliative care. J Pain Symptom Manage 2004;27(1):44–52.

5. Bruera E, Valero V, Driver L, et al. Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. J Clin Oncol 2006;24(13):2073–2078.

6. Hwang SS, Chang VT, Rue M, Kasimis B. Multidimensional independent predictors of cancer-related fatigue. J Pain Symptom Manage 2003;26(1):604–614.

7. Okuyama T, Akechi T, Kugaya A, et al. Development and validation of the cancer fatigue scale: a brief, three-dimensional, self-rating scale for assessment of fatigue in cancer patients. J Pain Symptom Manage 2000;19(1):5–14.

8. Ahlberg K, Ekman T, Gaston-Johansson F, Mock V. Assessment and management of cancer-related fatigue in adults. Lancet 2003;362(9384):640–650.

9. Konsman JP, Parnet P, Dantzer R. Cytokine-induced sickness behaviour: mechanisms and implications. Trends Neurosci 2002;25(3):154–159.

10. Tisdale MJ. Cachexia in cancer patients. Nat Rev Cancer 2002;2(11):862–871.

11. Greenberg DB, Gray JL, Mannix CM, Eisenthal S, Carey M. Treatment-related fatigue and serum interleukin-1 levels in patients during external beam irradiation for prostate cancer. J Pain Symptom Manage 1993;8(4):196–200.

12. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. Psychosom Med 2002;64(4):604–611.

13. Rich T, Innominato PF, Boerner J, et al. Elevated serum cytokines correlated with altered behavior, serum cortisol rhythm, and dampened 24-hour rest-activity patterns in patients with metastatic colorectal cancer. Clin Cancer Res 2005;11(5):1757–1764.

14. Collado-Hidalgo A, Bower JE, Ganz PA, Cole SW, Irwin MR. Inflammatory biomarkers for persistent fatigue in breast cancer survivors. Clin Cancer Res 2006;12(9):2759–2766.

15. Mills PJ, Parker B, Dimsdale JE, Sadler GR, Ancoli-Israel S. The relationship between fatigue and quality of life and inflammation during anthracycline-based chemotherapy in breast cancer. Biol Psychol 2005;69(1):85–96.

16. Wratten C, Kilmurray J, Nash S, et al. Fatigue during breast radiotherapy and its relationship to biological factors. Int J Radiat Oncol Biol Phys 2004;59(1):160–167.

17. Pusztai L, Mendoza TR, Reuben JM, et al. Changes in plasma levels of inflammatory cytokines in response to paclitaxel chemotherapy. Cytokine 2004;25(3):94–102.

18. Ahlberg K, Ekman T, Gaston-Johansson F. Levels of fatigue compared to levels of cytokines

and hemoglobin during pelvic radiotherapy: a pilot study. Biol Res Nurs 2004;5(3):203–210.

19. Knobel H, Loge JH, Nordoy T, et al. High level of fatigue in lymphoma patients treated with high dose therapy. J Pain Symptom Manage 2000;19(6): 446–456.

20. Dimeo F, Schmittel A, Fietz T, et al. Physical performance, depression, immune status and fatigue in patients with hematological malignancies after treatment. Ann Oncol 2004;15(8):1237–1242.

21. Geinitz H, Zimmermann FB, Stoll P, et al. Fatigue, serum cytokine levels, and blood cell counts during radiotherapy of patients with breast cancer. Int J Radiat Oncol Biol Phys 2001;51(3):691–698.

22. Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. Blood 2005;106(8):2627–2632.

23. Nishimoto N, Yoshizaki K, Maeda K, et al. Toxicity, pharmacokinetics, and dose-finding study of repetitive treatment with the humanized anti-interleukin 6 receptor antibody MRA in rheumatoid arthritis. Phase I/II clinical study. J Rheumatol 2003;30(7):1426–1435.

24. Akechi T, Okuyama T, Akizuki N, et al. Associated and predictive factors of sleep disturbance in advanced cancer patients. Psychooncology 2007; 16(10):888–894.

25. Akechi T, Okuyama T, Sugawara Y, et al. Major depression, adjustment disorders, and post-traumatic stress disorder in terminally ill cancer patients: associated and predictive factors. J Clin Oncol 2004;22(10): 1957–1965.

26. Akechi T, Okuyama T, Sugawara Y, et al. Suicidality in terminally ill Japanese patients with cancer. Cancer 2004;100(1):183–191.

27. Akechi T, Okuyama T, Sugawara Y, et al. Screening for depression in terminally ill cancer patients in Japan. J Pain Symptom Manage 2006;31(1):5–12.

28. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV AXIS I Disorders (SCID), clinician version. Washington, DC: American Psychiatric Press, 1997.

29. Okuyama T, Tanaka K, Akechi T, et al. Fatigue in ambulatory patients with advanced lung cancer: prevalence, correlated factors, and screening. J Pain Symptom Manage 2001;22(1):554–564.

30. Vgontzas AN, Bixler EO, Lin HM, et al. IL-6 and its circadian secretion in humans. Neuroimmunomodulation 2005;12(3):131–140.

