Influence of the BDNF Val66Met polymorphism on coping response to stress in patients with advanced gastric cancer

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Abstract

Objective: Coping with cancer is an important determinant of psychological morbidity, quality of life, and treatment adherence in cancer patients. The aim of this study was to elucidate the association between the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism and coping response to stress in patients diagnosed with advanced gastric cancer.

Methods: Ninety-one subjects (60 males, 31 females) recently diagnosed with advanced gastric cancer were recruited. Coping style and distress level were examined using the Mini-Mental Adjustment to Cancer (Mini-MAC) scale and Hospital Anxiety and Depression Scale, and genotyping was evaluated. To examine the temporal stability of the Mini-MAC scores, a 6-week follow-up evaluation was conducted in 72 patients, after completion of two chemotherapy cycles.

Results: Coping style to cancer significantly differed between the Met carriers of BDNF Val66Met and the Val/Val homozygotes. The Met carriers were significantly more anxious than the Val/Val homozygotes.

Conclusion: The present findings suggest that the BDNF Val66Met polymorphism may be involved in individual coping responses to cancer. The Met allele of BDNF Val66Met may be predictive of an anxious coping style in patients with advanced cancer.

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Introduction

A cancer diagnosis can be very stressful, and a considerable number of cancer patients experience consequent psychological distress such as anxiety and depression [1–3]. Since psychological distress affects treatment adherence [4], quality of life [1], and survival in cancer patients [5], more attention has recently been given to the psychological aspect of cancer care. Psychological distress is determined by individual factors of perceiving and dealing with stressors, and not only with medical cancer care. Psychological distress is determined by individual factors such as cancer-related characteristics in cancer patients [6,7]. In particular, coping responses are known to crucially influence the development of psychological distress and psychiatric disorders in response to external stressors [8]. Therefore, a comprehensive understanding of coping responses to cancer may improve care services and quality of life for cancer patients.

Trait coping refers to cognitive, behavioral, and internal processing characteristics in individuals during stressful events [8,9]. The Mini-Mental Adjustment to Cancer (Mini-MAC) scale developed by Watson and Law [10] is useful in the assessment of trait coping in response to cancer. The Mini-MAC assesses five dimensions of mental adjustment to cancer: Anxious Preoccupation, Helplessness/Hopelessness, Fighting Spirit, Fatalism, and Cognitive Avoidance [10]. Previous studies showed that Anxious Preoccupation and Helplessness/Hopelessness coping styles were heavily influential in psychological morbidity [11] and quality of life [12] in cancer patients. Furthermore, the Helplessness/Hopelessness coping style was reportedly associated with a greater risk for depression [13] and a reduced rate of survival in breast cancer patients [5,14]. Since coping responses may be determined by complex interactions between genetics and environment, it is meaningful for understanding biological aspects of human coping responses to investigate how genetic predispositions contribute to individual differences in the employed coping strategy following external stressors such as a cancer diagnosis. To date, only one study has examined genetic influences on coping styles in cancer patients. The results of that study indicated an

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association between the 5-HTTLPR polymorphism and Anxious Preoccupation in patients with early stage breast cancer [15].

Substantial evidence suggests that the brain-derived neurotrophic factor (BDNF) gene may play a role in coping response [16,17]. BDNF regulates neuronal proliferation, differentiation, and survival. In addition, BDNF is associated with neuronal plasticity in response to stressful events [17]. The BDNF Val66Met (rs6265) polymorphism is a well-known, functional SNP of the BDNF gene. The Met allele of BDNF Val66Met may be related to a less adaptive genetic disposition toward adverse experience [18]. Moreover, transgenic mice with a BDNF Met/Met variant revealed that the Met/Met genotype is associated with increased anxiety-related behaviors [19]. Human studies indicated that Met allele carriers are more susceptible to geriatric depression than the Val/Val carriers [20,21]. Further, the Met allele is associated with reduced activity-dependent secretion of BDNF and poorer verbal episodic memory, compared to the Val allele [22].

