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Anticipatory nausea among ambulatory cancer patients undergoing chemotherapy: Prevalence, associated factors, and impact on quality of life

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The purposes of this study were to investigate the prevalence of anticipatory nausea (AN), its associated factors, and its impact on quality of life (QOL) among ambulatory cancer patients receiving chemotherapy. Patients were randomly selected to participate in this study, and were asked to complete the Morrow Assessment of Nausea and Emesis scale, the Hospital Anxiety and Depression Scale, the Short-form Supportive Care Needs Survey questionnaire, and the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire. Complete data were available for 214 patients. A total of 10.3% of the patients experienced very mild to severe AN. The presence of AN was significantly associated with most domains of the investigated patients' outcome, including psychological distress and perceived needs, with the exception of the health system and information domain of patients' needs, and the physical functioning domain of QOL. Anticipatory nausea was also associated with QOL even after adjustments for age, sex, performance status, and psychological distress. The prevalence of AN in ambulatory cancer patients who receive chemotherapy may not be as high as previously reported. However, given its potentially significant impact on relevant outcome, including QOL, AN should not be neglected in current clinical oncology practice. (*Cancer Sci* 2010; 101: 2596–2600)

Nausea and vomiting are frequently described as the most troublesome adverse effects of chemotherapy and often have a profound negative impact on patient quality of life (QOL). The nausea and vomiting that often accompany later treatments commences even prior to the chemotherapeutic agent being given, and this phenomenon has been defined as anticipatory nausea (AN) and vomiting.[1] Anticipatory nausea and vomiting can best be understood in terms of classical conditioning. Typically, AN and vomiting is a learned response to one or more distinctive features of the chemotherapy clinic (conditioned stimuli) associated with the administration of emetogenic chemotherapy (unconditioned stimuli).[2] Previous studies have indicated that approximately 30–60% of patients experience AN, although the occurrence rate differs depending on many factors, including the type of chemotherapy, post-chemotherapy vomiting, age, gender, and anxiety level.[3–8] Once AN and vomiting develops, it is difficult to control by pharmacological means and often persists for up to 1 year.[9,10]

Recent advances in supportive therapy for preventing chemotherapy-induced nausea and vomiting (CINV), including the addition of corticosteroids to 5-HT3 receptor antagonists and/or neurokinin-1 receptor antagonists, has improved the management of CINV,[11–13] and this progress has drastically changed patient perceptions of the side-effects of cancer chemotherapy. For example, studies investigating patient perceptions of the side-effects of cancer chemotherapy in the 1990s repeatedly indicated that CINV is one of the most important and distressing symptoms for cancer patients receiving chemotherapy.[14,15] However, a similar report in 2002 showed a marked change, indicating that fatigue and psychosocial QOL concerns, but not CINV, predominated.[16]

Recent improvements in anti-emetic therapy for CINV have probably contributed to the amelioration and/or reduction of AN among cancer patients receiving chemotherapy. However, several studies have shown that CINV, including AN, remains a significant problem in patients receiving moderately or highly emetogenic regimens, even after treatment with 5-HT3 receptor antagonists and corticosteroids, and physicians and nurses might underestimate the risk of delayed CINV.[17,18] In addition, very few studies have investigated the potential impact of AN on the relevant outcomes of patients, including psychological distress and QOL, although a few studies have revealed the serious influence of CINV on the QOL of cancer patients.[19–21]

The purposes of this study were to investigate the prevalence of AN, its associated factors, including patient characteristics and relevant outcomes, such as psychological distress, patient's perceived needs, and QOL, and its impact on QOL among ambulatory cancer patients receiving chemotherapy with standard anti-emetic pharmacological regimens.