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SUPPORTIVE CARE INTERNATIONAL

Quality of end-of-life treatment for cancer patients in general wards and the palliative care unit at a regional cancer center in Japan: a retrospective chart review

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Abstract
Goals In Japan, most cancer patients die in the hospital. The aim of this study was to assess the quality of end-of-life treatment for dying cancer patients in general wards and palliative care unit (PCU).
Materials and methods A retrospective chart review study was conducted. The following data on cancer patients who died in general wards (N=104) and PCU (N=201) at a regional cancer center were collected: do-not-resuscitate (DNR) decisions, treatments in the last 48 h of life, and aggressiveness of cancer care for dying patients.
Main results DNR orders were documented for most patients (94% in general wards, 98% in PCU, p=0.067) and families usually consented (97%, 97%, p=0.307). Comparison of general wards with PCU showed that, in the last 48 h of life, significantly more patients in general wards received life-sustaining treatment (resuscitation, 3.8%, 0%, p=0.001; mechanical ventilation, 4.8%, 0%, p=0.004), large volume hydration (>1,000 ml/day, 67%, 10%, p<0.001) with continuous administration (83%, 5%, p=0.002) and fewer palliative care drugs (strong opioids, 68%, 92%, p< 0.001; corticosteroids, 49%, 70%, p<0.001; nonsteroidal anti-inflammatory drugs, 34%, 85%, p<0.001). Regarding aggressiveness of cancer care, patients received a new chemotherapy regimen within 30 days of death (3.0%), chemotherapy within 14 days of death (4.3%), and intensive care unit admission in the last month of life (3.3%).
Conclusion We found that families, not patients, consented to DNR, and life-sustaining treatments were appropriately withheld; however, patients on general wards received excessive hydration, and the use of palliative care drugs could be improved. Application of our findings can be used to improve clinical care in general wards.

Keywords Quality of health care · Palliative care · Terminal care · Decision making · Retrospective study · Neoplasm · Japan

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Introduction

For cancer patients in the last days of life, there are a wide variety of issues, including distressing physical symptoms, psychological concerns, decreased physical and communication abilities, and the ethical considerations of treatment [1, 2]. Providing appropriate care for these patients is very important.

Unfortunately, poor-quality end-of-life care occurs in hospital settings. The SUPPORT study revealed substantial shortcomings in the care of seriously ill hospitalized adults: patients' preferences regarding resuscitation were unknown to their physicians (47%), do-not-resuscitate (DNR) orders were written within 2 days of death (46%), patients received mechanical ventilation (46%), and patients suffered moderate-to-severe pain in the last 3 days of life (50%) [3]. After publication of the SUPPORT study, many studies reported inadequacy of end-of-life treatment in general wards. Especially in the last 48 h of life, many patients received inappropriate life-sustaining treatment [4–9] and inadequate pain and symptom management [4–6, 9–11]. The current status of end-of-life treatment should be investigated to improve the clinical care of dying hospitalized patients. Recently, quality indicators (QIs) of end-of-life cancer care have been identified: intensive use of chemotherapy, low rates of hospice use, and interventions resulting in emergency room visits, hospitalization, or intensive care unit (ICU) admissions [12]. These indicators were effectively utilized to assess the aggressiveness of cancer care using administrative data [13–15] and applied in a hospital setting [16].

In Japan, cancer is the leading cause of death (30% of all deaths), and 91% of cancer patients died in hospital in 2005 [17]. Palliative care developed from inpatient care for terminal cancer patients in Japan. In 1990, coverage for care in a palliative care unit (PCU) was included in National Health Insurance, and the number of PCUs has increased from 5 to 163 in 2007. Coverage for care provided by the palliative care team (PCT) began in 2002. These interdisciplinary teams cooperate with attending physicians to provide specialized care in general wards. Also in 2002, the Japanese Ministry of Health, Labor and Welfare designated a regional cancer center to provide standardized cancer diagnosis and treatment, which included palliative care. Only 5% of cancer patients died in PCU; therefore, a major task is to help staff on the general wards provide appropriate end-of-life care for dying cancer patients. This is also the case with Western countries. Previous studies investigated some aspects of quality of end-of-life care in Japan as follows: satisfaction of end-of-life care for cancer patients who died in PCUs [18], the efficacy of PCTs [19, 20], documentation of DNR orders in a teaching hospital [21], treatments and status of disclosure in the last 48 h of life in PCU and those provided in a geriatric hospital, where 42% of patients had cancer [22]. It is unclear who actually consents to DNR; however, in Japan, a cultural feature is that the family plays a greater role in this type of decision making [23–25]. There is also limited information about the comprehensive aspects of end-of-life treatment provided for dying cancer patients in general wards, and there are no data regarding QIs because of underdeveloped cancer registries in Japan. Improvements in the end-of-life treatment in general wards can be made by comparing practices that occur in PCU. In addition, understanding the aggressiveness of cancer care can be accomplished by using QIs.

The aim of this study was to assess quality of end-of-life treatment for dying cancer patients in general wards and the PCU at a regional cancer center in Japan. In particular, we focused on DNR decision making, treatments in the last 48 h of life, and aggressiveness of cancer care for dying patients.

Materials and methods

Patients and settings

Data were collected retrospectively on cancer patients who died in general wards and the PCU from September 2004 to February 2006 at Tsukuba Medical Center Hospital in Ibaraki Prefecture, Japan. The inclusion criteria were as follows: (1) died from cancer; (2) aged 20 years or older at the time of death; and (3) hospitalized for 3 days or more. The cancer sites could not be matched between settings because various clinical departments including respiratory medicine, general thoracic surgery, gastroenterology, gastroenterological surgery, general medicine, and palliative medicine participated in this study. These departments represented 88% of all cancer deaths in general wards and 100% in PCU during the study period. The exclusion criteria were as follows: (1) recruited by other study for bereaved family members; (2) bereaved family members would suffer serious psychological distress as determined by the attending physician; (3) cause of death was treatment or injury related; and (4) no bereaved family member aged 20 years or older.

