Association Between Depression and Anxiety Status of Breast Cancer Patients Undergoing Adjuvant Chemotherapy and Chemotherapy-induced Adverse Events.

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Abstract

Purpose: The response to a breast cancer diagnosis encompasses aspects related to emotion and psychology, and patients with breast cancer are more likely to experience psychological distress. This study therefore aimed to explore the relationship between depression and anxiety status and adverse events during adjuvant chemotherapy in Chinese breast cancer patients.

Methods: This prospective study was conducted on 290 postoperative early-stage breast cancer patients (response rate 96.7%) in China. Depression and anxiety status before adjuvant chemotherapy and after 2 cycles of chemotherapy were assessed by the Hospital Anxiety and Depression Scale (HADS). Adverse events that occurred throughout the course of chemotherapy were graded and recorded according to CTCAE 4.02.

Results: The rates of depression and anxiety were 20.0% and 31.4%, respectively, at baseline. After 2 cycles of chemotherapy, the rates of depression and anxiety were 25.2% and 29.0%, respectively. The incidence of grade two or higher myelosuppression induced by chemotherapy was correlated with depression before chemotherapy ($P=0.037$) and after 2 cycles of chemotherapy ($P=0.009$). Multivariate analysis showed that the incidence of myelosuppression was significantly related to depression before chemotherapy ($P=0.032$) and after 2 cycles of chemotherapy ($P=0.006$). There was no association between depression and anxiety status and other adverse events ($P>0.05$).

Conclusions: We observed an association between depression and anxiety status in breast cancer patients receiving adjuvant chemotherapy and chemotherapy-induced myelosuppression. Monitoring the psychological status of breast cancer patients undergoing chemotherapy may help to optimize the management of adverse events.

The study is registered (ClinicalTrials.gov identifier: NCT05055375)

Introduction

Breast cancer is the most common malignancy among women worldwide. In 2020, more than 400,000 women were diagnosed with breast cancer in China, ranking first among new cancer cases[1]. The treatment modalities for primary breast cancer include surgery, chemotherapy, radiotherapy and hormonal therapy, among which adjuvant chemotherapy is an important strategy to improve the survival of breast cancer patients. Although chemotherapy improves the survival rate of these patients, the aggressiveness of the chemotherapy regimen may elicit adverse side effects. In fact, cancer and treatment-related adverse effects are major stressors among breast cancer patients undergoing treatment for the disease[2]. Adverse events mainly included gastrointestinal events, anemia, myelosuppression, alopecia and so on.

During the long treatment period, breast cancer patients often suffer from a variety of psychological disorders, such as depression, anxiety and distress. It has been reported that the prevalence rates of depressive and anxious disorders in cancer patients vary widely from 1–58%[3–5]. Breast cancer survivors have been found to be more likely to develop depression than the general population. Previous meta-analyses have reported that the prevalence of anxiety and depression among breast cancer patients reached 41.9% and 32.2%, respectively[6, 7]. Similarly, breast cancer survivors in China were found to experience a high level of depression and anxiety symptoms[8]. Independent risk factors for the development of depression include age, social status, and underlying diseases[9, 10].

It has long been recognized that depression and anxiety can affect the physiological function, treatment compliance, psychological function, and quality of life of patients with breast cancer and may even be an important factor for survival in these patients[11]. Depression may also cause immune dysfunction through an overactive hypothalamic-pituitary-adrenal (HPA) axis[12]. Patients with immune dysfunction may be more likely to experience chemotherapy-related adverse events during chemotherapy. Indeed, the relationship between depression and anxiety status and adverse events induced by chemotherapy in Chinese patients with breast cancer remains unclear. Further prospective trials exploring this relationship are essential to closing this knowledge gap.

In our study, we investigated the relationship between depression and anxiety status and adverse events during adjuvant chemotherapy in Chinese breast cancer patients with the purpose of identifying high-risk patients through psychological state monitoring to better manage adverse events in this population.