Material and Methods

Subjects. The study subjects were ambulatory cancer patients attending the outpatient oncology unit at Nagoya City University Hospital (Nagoya, Japan). The subjects who were receiving chemotherapy were also treated with standard anti-emetic pharmacological regimens that were decided in advance based on an evidence-based agreement among a steering committee of the outpatient oncology unit (e.g., 5-HT3 receptor antagonists and corticosteroid treatment for high emetogenic chemotherapy regimen[13]). However, neurokinin-1 receptor antagonists (e.g., aprepitant)[22] were not available in Japan during the study period. Potential participants who had undergone chemotherapy at least once were consecutively sampled at random using a visiting list and a random number table.

The eligibility criteria for inclusion in the study were: (i) a diagnosis of cancer (patients with double cancer and patients who had already received chemotherapy were also eligible); (ii) an age of 20 years or older; (iii) an awareness of the cancer diagnosis; and (iv) a general condition sufficient to enable the completion of the survey questionnaire (0–3 on the Eastern Cooperative Oncology Group [ECOG] performance status). The

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exclusion criteria were patients with: (i) severe mental or cognitive disorders (e.g., uncontrolled schizophrenia, dementia, or delirium); (ii) an inability to understand the Japanese language; and (iii) their first visit to the outpatient oncology unit (such cases were excluded to avoid excessive burden to the patient, as an explanation regarding the chemotherapy was given to each patient during their first visit).

This study was approved by the Institutional Review Board and Ethics Committee of Nagoya City University Graduate School of Medical Sciences, and was conducted in accordance with the principles laid down in the Helsinki Declaration. Written consent was obtained from each patient after a thorough explanation of the purpose and method of the study had been provided.

Procedure. After informed consent had been obtained, the patients were asked to complete the self-administered questionnaires (described below) at home and return them the following day. When the questions were answered inadequately, clarifications were sought over the telephone.

Anticipatory nausea. Anticipatory nausea was measured using part of the Morrow Assessment of Nausea and Emesis (MANE)[23] because, to the best of our knowledge, a validated structured interview method for assessing AN is not available and only the MANE was capable of addressing AN among several patient self-reporting tools for CINV.[24] The MANE assesses AN using three patient self-reported questions: (i) ''Did you experience nausea before your first (or most recent, depending on which cycle was being assessed) chemotherapy treatment? (yes/no)''; (ii) ''How would you describe the nausea at its worst before treatment?'' (indicated by circling a number from 1 to 6, with 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe, and 6 = intolerable); and (iii) ''How many hours before treatment did the nausea first occur?'' (total number of hours written in). To develop the Japanese version, the items were translated into Japanese by two researchers and the verbal expressions were carefully checked. Because AN is more common than anticipatory vomiting, we focused on AN in the current study.

We investigated potential associations between AN and several medical factors (cancer site, chemotherapeutic regimen, emetogenic level, purpose of chemotherapy, and performance status) and patient characteristics (age, sex). We also assessed three different factors (psychological distress, patient's perceived need, and QOL) that are relevant as patient outcomes and potentially associated with AN.

Psychological distress. The Hospital Anxiety and Depression Scale (HADS) has been developed to evaluate psychological distress, including anxiety and depression, in medically ill patients and does not contain any questions regarding physical symptoms.[25] The HADS is a self-reported questionnaire consisting of 14 items. Subjects are asked to rate how they felt during the previous week using a four-point Likert scale. The HADS consists of an anxiety and a depression subscale (0–21 points each), and the total score can range from 0 to 42. A higher score indicates a more severe degree of depression and anxiety. The Japanese version of the HADS has been validated for cancer populations.[26]

Patients' perceived needs. The Short-form Supportive Care Needs Survey questionnaire (SCNS-SF34) is a self-administered instrument for assessing the perceived needs of patients with cancer.[27] The SCNS-SF34 consists of 34 items covering five domains of need: (i) psychological; (ii) health system and information; (iii) physical and daily living; (iv) patient care and support; and (v) sexuality. The respondents were asked to indicate the level of their need for help over the last month in relation to their having cancer using the following five response options: 1 (No need [Not applicable]), 2 (No need [Satisfied]), 3 (Low need), 4 (Moderate need), 5 (High need). The subscale scores were obtained by summing the individual items. In addition, the total score was obtained by summing all the subscales (range, 34–170). A higher score indicated a higher perceived need. The validity and reliability of the Japanese version of the SCNS-SF34 has been established.[28]