Tsukuba Medical Center Hospital is a regional cancer center, in the suburbs of Tokyo. It has 409 beds (6 ICU beds and 20 PCU beds) and plays a central role in cancer treatment, community health care, and emergency medical care in Ibaraki Prefecture, Japan. PCU was certified in 2000 and provides specialized palliative care for patients in PCU and consultation, as requested, for general wards. During the study period, 188 patients died in general wards, and 242 patients died in PCU.

Procedure

We mailed a letter to identified bereaved families to inform them about the study. They were instructed to check and return the form in the enclosed envelope if they refused to participate in the chart review study in October 2006. The chart review was conducted between October and December 2006. Data were excluded for unknown addresses or if bereaved families declined to participate. A qualified research nurse (K.S.) reviewed all medical charts under the supervision of a PCU doctor. Initially, 20 medical charts were randomly selected and independently abstracted by two researchers (K.S. and M.M., also a licensed research nurse) to assure inter-rater reliability. The average rate of accordance was 93% between the reviewers; therefore, good inter-rater reliability was assured. The Ethics Committee of Tsukuba Medical Center Hospital approved this study.

Measures

Data were collected on five major categories: (1) patients' characteristics; (2) DNR decisions; (3) treatments in the last 48 h of life; (4) palliative care drugs in the last 48 h of life; and (5) QIs of end-of-life cancer care. Content validity was checked by two palliative care doctors and two research nurses before the medical chart review. A data collection sheet was utilized for documentation.

Patients' characteristics included information about sex, age, primary cancer site, cancer stage, and experience of cancer treatment (surgery, chemotherapy, and radiotherapy), length of time since cancer diagnosis, length of hospital stay, palliative care referral, length of time since palliative care referral, and length of PCU stay. Information concerning DNR decisions included: documentation of DNR order, patient or family consent to DNR, and length of time between documentation and death. Treatments in the last 48 h of life were comprehensively surveyed in reference to previous studies (see Table 4) [1, 4–6, 11]. We reviewed whether palliative care drugs were used in the last 48 h of life. They included ten classes of drugs which Nauck et al. [26] reported to be the most common in PCU (see Table 5). In addition, use of strong opioids, types of opioids in Japan (i.e., morphine, fentanyl, and oxycodone), methods [routine and as required (PRN)], and routes of administration were surveyed. We used QIs which Earle et al. [12] had identified and were available for our hospital setting to assess aggressiveness of cancer care near the end of life. QIs were identified during the chart review: new chemotherapy regimen within 30 days of death, chemotherapy within 14 days of death, more than 14 days hospital stay in the last month, admitted to the ICU in the last month, and 3 or fewer days PCU stay in the last month of life.

Data analysis

First, we calculated the relative frequency for categorical variables and the median, mean, and standard deviation (SD) for quantitative variables. For patients' characteristics,

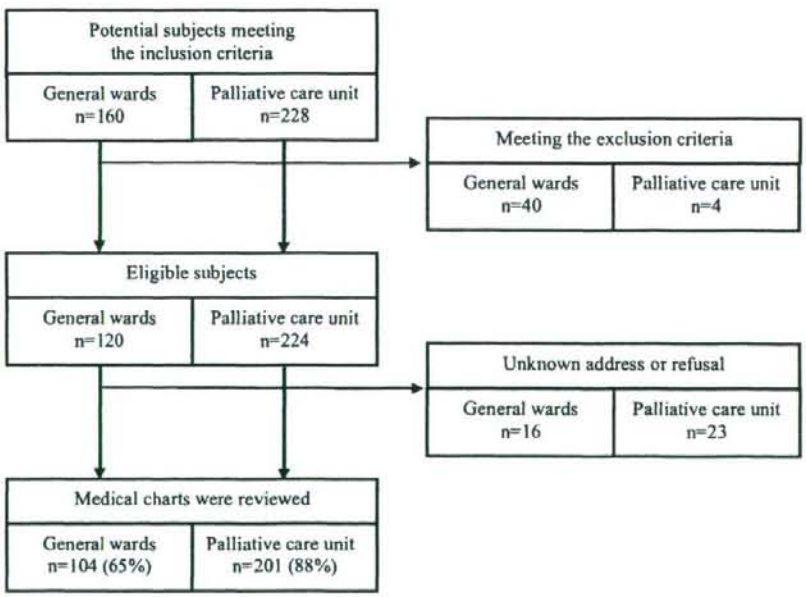

Fig. 1 Flow chart showing the patients' entry into the study

we separately calculated results from general wards and PCU and then compared the differences between the settings. For DNR decisions and treatments and palliative care drugs in the last 48 h of life, we also separately calculated results and then compared the differences to examine quality of end-of-life treatment for dying cancer patients in general wards. For aggressiveness of cancer care for dying patients, the calculated results combined for all settings were used to examine quality of end-of-life treatment throughout the hospital because these indicators were unsuited for comparing the aggressiveness between general wards and PCU. Statistical tests included Fisher's exact test, Cochran–Armitage exact trend test, or Wilcoxon test, as appropriate. A p value of less than 0.05 was considered statistically significant. All statistical analyses were performed with SAS version 9.1 for Windows (SAS Institute, Cary, NC).

Results

The patients' entry into the study is shown in Fig. 1. During the study period, patients who died in general wards (n=160) and PCU (n=228) were identified as potential subjects meeting the inclusion criteria. Among potential subjects, 44 were excluded due to participation in the other study (n=23 in general wards, n=0 in PCU), serious psychological distress as determined by the attending physician (n=8, n=0), treatment- or injury-related deaths (n=3, n=1), or no bereaved adult members (n=2, n=2). Subjects were also excluded if the bereaved family had no known address (n=3, n=8) or refused to participate (n=13, n=15). Finally, 104 (65%) medical charts from general wards and 201 (88%) from PCU were reviewed.