Materials And Methods

Patient selection

We identified 300 patients from a prospective, observational cohort with a primary diagnosis of breast cancer between 1 March 2019 and 30 April 2021 in the Medical Oncology Department at the National Cancer Center in China. Ethical approval was obtained from the Institutional Review Board of the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital. This study have been registered on ClinicalTrials.gov database.

Inclusion criteria included the following: (a) age 18–75 years old, (b) had undergone surgery for breast cancer, (c) were diagnosed with stage I-III breast cancer, (d) planned to receive postoperative adjuvant chemotherapy, and (e) voluntarily provided written informed consent. Those who 1) had difficulty understanding the questionnaire or communicating in Chinese, 2) had a history of psychiatric disorders, 3) had a history of neoadjuvant chemotherapy before surgery, or 4) had metastatic disease were excluded from the study.

Demographic and clinical characteristics. The demographic data consisted of age, educational level, menopausal status, and family history of cancer. The clinical characteristics included tumor stage, chemotherapy regimens, and number of chemotherapy cycles.

Assessment instruments

The Hospital Anxiety and Depression Scale (HADS) was used to assess the psychological status of our patients, which was developed in English by Zigmond and Snaith in 1983[13] and then translated and validated in Cantonese/Chinese in 1995 by Lam et al[14]. Questionnaires were provided to the patients to complete before the first chemotherapy and again after 2 cycles of chemotherapy to evaluate their anxiety and depression before and during chemotherapy. The scale includes two parts: anxiety (anxiety, A) and depression (depression, D), with a total of 14 items—7 items with single numbers for anxiety and 7 items with double numbers for depression. Each item is scored 0–3 points. Total scores for each subscale are calculated individually, with a higher score indicating more anxiety or distress. In each of the two subscales, a score of below 8 indicates no anxiety/depression, 8–10 indicates possible anxiety/depression case, and 11–21 indicates definite anxiety/depression[15]. Thus, based on previous research, we adopted a threshold subscale score of 8 for anxiety and depression in this study.

All patients received conventional chemotherapy regimens include anthracycline-, taxane-, or combined anthracycline and taxane-based chemotherapy specified by the NCCN guidelines, based on their disease states, and for Her2-positive patients, anti-Her2 has been added. Dexamethasone and 5-hydroxytryptamine receptor (5HT3) prophylactic antiemetic therapy were administered before each cycle of chemotherapy for moderate and low emetogenic chemotherapy. Dexamethasone, 5HT3, and neurokinin-1 (NK-1) receptor antagonist prophylactic antiemetic therapy were administered to patients receiving hyperemetic chemotherapy. Adverse events (gastrointestinal events, anemia, myelosuppression, alopecia, elevation of transaminase) were monitored continuously and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.2.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 software. Cronbach's α values were calculated to assess the internal consistency of each questionnaire. Chi-squared analysis was used to examine whether there was a significant relationship between adverse events induced by chemotherapy and psychological symptoms and demographic and clinical characteristics. We used a logistic regression model to investigate potential risk factors for adverse events. A probability value of $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 300 breast cancer patients fulfilled the inclusion criteria, and all patients provided informed consent. Eight patients dropped out due to discontinuation of treatment at our hospital, and two patients were excluded due to incomplete questionnaires. Thus, a total of 290 valid cases were analyzed, and information on the demographic and clinical characteristics of these patients is presented in Table 1. The ECOG performance scores of all patients were 0-1. Internal consistency measurements of the HADS subscale questionnaires before chemotherapy and after 2 cycles of chemotherapy yielded Cronbach's alpha coefficients of 0.883 and 0.890, respectively. Overall, the mean age of the patients was 47.09 ± 9.45 years, and 40.7% were older than 50 years. 5.9% of patients received anthracycline-based chemotherapy, 40.3% of patients received taxane-based chemotherapy and 53.8% of patients received combined anthracycline and taxane-based chemotherapy. Among them, more than half of the patients were diagnosed with stage $\geq$ cancer (50.7%), and 85.5% had received 6–8 cycles of chemotherapy.