Quality of life. Patient QOL was assessed using the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30.[29] The QLQ-C30 is a 30-item, self-reported questionnaire covering functional (global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning) and symptom-related aspects (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties) of QOL in cancer patients. The validity and reliability of the Japanese version of the EORTC QLQ-C30 has been confirmed.[30] A high functional score represents a high QOL. A high symptom score indicates a strong symptom. In the present study, we used the global health status scale and the five functional dimension scales.

Chemotherapeutic regimens. Information regarding chemotherapeutic regimens and the purpose of the chemotherapy (curative or palliative intent) were obtained from the patients' medical records. In addition, we evaluated the emetogenic levels of antineoplastic agents and divided them into four levels (level 1, coded as 1: minimal risk; level 2, coded as 2: low risk; level 3, coded as 3: moderate risk; level 4, coded as 4: high risk) according to a schema produced by an expert consensus conference in 2004.[9] Because most chemotherapeutic regimens usually include multiple antineoplastic agents, we assessed the emetogenic levels using the highest emetogenic level involved in the regimen in each case. For example, FOLFOX regimens containing fluorouracil (emetogenic level 2) and oxaliplatin (emetogenic level 3) were rated as level 3.

Sociodemographic and biomedical factors. An ad-hoc self-administered questionnaire was used to obtain information on the patients' sociodemographic statuses, including their marital status, whether they were living with others, level of education, and employment status. The performance status, as defined by the ECOG, was evaluated by registered nurses. All other medical information (e.g., cancer site) was obtained from the patients' medical records.

Statistical analysis. To investigate associations between AN and several medical factors (cancer site, chemotherapeutic regimen, emetogenic level, purpose of chemotherapy, and performance status) and patient characteristics (age, sex), the χ^2-test and/or Fisher's exact test were used, as appropriate. To evaluate the impact of AN on the three patient outcomes, the difference between the presence of AN and the patients' psychological distress, perceived needs, and/or QOL were investigated using an unpaired *t*-test and multiple regression analysis to adjust for age, sex, and performance status. Furthermore, to investigate the potential contribution of AN to QOL in more detail, a multiple regression analysis was carried out. In this multiple regression analysis, the global health status score of the EORTC QLQ-C 30 was entered as a dependent variable, and the presence of AN was entered as an independent variable after adjusting for potentially confounding factors, namely, age, sex, performance status, and psychological distress (HADS total score). To assess the emetogenic levels of the chemotherapeutic regimens and the degree of AN, Spearman's rank correlation test was used.

A *P*-value of <0.05 was regarded as being statistically significant, and all reported *P*-values were two-tailed. All statistical procedures were carried out using SPSS version 15.0J version software for Windows (SPSS, Chicago, IL, USA).

Results

Patient characteristics. Among a total of 243 eligible patients identified for the study, 214 patients agreed to participate in the

study (response rate, 88%). We compared the medical differences (cancer site, performance status, purpose of chemotherapy) and sociodemographic differences (age, sex) between those who participated in the study ($n = 214$) and those who did not ($n = 29$). The results of this analysis indicated that older patients were more likely to decline the study, but other factors did not show any statistically significant difference. The sociodemographic and clinical characteristics of the study patients are shown in Table 1. Breast and colorectal cancer were the most common cancers, and more than half of the subjects were receiving chemotherapy for palliative intent. The FOLFOX regimen containing fluorouracil and oxaliplatin was the most common chemotherapeutic regimen ($n = 25$, 12%; emetogenic level = 3) followed by the FEC100 regimen containing 5-fluorouracil, epirubicin and cyclophosphamide ($n = 19$, 9%; emetogenic level = 4); paclitaxel alone ($n = 17$, 8%; emetogenic level = 2); the FOLFIRI regimen containing fluorouracil and irinotecan ($n = 15$, 7%; emetogenic level = 3); gemcitabine alone ($n = 12$, 6%; emetogenic level = 2); and trastuzumab alone ($n = 12$, 6%; emetogenic level = 1). Only 23 subjects (11%) received chemotherapeutic regimens with a high emetogenic level (emetogenic level = 4): the FEC100 regimen mentioned above ($n = 19$, 9%), the ABVD regimen containing adriamycin, bleomycin, vincristine, and dacarbazine ($n = 3$, 1.4%), and a combination of tegafur and cisplatin ($n = 1$, 0.5%). Moderate, low, and minimal emetogenic level regimens were given to 96 (45%), 69 (32%), and 26 (12%) subjects, respectively. A weak but statistically significant association was observed between the emetogenic levels of the chemotherapeutic regimens and the degree of AN ($r = 0.21$, $P < 0.01$).