Although there has been little research on a direct association between BDNF gene polymorphisms and coping styles to stress exposure in humans, substantial evidence of relationships between the BDNF Val66Met gene polymorphism and psychiatric symptoms related to stress responses provides indirect evidence for their possible association. A genetic association study in healthy university students showed that Met allele carriers of BDNF Val66Met experienced higher anxiety during a physical-stress procedure and higher anticipatory cortisol response than a Val/Val homozygous group [23]. In addition, a study in patients diagnosed with acute leukemia revealed that the BDNF Val66Met polymorphism is associated with development of depression/adjustment disorders in people undergoing stressful life events [24]. These findings suggest that the Met allele confers a genetic risk for coping responses associated with anxiety or depression.

The aim of the present study was to elucidate the influence of the BDNF Val66Met polymorphism on coping responses to stressful situations in cancer patients. To control external confounding factors that may affect individual coping responses, we recruited people exposed to similar situation which were within 1 month after diagnosis of advanced, non-resectable gastric cancer. A follow-up was conducted 6 weeks later, after 2 cycles of chemotherapy, to determine whether the initially measured coping style had remained stable over time. We hypothesized that subjects who carried the Met allele of BDNF Val66Met would be more likely to exhibit anxious or helpless/hopeless coping styles than those subjects with the Val/Val genotype.

Method

Subjects

A total of 91 participants (60 males, 31 females) diagnosed with advanced gastric cancer were recruited from the outpatient clinic in the Yonsei Cancer Center, and the Oncology Clinic at Gangnam Severance Hospital. Participants were newly diagnosed with metastatic or recurrent non-resectable gastric cancer, and had recently decided to undergo palliative chemotherapy. All participants were enrolled in a clinical trial of specific combination chemotherapy (the randomized phase II trial of S-1 or capetitabine in combination with oxaliplatin). Participants were outpatients with metastatic or locally advanced adenocarcinoma of the stomach confirmed by histology, and were aware of their diagnosis. None had undergone prior chemotherapy or had been diagnosed with other advanced-stage diseases. Participants with an Eastern Cooperative Oncology Group performance status score of three or above and with any neurological disorders were excluded. All participants were Korean. Written informed consent was obtained from all participants before the study, and the protocol was approved by the Institutional Review Board. Psychiatric evaluation was performed within 1 month after the diagnosis and 1 week before the first cycle of chemotherapy. All participants were genotyped and completed self-report assessments of coping styles and distress levels. Demographic and clinical data were collected from medical charts and interviews with oncologists and research nurses.

Assessment

Mini-Mental Adjustment to Cancer (Mini-MAC) scale

The Mini-MAC scale is a widely used, disease-specific instrument that evaluates mental adjustment and coping styles to cancer [10]. This scale consists of 29 items with a 4-point Likert scale and specifies five adjustment styles: Anxious Preoccupation, Helplessness/Hopelessness, Fatalism, Fighting Spirit, and Cognitive Avoidance. The Anxious Preoccupation dimension is characterized by a constant preoccupation with cancer and feelings of devastation, anxiety, and fear. The Helplessness/Hopelessness dimension is characterized by feelings of giving up, being overwhelmed by knowledge of the diagnosis, and a pessimistic attitude. The Fighting Spirit dimension is characterized by a determination to fight the illness and the adoption of an optimistic attitude. The Fatalism dimension refers to the tendency to put oneself in the hands of God. The Cognitive Avoidance dimension measures the tendency to ignore problems or emotions. The Korean version of this scale has been validated for Korean sample [25].

Hospital Anxiety and Depression Scale (HADS)

Levels of depression and anxiety were defined in this study as phenotypes of stress response. Distress level was assessed using the HADS designed to assess the psychological distress of patients in medical and surgical settings. It is composed of 14 items that reflect two dimensions: anxiety and depression. This scale is a 4-point Likert scale that ranges from 0 to 3. We used the Korean version of the HADS previously validated for the Korean population [26].

Eastern Cooperative Oncology Group (ECOG) performance status scale

The ECOG performance status scale was used to assess the physical ability of patients [27]. On the ECOG, the daily living ability of cancer patients is rated from 0 to 4 by an observer. Zero indicates that the patient is able to carry out all normal activities without restriction, and 4 indicates that the patient is completely disabled.

