The Effect of Temperament on the Association Between Pre-treatment Anxiety and Chemotherapy-Related Symptoms in Patients With Breast Cancer

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Objective   Pre-treatment anxiety (PA) before chemotherapy increases complaints of chemotherapy-related symptoms (CRS). The results on the association have been inconsistent, and the effect of temperament remains unclear. We aimed to determine whether PA is a risk factor for CRS and the effect of differing temperaments on CRS.

Methods   This prospective study comprised 176 breast cancer patients awaiting adjuvant chemotherapy post-surgery. We assessed CRS, PA, and temperament using the MD Anderson Symptom Inventory (MDASI), the Hospital Anxiety and Depression Scale, and the short form of the Temperament and Character Inventory-Revised, respectively. The MDASI was re-administered three weeks after the first chemo-cycle.

Results   PA showed weak positive correlation with several CRS after the first cycle; no CRS was significantly associated with PA when pre-treatment depressive symptoms and baseline CRS were adjusted in multiple regression analysis. Moderation model analysis indicated that the PA effect on several CRS, including pain, insomnia, anorexia, dry mouth, and vomiting, was moderated by harm avoidance (HA) but not by other temperament dimensions. In particular, PA was positively associated with CRS in patients with low HA.

Conclusion   The results in patients with low HA indicate that more attention to PA in patients with confident and optimistic temperaments is necessary.   **Psychiatry Investig 2022;19(11):949-957**

Keywords   Anxiety; Breast cancer; Chemotherapy-related symptoms; Harm avoidance; Temperament.

INTRODUCTION

Chemotherapy-related symptoms (CRS) have a critical effect on the daily functioning and quality of life in patients with cancer during chemotherapy[1] and can lead to non-adherence of burdening treatments.[2] Particularly, chemotherapy-induced gastrointestinal symptoms such as vomiting, nausea, and loss of appetite are the most frequent and distressing symptoms despite advances in antiemetic treatments.[1,3] Sleep problems have also been frequently observed alongside fatigue and de-

pression throughout all chemotherapy phases.[4-6]

Previous research has attempted to identify patients vulnerable to CRS to facilitate early intervention. Anxiety, which tends to be at its most intense prior to starting the first chemotherapy cycle,[7-9] has been repeatedly associated with CRS complaints as a psychological and emotional risk factor for CRS. High anticipatory anxiety toward chemotherapy and anxious preoccupation with cancer just before or during one week prior to initiating chemotherapy elevate the possibility of CRS complaints.[10-12] Longitudinal studies have reported that anxiety traits measured before cancer diagnosis are an important predictor for CRS such as sleep problem, fatigue, and poor health-related quality even at 1−2-year follow-up after completing treatment.[13,14]

However, studies that have aimed to determine the association between pre-treatment anxiety (PA) before chemotherapy and CRS have reported inconsistent findings. According to Molassiotis et al.,[15] neither anxiety state nor anxiety traits before chemotherapy were a significant risk factor for nausea and vomiting after controlling for other demographic and treatment-related factors. Watson et al.[9] also found that baseline psychological variables and anxiety traits measured during the week prior to the first cycle were not significantly predictive of CRS, whereas previous experience of nausea and vomiting was an overwhelming influencing factor. Considering these inconsistencies between results of previous studies, PA in itself appears insufficient to cause CRS; thus, the effect could change according to other stable individual traits such as temperament or personality.

This study aimed to determine whether PA experienced by patients during a waiting period prior to forthcoming chemotherapy significantly affected complaints of CRS and whether the effect would differ depending on individual temperament. Few studies have investigated the role of various temperament dimensions involving patients with cancer in predicting an association between PA and CRS. Based on previous studies, we hypothesized that an anxious temperament would affect this association.