Description of AN. A total of 22 patients (10.3%) experienced AN. These patients reported the intensity of their AN as very mild ($n = 7$, 3.3%), mild ($n = 11$, 5.1%), moderate ($n = 3$, 1.4%), or severe ($n = 1$, 0.5%). The patient who experienced severe AN received chemotherapy containing irinotecan. The three patients who experienced moderate AN had received a chemotherapy regimen containing irinotecan, gemcitabine, or R-CHOP (containing rituximab, cyclophosphamide, doxorubicin, and vincristine). No patients reported their AN as ''very severe'' or ''intolerable''. Regarding the number of hours before treatment that the AN occurred, it ranged from approximately 0.2 h (12 min) before treatment to 720 h (30 days) before treatment. The mean and median number of hours were 43 h (SD = 150 h) and 2 h, respectively.

Associations between AN and patient characteristics and medical factors. Anticipatory nausea was significantly associated with a higher emetogenic level of chemotherapy. Other patient characteristics and medical factors, including age, sex, cancer site, type of chemotherapeutic regimen, purpose of chemotherapy, and performance status, were not significantly associated (Table 2).

Associations between AN and psychological distress, perceived needs, and QOL. The associations between AN and other patient outcomes, including psychological distress, perceived needs, and QOL, indicated that AN was significantly associated with most domains of the investigated patient outcomes in both univariate and multivariate analyses, except for the health system and information domain of patients' needs and the physical functioning domain of QOL (Table 3).

Anticipatory nausea and QOL. Finally, the presence of AN was independently associated with a lower QOL, even after adjustments for age, sex, performance status, and psychological distress (Table 4). Excluding AN, a younger age and a higher psychological distress were also significantly associated with a lower QOL.

Table 1. Characteristics of the ambulatory cancer patients undergoing chemotherapy who participated in this study ($n = 214$)

Characteristic		*n* (%)
Age (years)	Mean, 60 (SD = 12); median, 59 (range, 21–83)	
Sex	Female	128 (60)
Marital status	Married	159 (74)
Living with others	Living alone	30 (14)
Employment status	Full-time/part-time	67 (31)
	Housewife	52 (24)
Education	≥12 years	166 (78)
Cancer site	Breast	72 (34)
	Colorectal	56 (26)
	Lung	19 (9)
	Lymphoma	16 (8)
	Stomach	14 (7)
	Others	37 (17)
Performance status†	0	170 (79)
	1	39 (18)
	2	4 (2)
	3	1 (1)
Chemotherapy	Curative intent	82 (38)
	Palliative intent	132 (62)

†Eastern Cooperative Oncology Group criteria.