BDNF genotyping

A blood sample was obtained from each participant and genomic DNA was extracted. The genotyping of the BDNF Val66Met (rs6265) functional polymorphism was performed using a single-base primer extension assay by employing the ABI PRISM SNAPSHOT Multiplex kit in accordance with the manufacturer’s instructions (Applied Biosystems, Foster City, CA, USA). Analysis was performed using GeneMapper software version 4.0 (Applied Biosystems).

Statistical methods

Analyses were conducted using SPSS 19.0 for Windows (SPSS Inc., Chicago, IL, USA). Multivariate analyses of covariance were computed with the coping styles as the dependent variables, and genotypes as the independent variable with confounding factors as the covariates to examine the association between BDNF genotype and coping style. To examine the temporal stability of the coping styles, Pearson correlation analyses were conducted for the Mini-MAC scores between the initial and 6-week follow-up points. All statistical tests were two-tailed, and the significance level was $p < 0.05$. The power of our sample to detect differences between genotypes of BDNF gene was calculated based on a two tailed alpha value of 0.05 using the G Power program [28]. With these parameters, the power analysis showed that our sample size had a power (0.80) to detect a medium effect size ($f = 0.39$).

The present study investigated the influence of the BDNF Val66Met polymorphism on individual coping responses in patients newly diagnosed with advanced gastric cancer. We found a significant difference in coping style between the Met allele carriers and the Val homozygous group. The Met allele carriers were significantly more likely to have a higher Anxious Preoccupation coping style than the Val homozygous group. These findings suggest that BDNF Val66Met polymorphism may facilitate an anxious coping response, and confer vulnerability to anxiety or depression in cancer patients.

Since coping responses are determined as the interactions between individual vulnerability and external stress levels, it is very important to control external stress levels when assessing individual vulnerability of coping responses. However, it is difficult to investigate coping responses to the same stressful situations among humans in real life. The strength of our study is that the genetic study of coping responses was conducted in people facing similar stressors. All participants in the present study were newly diagnosed with advanced gastric cancer and scheduled to receive chemotherapy for the first time; thus, the time of initial assessment was presumably characterized by high stress levels for the participants, owing to emotions concerning the cancer diagnosis and fear of chemotherapy. Therefore, the relatively homogeneous sample and the similar stressor controlled for the effects of external factors on coping response.

The Met allele carriers of BDNF Val66Met were found to have significantly more anxious coping styles to external stressors than the Val homozygous group. Similarly, previous research suggests that the Met allele confers greater vulnerability to anxiety disorders than the Val allele [30]. In addition, the Met allele carriers are particularly sensitive toward anticipated stressful events and uncertainty [23,31]. A functional imaging study using an affective startle reflex paradigm revealed that Met allele carriers showed stronger activation in the right amygdala in response to emotional stimuli than the Val homozygous group [38], which reflect the associations between the Met allele and altered sympathovagal balance with lower parasympathetic activity, higher trait anxiety. The Met/Met genotype was also implicated in altered cardiac autonomic functions [33]. Further, research on extinction learning has shown that Met allele carriers exhibit impaired learning of safety cues when such learning relies on extinction mechanisms [34]. Taken together, the Met allele of BDNF Val66Met may confer vulnerability to anxiety disorders, suggesting a modulatory effect for BDNF Val66Met polymorphism on individual coping responses in patients newly diagnosed with advanced gastric cancer.