Table 1
Demographics and clinical characteristics of the patients
($N=290$)

Characteristic	Number of patients
Age (years)	
<50	172(59.3%)
≥ 50	118(40.7%)
Received anthracycline chemotherapy	
Yes	173(59.7%)
No	117(40.3%)
TNM stage	
Stage $\geq$	76(26.2%)
Stage $\geq$	148(51.0%)
Stage $\geq$	66(22.8%)
Number of chemotherapy cycles	
4	42(14.5%)
6–8	248(85.5%)

Prevalence of anxiety and depression

The rates of depression and anxiety were 20.0% (58/290) and 31.4% (91/290) at baseline. The mean (95% CI) HADS depression score was 4.63 (1.06, 8.20), and the mean anxiety score was 6.00 (2.41, 9.59). After 2 cycles of chemotherapy, the rates of depression and anxiety in chemotherapy were 25.2% (73/290) and 29.0% (84/290), respectively. The mean (95% CI) HADS depression score was 5.16 (1.36, 8.96), and the mean anxiety score was 5.72 (2.23, 9.21).

First, the most common adverse events observed in our study were grade 2 or higher myelosuppression (84.1%). A total of 26.9% of the patients experienced grade 2 or higher gastrointestinal events, while more than half of the patients (54.5%) experienced grade 1 or higher elevated transaminase. The incidences of grade 2 or higher anemia and alopecia were 22.1% and 16.2%, respectively. Afterward, we analyzed the correlation between common adverse events induced by chemotherapy (including gastrointestinal events, anemia, alopecia, and elevation of transaminase) and psychological symptoms before and during chemotherapy, and we found that the occurrence of grade two or higher myelosuppression during chemotherapy was correlated with depression during the early and middle stages of chemotherapy ($P=0.037$ and $P=0.005$) and with anxiety during the middle stages of chemotherapy ($P=0.009$). There was no statistical significance between depression and anxiety status and other adverse events, including gastrointestinal events, anemia, alopecia, and elevation of transaminase ($P>0.05$) (Table 2). In the multivariate analysis, after adjusting for age, prechemotherapy depression status, chemotherapy regimens, TNM stage, and number of chemotherapy cycles (univariate analysis between myelosuppression and demographic and clinical factors were shown in supplement Table S1), we found that prechemotherapy depression status was independently associated with the incidence of grade two or higher myelosuppression induced by chemotherapy, and this was statistically significant ($P=0.032$). In other words, these patient populations are more likely to develop myelosuppression (OR=3.258 [1.106–9.598]). The results of the multivariate analysis of the correlation between depression status before chemotherapy and myelosuppression induced by chemotherapy are shown in Table 3. Applying the same method to analyze depression and anxiety after 2 cycles of chemotherapy, and the multivariate analysis showed that the depression status of patients after 2 cycles of chemotherapy was associated with grade two or higher myelosuppression during chemotherapy ($P=0.006$, OR=4.463 [1.525–13.055]) (Table 4).

Table 2
Univariate analysis of common adverse events induced by chemotherapy and psychological symptoms