Patients' characteristics

Patients' characteristics are shown in Table 1. Among patients whose charts were reviewed, 71 and 55% were male and mean age was 71±9 and 68±12 years old in general wards and PCU, respectively. Primary cancer sites were lung (41% in general wards, 15% in PCU), hepatobiliary and pancreatic (28%, 17%), gastric (11%, 16%), and colorectal (6.7%, 17%).

In comparing patients' characteristics in general wards with those in PCU, significant findings include: more males

Table 1 Patients' characteristics

	General wards (N=104)		Palliative care unit (N=201)		p value
	n	(%)	n	(%)	
Sex, male	74	(71)	110	(55)	0.007**
Age, years (mean±SD)	71±9		68±12		0.100
Primary cancer site					
Lung	43	(41)	30	(15)	<0.0001***
Hepatobiliary and pancreatic	29	(28)	34	(17)	
Gastric	11	(11)	32	(16)	
Colorectal	7	(6.7)	35	(17)	
Head and neck	0	(0)	16	(8.0)	
Breast	1	(1.0)	15	(7.5)	
Other	13	(13)	39	(19)	
Cancer stage					
Local	7	(6.7)	2	(1.0)	0.002**
Regional	19	(18)	26	(13)	
Distant	74	(71)	171	(85)	
Experience of cancer treatment					
Surgery	26	(25)	118	(59)	<0.0001***
Chemotherapy	52	(50)	131	(65)	0.014*
Radiotherapy	45	(43)	93	(46)	0.630
Length of time since cancer diagnosis, months (median, mean±SD)	7, 14±27		18, 32±39		<0.0001***
Length of hospital stay, days (median, mean±SD)	27, 37±37		30, 45±65		0.296
Palliative care referral[a]	25	(24)	–		–
Length of time since palliative care referral, days (median, mean±SD)[b]	20, 31±27		61, 108±152		<0.0001***
Length of palliative care unit stay, days (median, mean±SD)	–		23, 37±60		–

Several total percentages are not 100% due to missing values.
SD Standard deviation
*p<0.05
**p<0.01
***p<0.001
[a] Palliative care referral to provide specialized care by PCT in general wards
[b] Median, mean, and SD calculated from patients with palliative care referral

(p=0.007), primary cancer sites were different (p<0.001), cancer stage was less advanced (p=0.002), fewer experienced surgical treatments (p<0.001) or chemotherapies (p=0.014), fewer with shorter length of time since cancer diagnosis (p<0.001), and shorter length of time since palliative care referral (p<0.001).

DNR decisions

Information about DNR decisions is shown in Table 2. DNR orders were documented for most patients (94% in general wards, 98% in PCU). Families (not patients) usually consented to DNR (97%, 97%). Median length of time between documentation of DNR and death was 8 days for general wards and 7 days for PCU. There was no significant difference between settings.

Treatments in the last 48 h

Treatments provided in the last 48 h of life are shown in Table 3. There were significant differences between general wards and PCU for the following: patients received life-sustaining treatment (resuscitation, 3.8% in general wards, 0% in PCU, p=0.001; mechanical ventilation, 4.8%, 0%, p=0.004; intubation, 3.8%, 0.5%, p=0.048); and had diagnostic testing (radiography, 27%, 14%, p=0.013; laboratory examination, 44%, 24%, p<0.001; electrocardiogram 63%, 1.5%, p<0.001). Meanwhile, significantly less palliative sedation (4.8%, 24%, p<0.001) was provided in general wards. Other treatments did not show significant differences between settings: oxygen inhalation (91%, 88%, p=0.556); intratracheal suction (41%, 37%, p=0.460); urinary catheter (61%, 50%, p=0.090); and therapeutic drainage (gastrointestinal fluids, 6.7%, 7.5%, p=1.000; percutaneous transhepatic cholangiole drainage, 3.8%, 3.0%, p=0.739).

Table 2 DNR decisions

	General wards (N=104)		Palliative care unit (N=201)		p value
	n	(%)	n	(%)	
Documentation of DNR order	98	(94)	197	(98)	0.067
Consent to DNR order[a]					
Patient	0	(0)	4	(2.0)	0.307
Family (not patient)	95	(97)	192	(97)	
Length of time between documentation and death, days (median, mean±SD)[a]	8, 17±29		7, 20±55		0.893

Several total percents are not 100% due to missing values
SD Standard deviation
[a] Percentage, median, mean, and SD calculated from patients with DNR orders

Approximately half of patients were given oral medicine (40% in general wards, 48% in PCU, p=0.185), and most received parenteral medication (98%, 97%, p=1.000); however, route of administration was significantly different. More patients had central venous access (21%, 4.6%, p< 0.001), and fewer had peripheral venous access (71%, 81%, p=0.027) or continuous subcutaneous infusion (44%, 83%, p<0.001). Vasopressors (21%, 0.5%, p<0.001), antibiotics (48%, 31%, p=0.006), and intravenous hyperalimentation (10%, 1.5%, p=0.002) were used significantly more in general wards. In addition, 88% in general wards and 87% in PCU received artificial hydration, while significantly more patients received large volume hydration (>1,000 ml/day, 67%, 10%, p<0.001) with continuous administration (83%, 5%, p=0.002).