METHODS

Study design and setting

This study was a secondary analysis of data from a prospective longitudinal study that had been conducted to investigate the effect of circadian genes on sleep-related factors in patients with breast cancer who had received chemotherapy. Participants in our study were enrolled between February 2012 and May 2014 at the Seoul National University Hospital, a tertiary general hospital in Seoul, Republic of Korea. Inclusion criteria comprised women with non-metastatic breast cancer aged 18−

70 years-awaiting adjuvant chemotherapy after having undergone surgery. We excluded patients who had been diagnosed with other types of cancer within the last five years (except thyroid cancer), and those with other significant medical conditions. Patients with a >1-month history of psychiatric treatment were also excluded due to the possibility of psychiatric disorders and psychotropic medications affecting the circadian rhythm.

Participants were recruited during their visit to the oncology outpatient clinic to plan adjuvant chemotherapy, which was 3−4 weeks after they had undergone a total mastectomy or breast conserving surgery. All patients were scheduled to receive outpatient chemotherapy every three weeks, with the first cycle typically scheduled to start within 1−2 weeks. Patients who met the inclusion criteria were provided with detailed information on the study, and informed consent was obtained from every participant. Baseline data were collected during the chemotherapy waiting period of 1−2 weeks, which ranged from the day chemotherapy was specifically planned to just prior to starting chemo-administration on the first cycle day. The participants completed questionnaires, including demographic and clinical information, and a series of scales to assess temperament, CRS, and emotional distress such as PA and depressive symptoms prior to starting chemotherapy. CRS and emotional distress were re-assessed three weeks after the first chemotherapy cycle.

A total of 213 women with breast cancer were enrolled at baseline. To increase participant homogeneity, the following patients were excluded: 1) six patients who received a non-highly emetogenic drug combination; 2) 15 patients who were administered goserelin, which suppresses ovarian functioning during chemotherapy and could affect CRS; 3) 15 patients with a history of recent medical conditions (orthopedic, neurological, endocrinological, and ophthalmological); and 4) one patient who declined to be followed up. Finally, data concerning 176 eligible participants were evaluated for our study. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. H-1105-092-363). The clinical trial registration number is NCT 01887925 (www.ClinicalTrials.gov).

Measures

Chemotherapy-related symptoms

The Korean version of the MD Anderson Symptom Inventory (MDASI) was used to assess CRS.[16] The MDASI is a 10-point self-reported scale that includes 13 core symptoms used to measure the severity of symptoms most commonly experienced in cancer treatment and six interference items to assess the effect on daily functioning.[17] A previous study demonstrated that

at least a 1.12 difference in scores on an MDASI scale was considered a significant change.[17] A score ≥3 for each scale has previously been used as the cut-off.[18] In our analysis, 12 core symptom measures were included, except for an item assessing sadness, to avoid the redundancy of measuring depression.

Anxiety and depression

The Korean version of the Hospital Anxiety and Depression Scale (HADS) was used to assess psychological distress before chemotherapy as a risk factor for CRS.[19,20] HADS was developed and has been used intensively to identify anxiety disorder and depression among nonpsychiatric patients in hospital settings.[19,21] All physical symptoms of anxiety or depression were not included in the scale to prevent noise from somatic disorders on the scores.[21] HADS comprises two self-rated subscales to measure anxiety (HADS-A) and depressive symptoms (HADS-D). Each subscale consists of seven items assessed on a four-point Likert scale, and the total score of the subscale ranges from 0 to 21.[19] A score ≥8 for each scale has previously been reported to be an appropriate cut-off score at the clinical level.[20,21]

Temperament

Temperament was assessed using the Korean version of the short form of the Temperament and Character Inventory (TCI)-Revised, which comprises 140 items assessed on a five-point Likert scale.[22,23] TCI measures four temperaments and three-character dimensions, based on Cloninger's psychobiological model for personality.[24] The temperament dimensions are "novelty seeking" (NS), "harm avoidance" (HA), "reward dependence" (RD), and "persistence" (P); each temperament measure has 20 or 21 items. In Cloninger's model,[24] each temperament is presumed to have underlying separate neurochemical and neuroanatomical mechanisms and produce an automatic emotional response to external stimulus. NS is related to the behavioral activation system and excitement-seeking behavior. HA involves a heritable bias toward pessimistic worry and fear of uncertainty, resulting in inhibited behavior to avoid anticipating harm and punishment. RD is regarded as a bias toward behavior that is rewarded with social approval, and P is regarded as perseverance despite frustration and fatigue. Previous empirical studies have reported that HA is an inherited stable individual difference, and that vulnerability remains even after an anxiety disorder has been treated.[25-27] Depressive states have been shown to significantly affect the scores.[28,29]

