

ORIGINAL

Effects of chemotherapy on quality of life and night-time sleep of colon cancer patients

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Abstract : Background : The aim of this study was to investigate quality of life (QOL) and night-time sleep disturbance in colon cancer patients with middle risk chemotherapy for proper antiemetic therapy. **Methods :** The study enrolled 139 patients with colorectal cancer. All patients received oxaliplatin or irinotecan-based chemotherapy. Patients completed a questionnaire about chemotherapy-induced nausea and vomiting and sleep disturbance. Sleep disturbance was checked, and the relationship between sleep disturbance and nausea was analyzed. **Results :** The prevalence of nausea was 48.9% (68/139). The degree of the nausea was slight/moderate/severe in 51/11/6 patients, and 12 patients had vomiting. Appetite showed no change/slightly decreased/half/one-fourth/none in 51/34/33/6/7 patients. There were significant differences in the mental component summary (MCS) score and the role-social component score (RCS). (MCS : nausea(+) vs nausea(-) 46.4 ± 1.1 vs 54.1 ± 1.1 p < 0.01 RCS : nausea(+) vs nausea(-) 33.1 ± 2.1 vs 41.6 ± 2.1 p < 0.01). Using the MCS with a cut-off score of 50, patients were divided into two groups, and nausea was significantly correlated with a low MCS score. Furthermore, patients were divided into two groups using a Pittsburgh Sleep Quality Index cut-off score of 6, and sleep disturbance was correlated with old age and second-line chemotherapy. **Conclusions :** Nausea affects QOL and night-time sleep of colon cancer patients with middle risk chemotherapy. *J. Med. Invest.* 67:338-342, August, 2020

Keywords : Chemotherapy, QOL, Sleep disturbance

INTRODUCTION

Nausea and vomiting are frequent adverse events of cancer chemotherapy. Persistent nausea and vomiting are accompanied by decreased food and fluid intake, leading to dehydration, electrolyte abnormalities, weight loss, poor nutrition etc., which markedly decrease the patient's quality of life (QOL). Therefore, it is very important to control and minimize nausea and vomiting to enable continuation of cancer chemotherapy (1).

Despite the use of antiemetic prophylaxis, cancer patients experience significant chemotherapy-induced nausea and vomiting during 30% to 45% of cycles, which reduces their QOL. Among the risk factors for chemotherapy-induced nausea and vomiting (CINV), younger age, female sex, low alcohol consumption, and pregnancy-associated emesis or motion sickness are the commonly cited patient-related factors.

A few studies have suggested an association between sleep disturbance and CINV (2). The gastrointestinal system is closely linked with the central nervous system. A community study showed that overall gastrointestinal symptoms including nausea are related to sleep disturbances (3). Another study showed that nausea is associated with anxiety and depression. In the case of

motion sickness, sleep deprivation can enhance susceptibility. Therefore, sleep and mood can be related to CINV. Moreover, since depression is prevalent in cancer patients, insomnia is three times more common than the 7.0% to 9.5% rate in the general population (4).

Whereas the development of antiemetic guidelines has helped to control the level of chemotherapy-induced vomiting (CIV), advances in the treatment of chemotherapy-induced nausea (CIN) are more limited. Moreover, CIN has a greater negative effect on patients' daily lives than CIV (3). In this regard, it would be helpful to assess the physiological and psychological factors associated with CIN and CIV in a relatively homogeneous study sample.

The aim of this study was to investigate QOL and night-time sleep of colon cancer patients with middle risk chemotherapy for proper antiemetic therapy.

PATIENTS & METHODS

Study Design and Setting

An open, multicenter, prospective, observational study was conducted in 11 general hospitals on Shikoku island in Japan. The protocol was approved by the clinical research ethics committees of all participating centers (TOCMS #1861). This study was conducted from April 2014 to March 2017. Clinical staff approached potentially eligible patients with colon cancer who visited individual departments. All participants provided written, informed consent.

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Patient Selection Criteria

The study enrolled 139 patients aged 35 to 89 years old with colorectal cancer. All patients received oxaliplatin or irinotecan-based chemotherapy. There were no specific eligibility criteria.

Patients' characteristics

The mean age of the patients was 64 (35-89) years, and there were 97 male and 42 female patients. Concerning the chemotherapy, 90 patients received first-line chemotherapy (oxaliplatin/irinotecan/both : 93/43/3). For antiemetic prophylaxis, a 5-HT₃, granisetron in 48 patients and palonosetron in 91 patients, was used. Aprepitant was used in 101 patients and not used in 38 patients. Stage was II/III/IV in 19/42/78 patients (Table 1).