Palliative care drugs in the last 48 h of life

Use of palliative care drugs in the last 48 h of life is shown in Table 4. Significantly more patients took eight of ten drugs such as strong opioids (68% in general wards, 92% in PCU, p<0.001), gastric protections (54%, 76%, p<0.001), corticosteroids (49%, 70%, p<0.001), nonsteroidal anti-inflammatory drugs (NSAIDs, 34%, 85%, p<0.001), neuroleptics (17%, 52%, p<0.001), and sedative/anxiolytics (15%, 47%, p<0.001), while fewer took antiemetics (20%, 8.0%, p=0.003) in general wards than in PCU. Among those patients taking strong opioids, morphine (92%, 74%, p=0.375) was used most frequently, followed by fentanyl (15%, 42%, p<0.001) and oxycodone (4.2%, 4.9%, p=0.757). Strong opioids, PRN, were used significantly less in general wards (58%, 76%, p=0.006).

Aggressiveness of cancer care near the end of life

Table 5 shows the QIs used to assess aggressiveness of cancer care near the end of life: new chemotherapy regimen within 30 days of death (3.0%, n=9), chemotherapy within 14 days of death (4.3%, n=13), more than 14 days in hospital in the last month of life (72%, n=221), admitted to the ICU in the last month of life (3.3%, n=10), and length of stay of 3 or fewer days in PCU (4.5%, n=9).

Among those patients who received chemotherapy near death and died in PCU, all new chemotherapy regimens were started before admission to PCU, and five of seven chemotherapy treatments were actually done in PCU. All were oral chemotherapy: three hormonal and two molecular targeted. Regarding proportion, for those with more than 14 days in hospital, 19 patients who died within 2 days of hospitalization were not included in the denominator because of the study criteria. Among those patients who were admitted to the ICU, five of ten patients died in ICU.

Table 3 Treatments in the last 48 h of life

Treatment	General wards (N=104)		Palliative care unit (N=201)		p value
	n	(%)	n	(%)	
Resuscitation	4	(3.8)	0	(0)	0.013*
Mechanical ventilation	5	(4.8)	0	(0)	0.004**
Intubation or use of airway[a]	4	(3.8)	1	(0.5)	0.048*
Tracheostomy[a]	5	(4.8)	1	(0.5)	0.019*
Oxygen inhalation	95	(91)	177	(88)	0.556
Intratracheal suction	43	(41)	74	(37)	0.460
Dialysis	1	(1.0)	0	(0)	0.342
Palliative sedation	5	(4.8)	48	(24)	<0.0001***
Urinary catheter[a]	63	(61)	100	(50)	0.090
Therapeutic drainage[a]					
Gastrointestinal fluids	7	(6.7)	15	(7.5)	1.000
Pleural fluids	8	(7.7)	3	(1.5)	0.009**
Percutaneous transhepatic cholangiole drainage	4	(3.8)	6	(3.0)	0.739
Ascites	0	(0)	2	(1.0)	0.549
Diagnostic testing					
Radiography	28	(27)	29	(14)	0.013*
CT scan	2	(1.9)	1	(0.5)	0.269
Laboratory examination	46	(44)	49	(24)	<0.0001***
Electrocardiogram	65	(63)	3	(1.5)	<0.0001***
Oral medication including rectal or transdermal	42	(40)	97	(48)	0.185
Parenteral medication	102	(98)	195	(97)	1.000
Route of administration[b]					
Central vein access	21	(21)	9	(4.6)	<0.0001***
Peripheral vein access	72	(71)	161	(83)	0.027*
Continuous subcutaneous infusion	45	(44)	161	(83)	<0.0001***
Vasopressor	22	(21)	1	(0.5)	<0.0001***
Antibiotic	50	(48)	63	(31)	0.006**
Blood transfusion					
Albumin transfusion	2	(1.9)	1	(0.5)	0.269
Red blood cell transfusion	5	(4.8)	5	(2.5)	0.317
Platelet transfusion	2	(1.9)	0	(0)	0.116
Chemotherapy	1	(1.0)	3	(1.5)	1.000
Artificial hydration (>50 ml/day)	92	(88)	174	(87)	0.720
Volume of infusion (the day before death)[c]					
<500 ml/day	9	(10)	73	(42)	<0.0001***
500–1,000 ml/day	21	(23)	84	(48)	
>1,000 ml/day	62	(67)	17	(10)	
Methods[c]					
Intermittent administration	16	(17)	165	(95)	<0.0001***
Continuous administration	76	(83)	9	(4.5)	
Intravenous hyperalimentation	10	(10)	3	(1.5)	0.002**
Tube feeding	2	(1.9)	3	(1.5)	1.000

CT Computed tomography
*p<0.05
**p<0.01
***p<0.001
[a] Newly insert or continued placement of tubes
[b] Percentages calculated from patients with parenteral medication
[c] Percentages calculated from patients with fluid infusion

Discussion

We investigated DNR decisions and the treatments provided for dying cancer patients in the last 48 h of life in general wards and PCU and the aggressiveness of end-of-life cancer care at a Japanese regional cancer center using QIs. This is the first study in Japan to examine the quality of end-of-life treatment for dying cancer patients