Statistical analyses

Descriptive statistics were used to present demographic and clinical characteristics. Pearson's correlation was performed to examine univariate associations among the MDASI, HADS,

and TCI variables. Hierarchical regression analysis was employed to examine the effect of PA on CRS; each temperament variable was tested in a moderation model using the Hayes Process Macro in SPSS.[30] In moderation analyses, all continuous variables were mean-centered for multicollinearity.[31] Referring to previous studies on risk factors for CRS, we adjusted for depressive symptoms (HADS-D) and CRS (MDASI) at baseline as covariates in all regression models. Other demographic and clinical characteristics such as age, education level, and disease stage were not included in this analysis because they were not significantly associated with CRS in the analysis of variance. IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA) was utilized for all analyses.

RESULTS

Participant characteristics

The sociodemographic and clinical characteristics of 176 women with breast cancer are presented in Table 1. The mean participant age was 47 years, and most women had early-stage cancer (stage II, approximately 55%; stage I, 33%). Approximately 70% of participants had undergone breast-conserving surgery, and the remaining participants had undergone total mastectomy. All participants were due to receive anthracycline-based treatment as the first cycle of adjuvant chemotherapy. No participants were prescribed psychotropic medication during the study period.

Intercorrelation among study variables and tests on the main effect of pre-treatment anxiety on chemotherapy-related symptoms

Table 2 presents the intercorrelation for the study variables. There was a positive but weak association between PA and several CRS such as pain (r=0.22, p<0.01), fatigue (r=0.24, p<0.01), nausea (r=0.16, p<0.05), insomnia (r=0.34, p<0.01), distress (r=0.38, p<0.01), shortness of breath (r=0.23, p<0.01), difficulty remembering (r=0.33, p<0.01), drowsiness (r=0.16, p<0.05), and numbness (r=0.21, p<0.01). All the above symptoms, except for drowsiness, also correlated weakly with pre-treatment depressive symptoms. Among the four temperament dimensions, only HA was significantly positively correlated with PA (r=0.51, p<0.01) and pre-treatment depressive symptoms (r=0.56, p<0.01). No associations were found among the temperament dimensions and CRS, other than a weak correlation between a few CRS and HA or NS. All CRS were correlated significantly with one another.

In subsequent hierarchical regression analysis, when controlling for pre-treatment depressive symptoms and CRS at baseline as covariates, no CRS were significantly associated with PA; i.e., the main effect of PA on CRS was not observed.

Table 1. Sociodemographic and clinical characteristics of the participants at baseline (N=176)

Characteristic	Value
Age (yr)	47.06±7.16
Age, ≥50 yr	68 (38.6)
Height (cm)	158.63±5.18
BMI (kg/m^2)	23.14±2.82
BMI ≥23 kg/m^2	86 (48.9)
Married	152 (86.4)
College graduates or higher	87 (49.4)
Working	29 (16.5)
Clinical stage of cancer	
I	59 (33.5)
II	97 (55.1)
III	19 (10.8)
ER/PR/HER2 status	
ER positive	128 (72.7)
PR positive	111 (63.1)
HER2 positive	93 (52.8)
Adjuvant chemotherapy regimens	
Fluorouracil-doxorubicin-cyclophosphamide (6 cycles)	100 (56.8)
Doxorubicin-cyclophosphamide (4 cycles)+ docetaxel (4 cycles)	76 (43.2)
Surgery	
Breast-conserving surgery	122 (69.3)
Total mastectomy	54 (30.7)
HADS-D	6.77±3.64
Not depressed	103 (58.5)
Depressed	73 (41.5)
HADS-A	6.56±3.77
Not anxious	116 (65.9)
Anxious	60 (34.1)