Table 1. Patient's characteristics

Factor	n=139
Age	64 (35-89)
Gender (M/F)	97/42
Line (first/beyond second)	90/49
Regimen (Oxaliplatin/Irinotecan/Both)	93/43/3
5-HT ₃ (Granisetron/Palonosetron)	48/91
Aprepitant (+/-)	101/38
Stage (II/III/IV)	19/42/78

Data Collection

Patients who agreed to participate in the study completed a questionnaire about CINV and sleep disturbance and returned it at their next clinical visit. The questionnaires were sent to the University of Tokushima and analyzed. Clinical data (cancer stage and treatments received) were obtained from a review of medical records.

Nausea, Vomiting, and Appetite loss

Nausea and vomiting were evaluated using self-assessed questionnaires. Nausea was considered present if a symptom of nausea was present, and vomiting was considered present if there was vomiting over a period of 7 days. Appetite loss was considered present if there was "half of intake compared with ordinary oral intake", "one-fourth compared with ordinary oral intake", or "Hard to take water and meals".

QOL

QOL was evaluated using the SF-36v2, and low QOL was defined as a total score lower than the national standard.

SF-36v2

The Optum SF-36v2 Health Survey asks 36 questions to measure functional health and well-being from the patient's perspective. It is a practical, reliable, and valid measure of physical and mental health that can be completed in five to ten minutes. We refer to it as a generic health survey because it can be used across ages (18 and older), diseases, and treatment groups, as opposed to a disease-specific health survey, which focuses on a particular condition or disease. Meaningful to patients, clinicians, researchers, and administrators across the health care spectrum, the SF-36v2 has a variety of applications including : 1. measuring health improvement or decline ; 2. predicting medical

expenses ; 3. assessing treatment effectiveness ; and 4. comparing disease burden across populations.

The SF-36v2 provides scores for each of the eight health domains and psychometrically-based physical component summary (PCS) and mental component summary (MCS) scores. Since the survey uses norm-based scoring, comparisons can be made with the other generic health surveys (SF-12v2 and SF-8). A preference-based utility index, called the SF-6D, is also available to help understand economic benefit. Multiple modes of administration are offered, including online, PDA, and more. The SF-36v2 is available in more than 170 translations for both standard four-week and acute one-week recall periods. This questionnaire consists of Physical functioning, Role physical, Bodily pain, General health, Vitality, Social functioning, Role emotional, and Mental health scores (5).

Sleep-Related Factors

Sleep quality and disturbance were assessed using the Pittsburgh Sleep Quality Index (PSQI), and a cut-off value of 6 was used to define significant poor sleep quality, which has been suggested for physically ill patients (6). The evaluation was done 7 days after the beginning of chemotherapy.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a self-administered questionnaire to assess subjective sleep quality during the previous month. The self-rated items of the PSQI generate seven component scores (range of subscale scores, 0-3) : sleep quality ; sleep latency ; sleep duration ; habitual sleep efficiency ; sleep disturbance ; use of sleeping medication ; and daytime dysfunction. The sum of these seven component scores yields one global score of subjective sleep quality (0-21), with higher scores representing poorer subjective sleep quality. The psychometric properties of the PSQI have been confirmed by previous studies (7).

Data Analysis

Bivariate correlations among nausea, vomiting, and sleep-related factors were evaluated. Univariable logistic regression analyses were conducted to examine variables associated with nausea and sleep disturbance. Statistical analyses were carried out using the JMP 10 statistical software package (SAS Institute Inc, Tokyo, Japan). Student's *t*-test was used to compare continuous variables. A P-value of less than 0.05 was considered significant.

RESULTS

Prevalence of nausea, vomiting, and appetite loss

The prevalence of nausea was 48.9% (68/139). The degree of the nausea was slight/moderate/severe in 51/11/6 patients, and 12 patients reported vomiting. Appetite showed no change/slightly decreased/half/one-fourth/none in 51/34/33/6/7 patients.

QOL

The SF-36v2 consists of 8 parts, and the physical components consist of physical functioning, role physical, and bodily pain. The mental factor consists of role emotional and mental health. Both physical and mental factors consist of social functioning, general health perceptions, and vitality. For the physical component summary (PCS) score, mental component summary (MCS) score, and the role-social component score (RCS), there was a significant difference in the MCS and RCS scores (Figure 1) (MCS : nausea(+) vs nausea(-), 46.4 ± 1.1 vs 54.1 ± 1.1 *p* < 0.01 ; RCS : nausea(+) vs nausea(-), 33.1 ± 2.1 vs 41.6 ± 2.1 *p* < 0.01).