Table 2. Association between anticipatory nausea (AN) and patient characteristics and several medical factors

		AN (+) ($n = 22$)	AN (–) ($n = 192$)	*P*-value
			n (%)	
Age (years)	<50	7 (15)	39 (85)	0.20
	≥50	15 (9)	153 (91)	
Sex	Female	14 (11)	116 (89)	0.76
	Male	8 (10)	76 (90)	
Cancer site	Breast	7 (10)	65 (90)	0.25
	Colorectal	7 (13)	48 (87)	
	Lung	0 (0)	19 (100)	
	Lymphoma	2 (13)	14 (88)	
	Stomach	2 (14)	12 (86)	
	Others	4 (11)	34 (89)	
Regimen	FOLFOX†	3 (12)	22 (88)	0.19
	FEC100‡	5 (26)	14 (74)	
	Paclitaxel	1 (6)	15 (94)	
	FOLFIRI§	2 (13)	13 (87)	
	Gemcitabine	2 (18)	9 (82)	
	Trastuzumab	0 (0)	12 (100)	
	Others	9 (8)	107 (92)	
Emetogenic level	Minimal or low risk	4 (4)	89 (96)	0.01
	Moderate or high risk	18 (14)	103 (86)	
Chemotherapy	Curative intent	10 (12)	72 (88)	0.47
	Palliative intent	12 (9)	120 (91)	
Performance status¶	0	16 (9)	153 (91)	0.43
	1–3	6 (13)	39 (87)	

†FOLFOX regimen contains fluorouracil and oxaliplatin. ‡FEC100 regimen contains 5-fluorouracil, epirubicin, and cyclophosphamide. §FOLFIRI regimen contains fluorouracil and irinotecan. ¶Using the European Organization for the Research and Treatment of Cancer QLQ-C30 questionnaire covering functional and symptom-related aspects of quality of life in cancer patients.

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Table 3. Association between anticipatory nausea (AN) and psychological distress, needs, and quality of life (QOL)

	AN (+) (n = 22)	AN (–) (n = 192)	P	P†
Psychological distress (HADS)	Mean (SD)			
Anxiety	7.5 (3.9)	5.1 (3.6)	0.004	0.005
Depression	8.2 (3.5)	5.9 (3.8)	0.007	0.010
Total	15.7 (6.7)	11.0 (6.9)	0.003	0.004
Needs (SCNS-SF34)				
Psychological	31.5 (8.1)	25.1 (10.2)	0.005	0.007
Health system and information	30.0 (9.2)	27.4 (10.0)	0.240	0.200
Physical and daily living	12.7 (4.1)	10.5 (4.2)	0.020	0.030
Patient care and support	12.8 (4.8)	10.7 (4.1)	0.030	0.030
Sexuality	6.1 (3.4)	4.4 (2.3)	0.030	0.002
QOL (EORTC QLQ C-30)				
Global health status	35.6 (21.5)	54.9 (23.0)	<0.001	0.001
Physical functioning	73.3 (19.4)	80.3 (17.6)	0.080	0.060
Role functioning	53.8 (19.2)	68.3 (28.5)	0.020	0.050
Emotional functioning	66.3 (19.5)	78.1 (19.9)	0.009	0.020
Cognitive functioning	64.4 (24.3)	75.7 (21.2)	0.020	0.020
Social functioning	57.6 (28.0)	73.5 (23.4)	0.004	0.010

†P, multivariate analysis adjusting for age, sex, and performance status. EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer QLQ-C30 questionnaire; HADS, Hospital Anxiety and Depression Scale; SCNS-SF34, Short-form Supportive Care Needs Survey questionnaire.

Table 4. Factors associated with quality of life in cancer patients receiving chemotherapy, multiple regression analysis

	Beta	SE	t	P
Anticipatory nausea	−0.13	4.49	−2.19	0.030
Age	0.13	0.11	2.27	0.020
Sex	0.03	2.85	0.43	0.670
Performance status†	−0.11	2.74	−1.96	0.051
Psychological distress‡	−0.50	0.20	−8.47	<0.001

†Defined by Eastern Cooperative Oncology Group criteria. ‡Total Hospital Anxiety and Depression Scale score.

Discussion

The current study showed that approximately 10% of ambulatory cancer patients receiving chemotherapy still experience AN. Furthermore, the findings also indicated that the presence of AN was significantly associated with a higher emetogenic level of chemotherapy and multiple patient outcomes, including psychological distress, perceived needs, and QOL. Anticipatory nausea also independently contributed to QOL.