Values are presented as mean±standard deviation or number (%). BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; HADS-D, Hospital Anxiety and Depression Scale-Depression; HADS-A, HADS-Anxiety

Tests on the moderating effect of temperament on the association between pre-treatment anxiety and chemotherapy-related symptoms

In further moderation model analysis, the effect of PA on each CRS was moderated by HA temperament only. There were significant interaction effects between PA and HA with respect to pain (B=-0.0104, t=-2.6513, p=0.009), insomnia (B=-0.0119, t=-2.8994, p=0.004), anorexia (B=-0.0131, t=-2.9320, p=0.004), dry mouth (B=-0.0104, t=-2.5876, p=0.011), and vomiting (B=-0.0135, t=-2.7944, p=0.006) (Table 3). Sim-

ple slope tests were conducted at one standard deviation (SD) above and below the mean of HA. For low HA, PA had a significant positive association with CRS such as pain (simple slope=0.23, t=2.69, p=0.008), insomnia (simple slope=0.29, t=3.29, p=0.001), anorexia (simple slope=0.22, t=2.41, p=0.017), dry mouth (simple slope=0.22, t=2.56, p=0.011), and vomiting (simple slope=0.22, t=2.22, p=0.028), whereas the slopes were not significant for high HA (Figure 1).

DISCUSSION

This study examined the effect of PA on complaints of CRS after the first chemotherapy cycle and its interactive association with various temperament dimensions derived from Cloninger's model of personality,[24] including NS, HA, RD, and P. We assessed 176 patients with breast cancer receiving anthracycline-based adjuvant chemotherapy. The study results indicated that PA was positively but weakly correlated with most CRS; no CRS was directly associated with PA when adjusting for pre-treatment depressive symptoms and CRS at baseline. On further analysis, we found that only HA moderated the effect of PA on CRS.

First, our findings indicated that PA was not a significant predictor for CRS after controlling for pre-treatment CRS and depression, although PA had a weak positive correlation with CRS. A study by Dranitsaris et al.[32] aimed to develop a tool to identify risk factors for nausea and vomiting. The multivariate analyses included a large sample pool and various potential risk factors; however, the PA level was not found to be a significant predictor for CRS. The inconsistent results among studies[9-12,15,32] could have resulted from other significant risk factors for CRS that may not have been controlled for. In particular, pre-treatment CRS or a history of symptoms have been repeatedly found to be among the most important risk factors for CRS.[15,32] We conducted additional regression analyses without covariates such as pre-treatment CRS and depressive symptoms at baseline and most CRS (except some gastrointestinal symptoms such as anorexia, vomiting, and dry mouth) were predicted by PA. Thus, it could be concluded that the direct effect of PA on CRS was generally insignificant under the condition that the effect of pre-treatment CRS was ruled out; however, there would be differences depending on the type of CRS.

Subsequently, we found that PA affected several important CRS, including pain, insomnia, anorexia, dry mouth, and vomiting, depending on HA temperament. A simple slope test showed that in low HA, the greater the PA patients complained of experience before chemotherapy, the more the CRS they complained of after chemotherapy. Moreover, PA was not a significant predictor of CRS in patients with high HA. These results showed that patients with low HA who could be regarded as

Table 2. Intercorrelations among study variables (N=176)