Sleep disturbance

Although there was no significant difference, there was a possible correlation between sleep disturbance and nausea (Figure 2).

Risk Factors for QOL and sleep disturbance

With an MCS cut-off score of 50, the patients were divided into two groups, and nausea was significantly correlated with a low MCS score (Table 2). Furthermore, patients were divided into two groups by a PSQI cut-off score of 6, and sleep disturbance was correlated with old age and second-line chemotherapy. Nausea was correlated with sleep disturbance, but it was not significant (Table 3).

Effect of antiemetic prophylaxis

There was no significant difference in the prevention of nausea and vomiting with and without aprepitant.

Component summary score

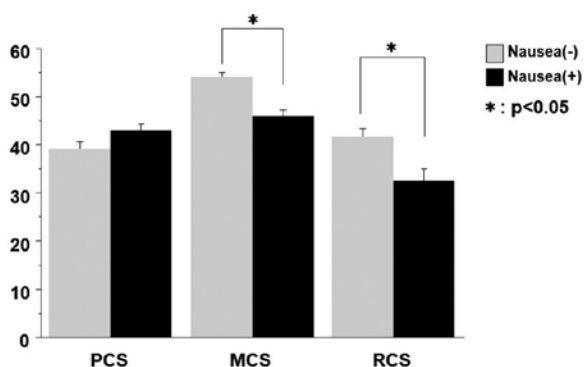


Figure 1. The effect of nausea on the component summary scores : physical component summary (PCS), mental component summary (MCS), and role-social component score (RCS).

PSQI score

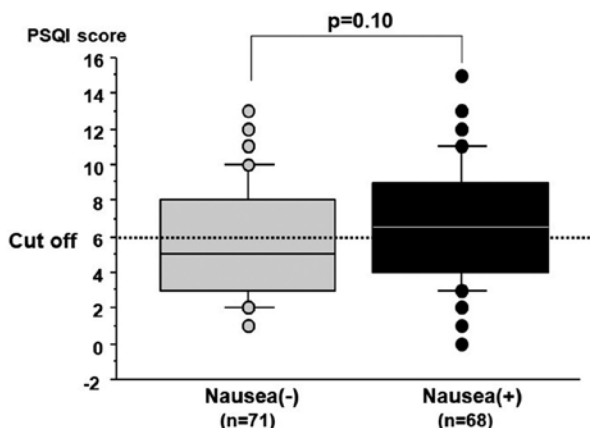


Figure 2. The effect of nausea on night-time sleep (PSQI score).

Table 2. Disturbance factor of MCS

Factor	MCS		p value	
	< 50 (n=64)	> 50 (n=75)		
Age	63.5	65.3	n.s.	
Gender	M/F	41/23	56/19	n.s.
Line	First/Second	45/19	45/30	n.s.
Nausea	yes/no	43/21	25/50	< 0.01
Vomit	yes/no	9/42	3/49	0.06
Apreptant	yes/no	44/20	57/18	n.s.

Table 3. Disturbance factor of night sleep

Factor	PSQI		p value	
	< 6 (n=69)	> 6 (n=70)		
Age	62.4	66.5	< 0.05	
Gender	M/F	50/19	47/23	n.s.
Line	First/Second	48/21	38/32	< 0.05
Nausea	yes/no	29/40	39/31	0.1
Vomit	yes/no	7/40	5/51	n.s.
Apreptant	yes/no	49/20	52/18	n.s.

DISCUSSION

The present study showed that the incidence of nausea was 48.9%, but about 75% of it was low grade. Furthermore, the incidence of vomiting was about 10%. Despite the administration of optimal antiemetic prophylaxis, appetite loss (half or more) was observed in about 35% of patients. Nausea was found to be positively correlated with the MCS and RCS scores, and nausea had a negative effect on sleep. A low MCS score was significantly correlated with nausea. The factors associated with poor nighttime sleep were older age (>70 years old) and chemotherapy line (more than second-line).

The associations between the presence of nausea and MCS and RCS scores were remarkable, and the prevention of nausea is very important to maintain the QOL of patients on chemotherapy. Interestingly, the present study showed a strong negative impact on patients' QOL with the presence of significant nausea or vomiting and their duration. In the present study, nausea had a higher impact on patients' QOL than vomiting, and nausea had a negative effect not only on the MCS, but also on the RCS. This finding is crucial, because one of the goals of chemotherapy regimens is to maximize the doses, albeit with shorter duration regimens (8). Therefore, the duration of CINV should be taken into account when antiemetic prophylactic treatment is prescribed. As shown in the present study, the development of significant nausea has an important negative impact on patients' QOL.