Table 4 Palliative care drugs in the last 48 h of life

Drug	General wards (N=104)		Palliative care unit (N=201)		p value
	n	(%)	n	(%)	
Strong opioids	71	(68)	185	(92)	<0.0001***
Morphine[a]	65	(92)	136	(74)	0.375
Fentanyl[a]	11	(15)	76	(41)	<0.0001***
Oxycodone[a]	3	(4.2)	9	(4.9)	0.757
Methods[a]					
Routine	70	(99)	184	(99)	0.479
As required (PRN)	41	(58)	140	(76)	0.006**
Route of administration[a]					
Oral, rectal, or transdermal	14	(20)	71	(38)	0.005**
Parenteral	60	(85)	165	(89)	0.294
Gastric protection	56	(54)	153	(76)	<0.0001***
Corticosteroids	51	(49)	140	(70)	<0.0001***
NSAIDs or acetaminophen	35	(34)	171	(85)	<0.0001***
Diuretics	28	(27)	43	(21)	0.318
Antiemetics	21	(20)	16	(8.0)	0.003**
Neuroleptics	18	(17)	105	(52)	<0.0001***
Sedatives/anxiolytics	16	(15)	95	(47)	<0.0001***
Laxatives	11	(11)	41	(20)	0.036*
Antidepressants	1	(1.0)	12	(6.0)	0.040*

NSAIDs Nonsteroidal anti-inflammatory drugs
*p<0.05
**p<0.01
***p<0.001
[a] Percentages calculated from patients with strong opioids

in general wards and to compare general ward care to PCU care. We are also the first to use QIs.

In this study, DNR orders were documented for 94–98% of patients. This was comparable to previous reports in Japan [21] and a little higher than abroad where 77–88% of patients had DNR orders [3, 7, 8, 11, 27]. Questionnaire surveys indicated that the end-of-life decision making was more often entrusted to families rather than to patients in Japan [23–25]. We confirmed that family (97%) usually consented to DNR. This family-centered decision making is a Japanese cultural feature that is seen less frequently in Western countries.

We found that life-sustaining treatments for dying cancer patients were generally withheld. In studies conducted abroad, 9–12% of patients who died of any disease in general wards received resuscitation, and 13–37% received mechanical ventilation in the last 48 h of life [4–7, 11]. In Japan, Masuda et al. [22] reported on patients in a geriatric

Table 5 Aggressiveness of cancer care near the end of life

Quality indicator of aggressive care	Total patients (N=305)		General wards (N=104)		Palliative care unit (N=201)	
	n	(%)	n	(%)	n	(%)
Proportion starting a new chemotherapy regimen within 30 days of death	9	(3.0)	6	(5.8)	3	(1.5)
Proportion receiving chemotherapy within 14 days of death	13	(4.3)	6	(5.8)	7	(3.5)
Proportion with >14 days in hospital in the last month of life[a]	221	(72)	75	(72)	146	(73)
Proportion admitted to the ICU in the last month of life	10	(3.3)	10	(9.6)	0	(0)
Proportion of palliative care unit patients with length of stay of 3 or fewer days	9	(4.5)	–		9	(4.5)

ICU Intensive care unit
[a] The denominator did not include 5 patients in general wards and 14 patients in PCU who hospitalized within 2 days because of the study criteria

ward; 42% had cancer, and among those patients, 11% received resuscitation, 11% had mechanical ventilation, and 16% were intubated. In our study, all patients died of cancer, and 3% were resuscitated, 5% placed on mechanical ventilation, and 4% were intubated in general wards; therefore, we conclude that there are less life-sustaining treatments provided for dying cancer patients. Concurrently, we note that families rather than patients usually do the DNR consent. Further study is needed to understand how much patients' preferences are reflected when families decide to forgo life-sustaining treatments.

Our results revealed contrasting styles of artificial hydration between settings. Although similar percentages of patients received artificial hydration, the methods of delivering fluids were completely different in terms of volume of hydration, continuous administration, route of administration, and hyperalimentation. Although the current evidence [28–33] is not in agreement regarding the palliative benefits of hydration, large volume hydration may not facilitate improvement in patients' outcomes in the final few days of life [29–30]. Therefore, the decision to hydrate should be personalized, based on careful assessment of symptoms, fluid administration, and patients' wishes [34]. Adjusting delivery of fluid (i.e., decreasing excess volume, using intermittent administration, or continuous subcutaneous infusion) may contribute to patients' comfort.

We also found that strong opioids were used sufficiently for end-of-life cancer patients, although use of palliative care drugs other than morphine may need to be improved in general wards. Strong opioids were used significantly less in general wards; however, usage was better than that reported in previous studies: Opioid usage in the last 48 h of life was 19–83% in general wards [4, 9, 21, 22] and 55–85% in PCU [10, 22, 26, 35]. However, fentanyl was far less used in general wards. This indicated an insufficient usage of opioid rotation. There was also significantly less usage of NSAIDs or other classes of palliative care drugs. Concomitant administration of opioids and NSAIDs or adjuvant analgesics and symptom management other than pain may be insufficient in general wards as compared to PCU. We suggest that physicians should be educated to increase use of palliative care drugs other than morphine to improve symptom management in general wards. Concurrently, more patients suffered from severe symptoms in PCU, thus requiring a variety of drugs to palliate intractable symptoms.

It is essential to discuss factors associated with the high use of opioids and palliative sedation and small volume hydration in PCU. Opioids and dehydration can cause delirium in terminally ill cancer patients [36], and thus, palliative sedation might be required to control delirium associated with frequent opioid use and small volume hydration in PCU. Some studies investigating the effectiveness of opioid rotation and hydration have found that hydration decreased myoclonus and sedation of dehydration [31], while hydration and opioid rotation decreased agitated delirium [37]. However, the latter finding was not confirmed by additional research [38], and beside, hydration did not improve delirium in the last few days of life [29]. The prevalence of hydration was similar, and opioid rotation was actively implemented in PCU. In addition, large-volume hydration may be unsustainable due to the presence of other fluid retention symptoms. As mentioned above, patients with severe symptoms can be easily transferred to PCU; therefore, the high use of opioids and sedation was considered to be reasonable.