Results

The mean scores of the Mini-MAC scale were 20.4 (SD = 5.1) for Anxious Preoccupation, 13.8 (SD = 3.9) for Helplessness/Hopelessness, 13.8 (SD = 2.7) for Fatalism, and 11.9 (SD = 2.0) for Fighting Spirit; the mean total score of the HADS was 14.0 (SD = 7.3). Demographic and clinical characteristics of participants are presented in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and clinical characteristics of participants (N = 91).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.7 ± 11.4</td>
</tr>
<tr>
<td>Male/female</td>
<td>61/30, 67.7/32.3</td>
</tr>
<tr>
<td>Body mass index</td>
<td>21.6 ± 3.0</td>
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<tr>
<td>Cancer type</td>
<td>91</td>
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<tr>
<td>Gastric adenocarcinoma</td>
<td>100.0</td>
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<tr>
<td>Cancer stage</td>
<td>75</td>
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<tr>
<td>Metastatic AGC</td>
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<tr>
<td>Recurrent AGC</td>
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<tr>
<td>ECOG</td>
<td>17.6</td>
</tr>
<tr>
<td>0</td>
<td>11, 12.1</td>
</tr>
<tr>
<td>1</td>
<td>78, 85.7</td>
</tr>
<tr>
<td>2</td>
<td>2, 2.2</td>
</tr>
<tr>
<td>Mini-MAC Anxious Preoccupation</td>
<td>20.4 ± 5.1</td>
</tr>
<tr>
<td>Mini-MAC Helplessness/Hopelessness</td>
<td>13.8 ± 3.9</td>
</tr>
<tr>
<td>Mini-MAC Fatalism</td>
<td>13.8 ± 2.7</td>
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<tr>
<td>Mini-MAC Fighting Spirit</td>
<td>11.9 ± 2.0</td>
</tr>
<tr>
<td>Mini-MAC Cognitive Avoidance</td>
<td>10.9 ± 2.1</td>
</tr>
<tr>
<td>HADS-total</td>
<td>14.0 ± 7.3</td>
</tr>
</tbody>
</table>

The mean scores of the Mini-MAC scale were 20.4 (SD = 5.1) for Anxious Preoccupation, 13.8 (SD = 3.9) for Helplessness/Hopelessness, 13.8 (SD = 2.7) for Fatalism, 11.9 (SD = 2.0) for Fighting Spirit, and 10.9 (SD = 2.1) for Cognitive Avoidance. The mean total score of the HADS was 14.0 (SD = 7.3). Demographic and clinical characteristics of participants are presented in Table 1.

The frequency of the BDNF Val66Met polymorphism was 24.2% (n = 22) for the Met/Met genotype, 45.1% (n = 41) for the Val/Met genotype, and 30.8% (n = 28) for the Val/Val genotype. The distribution was similar to that reported in other Korean samples [29]. The distribution of the BDNF genotype was also in accordance with the Hardy–Weinberg equilibrium (χ² = 0.82, NS). Because the frequency of Met/Met of BDNF was 24.2% (n = 22), we grouped the BDNF genotypes into two categories: Val/Val (i.e., Val homozygous group; n = 28, 30.8%), and Val/Met + Met/Met (i.e., Met allele carrier group; n = 63, 69.2%) to conserve statistical power.

Since the severity of depression and anxiety symptoms may influence coping style [35], MANCOVA was conducted with sex and HADS total score as covariates. Results showed a significant sex difference in coping between the two groups (p = 0.030). The gender distribution was 14 males and 14 females in the Val/Val group, and 47 males and 16 females in the Met allele carrier group. A significant sex difference was observed between the two groups (p = 0.030).

In the Val homozygous group, the mean scores from the Mini-MAC scale were 18.7 (SD = 5.7) for Anxious Preoccupation, 13.4 (SD = 3.9) for Helplessness/Hopelessness, 14.0 (SD = 3.3) for Fatalism; 11.7 (SD = 2.4) for Fighting Spirit; and 11.4 (SD = 2.6) for Cognitive Avoidance. In the Met allele carriers, the mean scores from the Mini-MAC scale were 21.2 (SD = 4.6) for Anxious Preoccupation, 14.0 (SD = 4.0) for Helplessness/Hopelessness, 13.6 (SD = 2.3) for Fatalism; 12.0 (SD = 1.7) for Fighting Spirit; and 10.6 (SD = 1.9) for Cognitive Avoidance. Significant differences in coping style were observed between the Val homozygous group and the Met allele carriers (p = 0.020). Since the severity of depression and anxiety symptoms may influence coping style, and because a sex difference was found between the two groups (p = 0.030), a post-hoc MANCOVA was conducted with sex and HADS total score as covariates. Results showed that the Met allele carriers had significantly higher Mini-MAC Anxious Preoccupation scores than the Val homozygote group [F = 2.855, df (5, 83), p = 0.020]. These results are shown in Table 2.