The present study examined the relationship between sleep and nausea in colorectal cancer patients. It was found that nausea was related to poor sleep quality, although not significantly, especially for elderly patients and patients with over second-line chemotherapy. Doctors who treat patients with chemotherapy take every effort to reduce the incidence of nausea. Prevention of nausea improves the quality of sleep and furthermore increases the QOL of patients on chemotherapy. As far as we are aware, few reports have examined sleep and nausea in colorectal cancer patients. In breast cancer patients, poor sleep quality was

associated with CINV after the first cycle of chemotherapy. Because an emesis response in the previous cycle is the strongest risk factor for CINV (9), clinicians should emphasize the management of poor sleep quality before a vicious cycle starts.

The association between poor sleep quality and CINV may be alternatively explained by autonomic nervous system (ANS) dysfunction. Greater reactivity and arousal of the ANS have been reported in individuals with insomnia (10). Insomnia-related ANS arousals were demonstrated as decreased high-frequency power and increased low-frequency power in heart rate variability analyses (11). Similarly, chemotherapy-induced adverse effects including CINV and fatigue are reportedly related to increased activity and/or reactivity of the ANS. The present study showed that age and chemotherapy regimen line were predictors of sleep disturbance. In addition to the fact that sleep problems are more frequent in cancer patients, younger age and female sex are predisposing factors for insomnia (12-14). On the other hand, in the general population, older age is a predisposing factor for insomnia. Thus, the risk factors are controversial.

With respect to sleep disturbances, there are various aberrations that can occur in, for example, including total sleep time, sleep-onset latency, nocturnal awakenings, and wake time after sleep onset, as well as daytime napping with a circadian rhythm perceived sleep disturbance and use of sleep aids. The detailed reasons for a sleep disturbance should always be investigated (15).

Because newer agents such as aprepitant are not always effective at controlling CINV, olanzapine, a serotonin-dopamine receptor antagonist, has been suggested as a treatment for CINV. A recent study showed that olanzapine improved global health status, emotional functioning, and insomnia in cancer patients, in part by reducing the incidence of delayed CINV. The present study showed that poor sleep quality was significantly associated with CINV. Another psychiatric medication, mirtazapine, a noradrenergic and specific serotonergic antidepressant, improves symptoms of nausea and insomnia in cancer patients (16). Sedative effects of olanzapine and mirtazapine might help the sleep problem to prevent CINV, in addition to stimulating appetite. These psychoactive drugs may act through receptors other than serotonin 5-HT₃, such as histamine-1 or serotonin 5-HT_{2C}. As there was a significant difference concerning chemotherapy line between PSQI score, the treatment with olanzapine and mirtazapine may be considered from the first line.

First, patients feel the nausea, the nausea affects sleep, and the disturbance of sleep affects the patient's mood. As a result, the incidence of nausea will increase. To break the vicious cycle, antiemetic prophylaxis is important (17, 18).

The use of aprepitant as secondary antiemetic prophylaxis for patients with oxaliplatin-based chemotherapy was effective. Aprepitant could be used as salvage antiemetic therapy in colorectal cancer patients receiving oxaliplatin-based chemotherapy. However, aprepitant did not contribute to decreasing the incidence of nausea and vomiting. In a previous study, aprepitant had a positive effect to prevent nausea. This was an observational study, it was not performed as a randomized, controlled study, the number in each group was different, and so on, resulting in no significant difference with aprepitant use (1).

The present study has several limitations. First, this study was performed with a single arm, and the number of patients enrolled was too small. Second, the period of the questionnaire was only 7 days and at only one point in time. Third, although the psychological condition affects this result, we didn't check the patient's psychological condition. Finally, this study was conducted in several institutions with different chemotherapy regimens, and chemotherapy regimens may have an effect.

CONCLUSION

Nausea affects the QOL and night-time sleep of colon cancer patients with middle risk chemotherapy, so that proper antiemetic therapy is needed.

CONFLICT OF INTEREST STATEMENT

Mitsuo Shimada received a research grant from Ono pharma, Chugai pharma and Taiho pharma. The other authors declare that they have no conflict of interest.

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None

COMPLIANCE WITH ETHICAL STANDARDS

This study was approved by The Ethics Committee of the Tokushima University Hospital, and patient information was obtained from their medical records [Approval number : 1861].

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

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