According to QIs, we suggest that cancer care at the regional cancer center in Japan should be less aggressive. Starting a new chemotherapy regimen within the last month was reported 5% in US [13] and in a Portuguese hospital [16], and chemotherapy within the last 2 weeks was 14–19% in US, 4% in Canada [14], and 11% in the Portuguese hospital. In this study, a new chemotherapy regimen within the last month was 3%, and chemotherapy within the last 2 weeks was 4%; moreover, the percentages were less if oral chemotherapy was excluded. We confirmed that chemotherapy was less frequently prescribed. In the USA, ICU use in the last month was reported about 12%, hospital stay longer than 14 days was 10–12%, and PCU stay shorter than 4 days was 14–17%. In this study, ICU use (3%) was less aggressive than in the USA. To our knowledge, these are the first data available to assess ICU use for dying cancer patients in Japan. Hospital stay or PCU use in this study is longer than in the USA. However, we cannot compare the aggressiveness of cancer care because the health care systems differ greatly between the USA and Japan.

This study has several limitations. First, all the data were collected at a single center. As palliative care resources may be adequate in this hospital, we cannot generalize our findings to the quality of end-of-life care in Japan. Second, our inclusion criteria allowed differences in primary cancer sites. In addition, patients with severe symptoms were more likely to be transferred to PCU. This indicated the possibility that different treatments were given to the different groups. Nevertheless, we identified 160 of 188 patients who died of a variety of cancers in general wards as potential participants for this study; therefore, we consider our findings reflected the care practices in general wards. Third, 24% of patients who died in general wards had received specialized palliative care. This means that the care practices in general wards were higher for these patients; thus, we may have underestimated the differences for the remaining patients. To further elucidate the quality of end-of-life care in Japan, additional information about the end-of-life care in general wards without palliative care

resources is required. Fourth, patients who died in PCU had a longer duration since cancer diagnosis and had received more cancer treatments. Therefore, they may have had increased opportunities to discuss treatment options. Finally, data may not be fully validated because this study was a retrospective medical chart review. We established a high inter-rater reliability, although the documentation itself may have been incorrect. In addition, we did not collect information about symptoms because the documentation in the medical and nursing records was insufficient [39, 40].

Future studies should include nationwide surveys to assess the quality of end-of-life treatment and establish achievable benchmarks for care in Japan. Information that highlights the quality differences among settings or rationale for differences is useful for planning interventions to improve the quality of end-of-life care.

Conclusion

We identified several features of end-of-life treatment in the last 48 h of life for cancer patients who died in general wards at a Japanese regional cancer center. Families, not patients, usually consented to DNR; life-sustaining treatments were appropriately withheld; in general wards, patients received more than 1,000 ml/day of continuous hydration; strong opioids were sufficiently used; however, palliative care drugs, other than morphine, were used less frequently. We suggest that end-of-life treatment can be improved, for example, artificial hydration could be decreased in volume and intermittently or subcutaneously administered for the comfort and convenience of the patient. Physicians should be educated about the use of palliative care drugs other than morphine in general wards.

In addition, we are the first in Japan to assess the aggressiveness of cancer care for dying patients by using QIs. We suggest that cancer care at the regional cancer center in Japan could be less aggressive and more in order with palliative care philosophies.