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1. PA																		
2. Pre-treatment depression	0.74**																	
3. NS	0.05	-0.02																
4. HA	0.51**	0.56**	-0.12															
5. RD	0.01	-0.11	0.19*	-0.32**														
6. P	0.02	0.01	-0.03	-0.03	0.05													
7. Pain	0.22**	0.22**	0.09	0.10	-0.02	-0.10												
8. Fatigue	0.24**	0.25**	0.02	0.14	-0.14	0.03	0.74**											
9. Nausea	0.16*	0.16*	0.04	0.08	-0.06	-0.01	0.63**	0.67**										
10. Insomnia	0.34**	0.32**	-0.01	0.12	0.01	-0.10	0.57**	0.68**	0.64**									
11. Distress	0.38**	0.40**	0.07	0.18*	0.03	0.02	0.62**	0.63**	0.58**	0.63**								
12. Shortness of breath	0.23*	0.26*	0.04	0.16*	-0.08	-0.05	0.75**	0.67**	0.68**	0.55**	0.59**							
13. Difficulty remembering	0.33**	0.39**	0.20**	0.21**	-0.05	-0.01	0.57**	0.60**	0.51**	0.53**	0.63**	0.62**						
14. Anorexia	0.13	0.12	0.06	0.07	-0.01	0.04	0.63**	0.61**	0.75**	0.61**	0.61**	0.66**	0.52**					
15. Drowsiness	0.16*	0.15	0.14	0.08	0.07	-0.00	0.60**	0.62**	0.60**	0.43**	0.57**	0.58**	0.52**	0.63**				
16. Dry mouth	0.13	0.11	0.10	0.07	0.04	-0.01	0.69**	0.62**	0.68**	0.57**	0.61**	0.66**	0.57**	0.71**	0.68**			
17. Vomiting	0.12	0.15*	0.02	0.04	0.02	-0.09	0.53**	0.46**	0.79**	0.55**	0.54**	0.61**	0.39**	0.67**	0.58**	0.58**		
18. Numbness	0.21**	0.27**	0.13	0.15*	-0.14	0.00	0.68**	0.64**	0.61**	0.52**	0.52**	0.69**	0.61**	0.56**	0.58**	0.57**	0.62**	

*p<0.05; **p<0.01. PA, pre-treatment anxiety; NS, novelty seeking; HA, harm avoidance; RD, reward dependence; P, persistence

**Table 3.** Regression results of the moderating effect of HA on the relationship between PA and CRS (N=176)

Variable	B	SE	t	p	LL 95% CI	UL 95% CI
Pain						
Constant	1.0542	0.5663	1.8951	0.060	-0.0439	2.1523
PA	0.1166	0.0707	1.6490	0.101	-0.0230	0.2561
HA	-0.0173	0.0200	-0.8663	0.388	-0.0569	0.0222
PA*HA	-0.0104	0.0039	-2.6513	0.009	-0.0181	-0.0026
Pre-treatment pain	0.3457	0.0684	5.0505	<0.001	0.2106	0.4808
Pre-treatment depression	0.0331	0.0755	0.4377	0.662	-0.1160	0.1821
Insomnia						
Constant	1.5078	0.5746	2.6241	0.010	0.3735	2.6420
PA	0.1640	0.0753	2.1780	0.031	0.0154	0.3126
HA	-0.0207	0.0212	-0.9796	0.329	-0.0625	0.0211
PA*HA	-0.0119	0.0041	-2.8994	0.004	-0.0200	-0.0038
Pre-treatment insomnia	0.5029	0.0764	6.5846	<0.001	0.3521	0.6536
Pre-treatment depression	0.0507	0.0797	0.6361	0.526	-0.1067	0.2081
Anorexia						
Constant	2.0262	0.6240	3.2471	0.001	0.7944	3.2581
PA	0.0840	0.0807	1.0403	0.300	-0.0754	0.2434
HA	-0.0083	0.0228	-0.3633	0.717	-0.0533	0.0367
PA*HA	-0.0131	0.0045	-2.9320	0.004	-0.0219	-0.0043
Pre-treatment anorexia	0.4992	0.1052	4.7436	<0.001	0.2915	0.7069
Pre-treatment depression	-0.0225	0.0859	-0.2617	0.794	-0.1920	0.1470
Dry mouth						
Constant	2.0565	0.5714	3.5990	<0.001	0.9285	3.1845
PA	0.1098	0.0731	1.5023	0.135	-0.0345	0.2540
HA	-0.0001	0.0207	-0.0067	0.995	-0.0410	0.0407
PA*HA	-0.0104	0.0040	-2.5876	0.011	-0.0184	-0.0025
Pre-treatment dry mouth	0.4478	0.0875	5.1201	<0.001	0.2752	0.6205
Pre-treatment depression	-0.0064	0.0773	-0.0834	0.934	-0.1589	0.1461
Vomiting						
Constant	0.9973	0.6779	1.4713	0.143	-0.3408	2.3355
PA	0.0757	0.0876	0.8649	0.388	-0.0971	0.2486
HA	-0.0226	0.0248	-0.9086	0.365	-0.0716	0.0265
PA*HA	-0.0135	0.0048	-2.7944	0.006	-0.0231	-0.0040
Pre-treatment vomiting	0.2688	0.1577	1.7047	0.090	-0.0425	0.5801
Pre-treatment depression	0.1182	0.0924	1.2793	0.203	-0.0642	0.3006