Regarding the prevalence of AN, the current study unexpectedly indicated a lower proportion than previous studies, which reported prevalences of more than 30%.[3,6] Furthermore, the fact that no patients reported their AN as ''very severe'' and/or ''intolerable'' might imply that the severity of the AN symptom itself is not so serious. These findings partly reflect the development of supportive therapy for CINV, including the novel antiemetic drugs and regimens used in current clinical oncology practice. However, because a sampling bias might exist (e.g., only 11% of the subjects received chemotherapeutic regimens with a high emetogenic level, and patients who received highly emetogenic chemotherapy regimens might have been more likely to refuse to participate in the study or to have been treated in an inpatient setting), the lower prevalence of AN should be interpreted with caution and the actual prevalence rate of AN among all cancer patients who receive chemotherapy is probably higher than the finding obtained in the current study. In addition, as the neurokinin-1 receptor antagonist, aprepitant,[22] has been available in Japan since 2009, further studies regarding the prevalence rate of AN in current clinical oncology practice are needed.

The present study also indicated that the experience of AN might be associated with a broad range of relevant patient outcomes, including psychological status, patients' needs in several dimensions, and many aspects of QOL. From a clinical viewpoint, these associations may suggest a potentially negative impact of AN on psychological status, patients' needs, and QOL, although the current study design did not reveal causality between AN and these factors. In particular, the significant association between AN and the global score for QOL after adjustments for several biomedical and psychosocial variables suggests that the management of AN might contribute to providing a better QOL. In addition, to the best of our knowledge, this is the first study to address the association between AN and patients' perceived needs. Because patients' perceived needs reflect the actual necessity of help, a significant association between AN and multiple dimensions of patients' needs suggest a potentially serious impact of AN on the daily lives of patients. Considering that once AN occurs it usually does not spontaneously diminish, and in view of the potential impact of AN on patient outcomes, AN should not be neglected in current clinical oncology practice. In addition, as very few studies have investigated the impact of AN on QOL, more studies, especially longitudinal prospective studies, are needed.

Although it was not the principal purpose of our study, we would like to discuss management strategies for AN. Needless to say, considering the mechanism for the development to AN, controlling CINV itself is likely the most relevant issue for preventing AN.[9] However, the present study, as well as previous studies, indicate that a not negligible number of patients still suffer from AN. Several management strategies for alleviating AN, especially psychobehavioral interventions, including cognitive distraction, hypnosis, relaxation, and systematic desensitization, have been suggested, but evidence-based systematic reviews suggest that only systematic desensitization can be ''tentatively recommended'' for the management of AN among adult cancer patients.[9,31,32] However, the use of systematic desensitization remains difficult to implement because most patients are treated in a setting where the necessary expertise is not available.[9] These facts strongly suggest the need to develop novel brief interventions for reducing AN.

The present study has several limitations. First, the investigation was cross-sectional in design, precluding any conclusions from being made with regard to causality. Second, although we used part of the MANE to assess AN, the lack of rigorous psychometric evaluation might be a problem. For example, the sensitivity and specificity of this tool for detecting AN as well as the applicability of the MANE to Japanese populations have not been clearly shown. Third, as the present study was carried out at one institution, an institutional bias might exist. Fourth, because we focused on AN only, the findings regarding anticipatory vomiting were lacking. Finally, because this study focused on ambulatory cancer patients attending the outpatient oncology unit and did not include patients undergoing chemotherapy in an inpatient setting, such as the numerous cancer patients who must undergo highly emetogenic chemotherapy regimens, particularly those including cisplatin, for the treatment of lung, esophagus, and head and neck cancer, and because a sampling bias was observed (i.e., the participants were younger than the decliners), the results might not be applicable to patients in other clinical oncology settings, especially

among inpatients and/or elderly patients. In addition, while AN generally occurs prior to the fourth chemotherapy cycle,[1] the sampling method of the current study (the subjects were randomly selected consecutive patients who had undergone chemotherapy at least once) might have produced another sampling bias.

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