The Mini-MAC scale was administered again to 72 subjects (51 males, 21 females) 6 weeks later, after participants had completed 2 chemotherapy cycles. Pearson correlation coefficients for the 2 time periods indicated relative score stability of the Anxious Preoccupation, Helplessness/Hopelessness, Fatalism, and Cognitive Avoidance dimensions (coefficients ranged from 0.45 to 0.68, p = 0.001). The correlation coefficient of Fighting Spirit was relatively low. Pearson correlation coefficients between initial and follow-up scores are presented in Table 3.

Table 2

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Mini-MAC subscale scores according to genotype of the BDNF Val66Met polymorphism.</th>
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</thead>
<tbody>
<tr>
<td>MANCOVA</td>
<td>Genotype</td>
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<tr>
<td></td>
<td>Val/Val</td>
</tr>
<tr>
<td></td>
<td>(n = 28)</td>
</tr>
<tr>
<td>Hotelling’s trace</td>
<td>F = 2.855, df (5, 83), p = 0.020&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anxious Preoccupation</td>
<td>18.7 ± 5.7</td>
</tr>
<tr>
<td>Helplessness/Hopelessness</td>
<td>13.4 ± 3.9</td>
</tr>
<tr>
<td>Fatalism</td>
<td>14.0 ± 3.3</td>
</tr>
<tr>
<td>Fighting Spirit</td>
<td>11.7 ± 2.4</td>
</tr>
<tr>
<td>Cognitive Avoidance</td>
<td>11.4 ± 2.6</td>
</tr>
</tbody>
</table>

Data are mean ± SD. All tests are two-tailed. Sex and HADS total score was used as covariates.

<sup>a</sup> p < 0.05.

Discussion

Contrary to our prediction, there was no significant difference in the Helplessness/Hopelessness coping style between the BDNF genotype groups. Previous research on the relationship between depression and BDNF genes indicates that Met allele carriers are more likely to
experience depression than Val homozygous individuals [20,35,36]. In addition, because the Met allele is related to lower activity-dependent secretion of BDNF and altered hippocampal/prefrontal cortex function [22], the Met allele may confer a genetic risk for depression. Thus, these findings suggest an association between the Met allele of BDNF Val66Met polymorphism and Helplessness/Hopelessness coping style, which has been associated with a greater risk for depression [13]. The discrepancy between previous findings and the present result may be explained by a Type II error. An association between BDNF Val66Met polymorphism and the Helplessness/Hopelessness coping style may be more subtle and not have reached statistical significance in the present study because of its small sample size. The influence of BDNF on coping responses to a similar stressor should be further examined in a larger sample.

The present study had several limitations. First, the sample size was relatively small. The small sample size in this study warrants caution in drawing conclusions as the power to detect subtle effects is limited. While the observed genetic influence on coping style in the present study should be interpreted as preliminary, the results may be meaningful because the participants were relatively similar and exposed to a similar, real-life stressor. Second, we hypothesized that coping styles to cancer are considered as a heritable trait. Several studies showed relationships between coping response and stable personality traits, suggesting that coping is a part of one's global personality [37,38]. In addition, previous research from twin subjects suggested that coping styles are moderately heritable [39]. However, there has been some controversy regarding the issue of whether coping responses are of trait or state factors. Although the significant correlation between coping response at the initial and 6-week follow-up phases observed in the present study reflects its stability over time, it is still questionable as to whether coping style is a trait or a transient state. Finally, we did not measure other individual factors, such as personality traits, that may have influenced coping response and consequently confounded the present results.

In conclusion, a BDNF genetic variant may critically influence coping styles to acute stress in cancer patients. The Met allele of the BDNF Val66Met may reliably predict certain coping traits, such as an anxious coping response, in patients with advanced cancer. To confirm the role of BDNF in genetic predispositions to coping styles, further investigation is required with a larger sample.

Conflict of interest

The authors have no actual or potential conflict of interest to declare.

Acknowledgments

The present study was performed collaboratively to the phase II clinical study of oxaliplatin in combination with S-1 versus cetuximab in patients with metastatic or recurrent gastric cancer (NCT00985556).

References