Unstandardized regression coefficients are reported. Bootstrap sample size=5,000. PA, pre-treatment anxiety; HA, harm avoidance; CRS, chemotherapy-related symptoms; SE, standard error; LL, lower limit; CI, confidence interval; UL, upper limit

having optimistic and confident personalities were more susceptible to negative emotional states than those with high HA who could be considered apprehensive and vulnerable to anxiety.[33] This finding differed from what we had expected. However, as hypothesized, the anticipatory anxiety of patients with low HA played a role in precautionary behavior under a serious medical situation. That is, anxiety was associated with attentional bias toward a potential threat, enabling the implementation of precautionary behavior and preparedness for danger and disaster.[33-35]

Similarly, a substantial body of previous studies on preventive health behavioral theories have suggested that perceived risk is a critical determinant of precautious behavior for health.[36] Furthermore, the results indicated that self-efficacy and dispo-
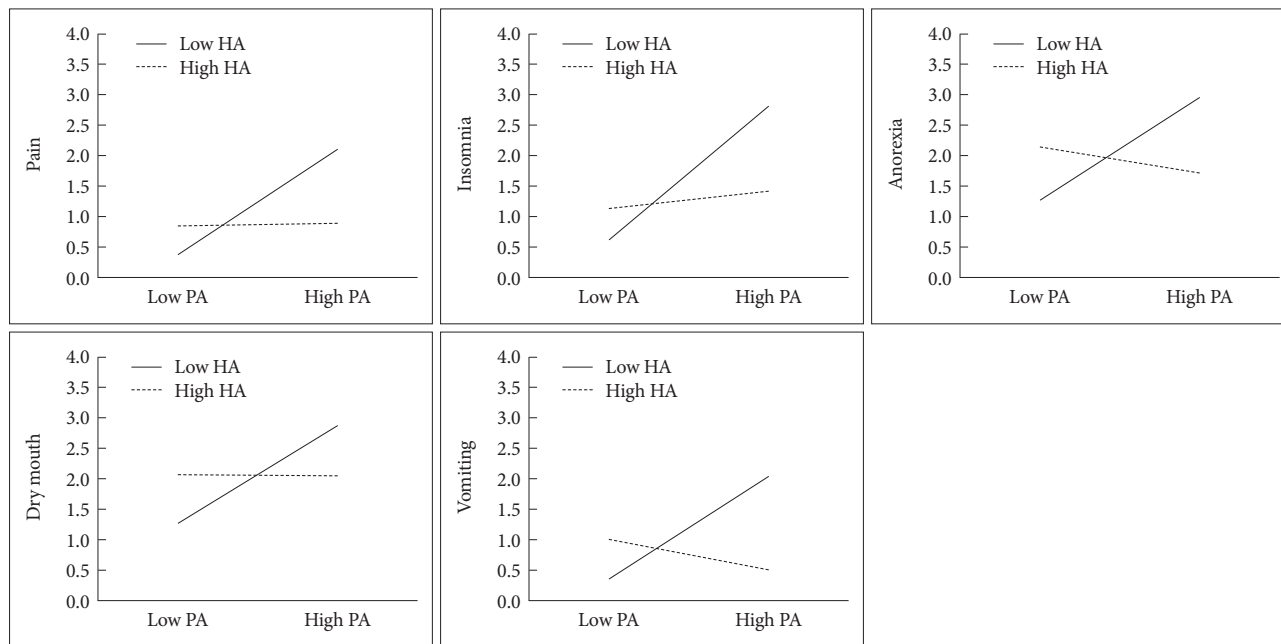
Figure 1. CRS predicted by PA moderated by HA. Low, one standard deviation below the mean; High, one standard deviation above the mean. CRS, chemotherapy-related symptoms; PA, pre-treatment anxiety; HA, harm avoidance.