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References

1. Ellershaw J, Ward C (2003) Care of the dying patient: the last hours or days of life. BMJ 326(7379):30–34
2. Plonk WM Jr, Arnold RM (2005) Terminal care: the last weeks of life. J Palliat Med 8(5):1042–1054
3. The SUPPORT Principal Investigators (1995) A controlled trial to improve care for seriously ill hospitalized patients. The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT). JAMA 274(20):1591–1598
4. Toscani F, Di Giulio P, Brunelli C, Miccinesi G, Laquintana D (2005) How people die in hospital general wards: a descriptive study. J Pain Symptom Manage 30(1):33–40
5. Solloway M, LaFrance S, Bakitas M, Gerken M (2005) A chart review of seven hundred eighty-two deaths in hospitals, nursing homes, and hospice/home care. J Palliat Med 8(4):789–796
6. Paice JA, Muir JC, Shott S (2004) Palliative care at the end of life: comparing quality in diverse settings. Am J Hosp Palliat Care 21 (1):19–27
7. Fins JJ, Miller FG, Acres CA, Bacchetta MD, Huzzard LL, Rapkin BD (1999) End-of-life decision-making in the hospital: current practice and future prospects. J Pain Symptom Manage 17 (1):6–15
8. Oh DY, Kim JH, Kim DW et al (2006) CPR or DNR? End-of-life decision in Korean cancer patients: a single center's experience. Support Care Cancer 14(2):103–108
9. Bailey FA, Burgio KL, Woodby LL et al (2005) Improving processes of hospital care during the last hours of life. Arch Intern Med 165(15):1722–1727
10. Aldasoro E, Alonso AP, Ribacoba L et al (2005) Assessing quality of end-of-life hospital care in a southern European regional health service. Int J Technol Assess Health Care 21(4):464–470
11. Goodlin SJ, Winzelberg GS, Teno JM, Whedon M, Lynn J (1998) Death in the hospital. Arch Intern Med 158(14):1570–1572
12. Earle CC, Park ER, Lai B, Weeks JC, Ayanian JZ, Block S (2003) Identifying potential indicators of the quality of end-of-life cancer care from administrative data. J Clin Oncol 21(6):1133–1138
13. Earle CC, Neville BA, Landrum MB, Ayanian JZ, Block SD, Weeks JC (2004) Trends in the aggressiveness of cancer care near the end of life. J Clin Oncol 22(2):315–321
14. Barbera L, Paszat L, Chartier C (2006) Indicators of poor quality end-of-life cancer care in Ontario. J Palliat Care 22(1):12–17
15. Grunfeld E, Lethbridge L, Dewar R et al (2006) Towards using administrative databases to measure population-based indicators of quality of end-of-life care: testing the methodology. Palliat Med 20(8):769–777
16. Braga S, Miranda A, Fonseca R et al (2007) The aggressiveness of cancer care in the last three months of life: a retrospective single centre analysis. Psychooncology 16(9):863–868
17. Statistics and Information Dept., Minister's Secretariat, Ministry of Health, Labour and Welfare (2006) Vital statistics of Japan 2005 (in Japanese). Ministry of Health, Labour and Welfare, Tokyo
18. Morita T, Hirai K, Sakaguchi Y et al (2004) Measuring the quality of structure and process in end-of-life care from the bereaved family perspective. J Pain Symptom Manage 27(6):492–501
19. Morita T, Imura C, Fujimoto K, Shishido H, Tei Y, Inoue S (2005) Changes in medical and nursing care in cancer patients transferred from a palliative care team to a palliative care unit. J Pain Symptom Manage 29(6):595–602
20. Morita T, Fujimoto K, Tei Y, Morita T, Fujimoto K, Tei Y (2005) Palliative care team: the first year audit in Japan. J Pain Symptom Manage 29(5):458–465
21. Tokuda Y, Nakazato N, Tamaki K, Tokuda Y, Nakazato N, Tamaki K (2004) Evaluation of end of life care in cancer patients at a teaching hospital in Japan. J Med Ethics 30(3):264–267
22. Masuda Y, Noguchi H, Kuzuya M et al (2006) Comparison of medical treatments for the dying in a hospice and a geriatric hospital in Japan. J Palliat Med 9(1):152–160
23. Voltz R, Akabayashi A, Reese C et al (1998) End-of-life decisions and advance directives in palliative care: a cross-cultural survey of patients and health-care professionals. J Pain Symptom Manage 16(3):153–162

24. Asai A, Miura Y, Tanabe N, Kurihara M, Fukuhara S (1998) Advance directives and other medical decisions concerning the end of life in cancer patients in Japan. Eur J Cancer 34(10):1582–1586
25. Ruhnke GW, Wilson SR, Akamatsu T et al (2000) Ethical decision making and patient autonomy: a comparison of physicians and patients in Japan and the United States. Chest 118(4):1172–1182
26. Nauck F, Ostgathe C, Klaschik E et al (2004) Drugs in palliative care: results from a representative survey in Germany. Palliat Med 18(2):100–107
27. Tschann JM, Kaufman SR, Micco GP (2003) Family involvement in end-of-life hospital care. J Am Geriatr Soc 51(6):835–840
28. Bozzetti F, Cozzaglio L, Biganzoli E et al (2002) Quality of life and length of survival in advanced cancer patients on home parenteral nutrition. Clin Nutr 21(4):281–288
29. Cerchietti L, Navigante A, Sauri A, Palazzo F (2000) Hypodermoclysis for control of dehydration in terminal-stage cancer. Int J Palliat Nurs 6(8):370–374
30. Morita T, Hyodo I, Yoshimi T et al (2005) Association between hydration volume and symptoms in terminally ill cancer patients with abdominal malignancies. Ann Oncol 16(4):640–647
31. Bruera E, Sala R, Rico MA et al (2005) Effects of parenteral hydration in terminally ill cancer patients: a preliminary study. J Clin Oncol 23(10):2366–2371
32. Lawlor PG, Gagnon B, Mancini IL et al (2000) Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. Arch Intern Med 160(6):786–794
33. Morita T, Tei Y, Tsunoda J, Inoue S, Chihara S (2001) Underlying pathologies and their associations with clinical features in terminal delirium of cancer patients. J Pain Symptom Manage 22(6):997–1006
34. Dalal S, Bruera E (2004) Dehydration in cancer patients: to treat or not to treat. J Support Oncol 2(6):467–479, 483
35. Goncalves JF, Alvarenga M, Silva A (2003) The last forty-eight hours of life in a Portuguese palliative care unit: does it differ from elsewhere? J Palliat Med 6(6):895–900
36. Centeno C, Sanz A, Bruera E (2004) Delirium in advanced cancer patients. Palliat Med 18(3):184–194
37. Bruera E, Franco JJ, Maltoni M, Watanabe S, Suarez-Almazor M (1995) Changing pattern of agitated impaired mental status in patients with advanced cancer: association with cognitive monitoring, hydration, and opioid rotation. J Pain Symptom Manage 10 (4):287–291
38. Morita T, Tei Y, Inoue S (2003) Agitated terminal delirium and association with partial opioid substitution and hydration. J Palliat Med 6(4):557–563
39. Stromgren AS, Groenvold M, Sorensen A, Andersen L (2001) Symptom recognition in advanced cancer. A comparison of nursing records against patient self-rating. Acta Anaesthesiol Scand 45(9):1080–1085
40. Stromgren AS, Groenvold M, Pedersen L, Olsen AK, Spile M, Sjogren P (2001) Does the medical record cover the symptoms experienced by cancer patients receiving palliative care? A comparison of the record and patient self-rating. J Pain Symptom Manage 21(3):189–196