sitional optimism related to the internal locus of control promote precautious and coping health behavior rather than an avoidant response in various health areas.[37] Recent studies on coronavirus disease 2019-related health behavior further found that dispositional optimism enhanced the intention to take precautionary measures against the pandemic spreading.[38] Regarding this study, when confronting a burdensome treatment, we found that if patients with confident and optimistic temperaments who were not habituated to fear in their daily lives were to experience anxiety, PA would be a very important signal for danger. Therefore, as PA increases, patients would become more vigilant to somatic changes and complain more to cope with the adverse effects of chemotherapy or to detect a potential sign of residual cancer.

We unexpectedly found that PA in patients with high HA did not significantly affect complaints of CRS. A tentative explanation for this finding would be that these patients' acute anticipatory anxiety would not be a reliable warning signal and would be alleviated easily as the aversive treatment became predictable. Cloninger[33] noted that individuals with a high HA tended to be intolerable to uncertainty and became hypervigilant to potential danger on exposure to an unpredictable aversive situation, which contributed to an unreliable evaluation of genuine risk and anxiety. Vulnerability to uncertainty itself, in turn, would make their PA more changeable when they learned about and could predict novel stimuli. When conducting additional analysis of the change in anxiety levels before and after chemotherapy using a t-test and a linear mixed model, all participants' anxiety levels were significantly higher at base-

line than after chemotherapy (t=6.09, p<0.001). This result was consistent with previous longitudinal studies that showed that anxiety in patients with cancer gradually abated as treatment progressed.[7,8] On further analysis, we divided participants into upper and lower half groups based on HA scores and found significant interaction effects between group and time (F=6.472, p=0.012). That is, although the high HA group's anxiety levels, measured before and after chemotherapy, were significantly higher than the low HA group's anxiety levels (t=-6.08, p<0.001; t=-4.36, p<0.001), anxiety in the high HA group was alleviated more rapidly compared with that in the low HA group after receiving the first cycle of treatment.

This study had several limitations. First, temperament measurements were performed at the same time as PA assessment. Psychological stresses such as PA and depressive symptoms at baseline could affect responses to temperament measurements. However, because the mean and SD scores of HA for all participants (mean=36.93, SD=10.67) did not differ significantly from those of the general female population (mean=36.57, SD=10.50) in a Korean TCI norm study,[39] the measured values in this study appear to reflect patients' ordinary temperament to a considerable extent. Second, this study included data at two time points around the first cycle. Future studies, including more long-term periods throughout the overall treatment course, are necessary to enable generalization of our findings regarding CRS risk factors.

Our study findings suggest that more attention should be given to the anticipatory anxiety of patients with confident and optimistic personalities before chemotherapy to decrease CRS

severity and improve quality of life during treatment. To prevent PA, advanced detailed informational intervention on the chemotherapy regimen and its adverse effect can help reduce patients' fear of the distressful treatment and facilitate adaptation to it. In fact, in their review, Ream and Richardson[40] found that informational interventions helped patients with cancer predict chemotherapy experience and resulted in lowered anxiety, increased coping behavior, and less disruption of daily life during chemotherapy.

PA was a significant predictor for several CRS in patients with low HA, which implies the need to manage the anxiety of patients with confident and optimistic personalities ahead of chemotherapy to decrease the severity of their CRS.

Availability of Data and Material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

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Funding Statement

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