Characteristic	Depression status before chemotherapy		<i>p</i> -value	Anxiety status before chemotherapy		<i>p</i> -value	Depression after 2 cycles of chemotherapy		<i>p</i> -value	Anxiety after 2 cycles chemotherapy	
	Yes	No		Yes	No		Yes	No		Yes	No
Myelosuppression $\geq$ Grade 2											
Yes	54(22.1%)	190(77.9%)	0.037	80(32.8%)	164(67.2%)	0.234	69(28.3%)	175(71.7%)	0.005	78(32.0%)	166(68.0%)
No	4(8.7%)	42(91.3%)		11(23.9%)	35(76.1%)		4(8.7%)	42(91.3%)		6(13.0%)	40(87.0%)
Gastrointestinal events $\geq$ Grade 2											
Yes	21(26.9%)	57(73.1%)	0.074	27(34.6%)	51(65.4%)	0.471	23(29.5%)	55(70.5%)	0.304	23(29.5%)	55(70.5%)
No	37(17.5%)	175(82.5%)		64(30.2%)	148(69.8%)		50(23.6%)	162(76.4%)		61(28.8%)	151(71.2%)
Anemia $\geq$ Grade 2											
Yes	16(25.0%)	48(75.0%)	0.257	17(26.6%)	47(73.4%)	0.347	20(31.3%)	44(68.7%)	0.204	21(32.8%)	43(67.2%)
No	42(18.6%)	184(81.4%)		74(32.7%)	152(62.3%)		53(23.5%)	173(76.5%)		63(27.9%)	163(72.1%)
Alopecia $\geq$ Grade 2											
Yes	12(25.5%)	35(74.5%)	0.300	19(40.4%)	28(59.6%)	0.144	15(31.9%)	32(68.1%)	0.245	18(38.3%)	29(61.7%)
No	46(18.9%)	197(81.1%)		72(29.6%)	171(70.4%)		58(23.9%)	185(76.1%)		66(27.2%)	177(72.8%)
ALT/AST $\geq$ Grade 1											
Yes	32(20.3%)	126(79.7%)	0.906	50(31.6%)	108(68.4%)	0.915	42(26.6%)	116(73.4%)	0.545	45(28.5%)	113(71.5%)
No	26(19.7%)	106(80.3%)		41(31.1%)	91(68.9%)		31(23.5%)	101(76.5%)		39(29.5%)	93(70.5%)
AST aspartate aminotransferase, ALT alanine aminotransferase; <i>P</i> -values were obtained from chi-squared tests for categorical variables											

Table 3
Multivariate analysis for the correlation of pre-chemotherapy depression status and myelosuppression induced by chemotherapy.

Variable	Myelosuppression $\geq$ Grade 2			
	OR	95%CI-	95%CI+	p-value
Depression status before chemotherapy	3.258	1.106	9.598	0.032
TNM stage				0.029
Stage I	1			
Stage II	2.687	1.290	5.598	
Stage III	1.900	0.804	4.486	
ORs and 95% CIs were from polytomous logistic regression models.				

Table 4
Multivariate analysis for the correlation of depression status after 2cycles of chemotherapy and myelosuppression induced by chemotherapy.

Variable	Myelosuppression $\geq$ Grade 2			
	OR	95%CI-	95%CI+	p-value
Depression status after 2 cycles of chemotherapy	4.463	1.525	13.055	0.006
TNM stage				0.028
Stage I	1			
Stage II	2.711	1.294	5.680	
Stage III	2.009	0.845	4.777	
ORs and 95% CIs were from polytomous logistic regression models.				

Discussion

We conducted this study to explore the relation between psychological distress and adverse events induced by chemotherapy. We used the HADS scale to assess psychological status since it has been used as a criterion for evaluating depression and anxiety in previous studies[16–19]. In this study, we analyzed 290 patients with breast cancer in China, and the rate of psychological distress was 20%-39.7%, which is comparable to previous reports[20–22]. The results reported in other studies also indicate the importance of assessing the mental health of such patients throughout the entire cancer treatment process[23, 24]. Since patients with a history of psychological disorders were excluded from our study, the symptoms of anxiety and depression detected herein are likely to be caused by the presence of cancer or subsequent treatment. Post hoc analysis showed that depression before and during the middle stage of chemotherapy was associated with the incidence of myelosuppression during the entire chemotherapy process. This indicates that patients with depression in these populations are more likely to develop myelosuppression during the course of chemotherapy. Thus, it is very important to dynamically screen the psychological status of breast cancer patients during chemotherapy.

In this study, the patients received conventional chemotherapy regimens, and no granulocyte colony stimulating factor (G-CSF) was used for primary prevention of myelosuppression. A total of 84.1% of patients had grade 2 or higher myelosuppression, which is similar to previous study results[25]. The occurrence of myelosuppression in our study reflected the true condition of the patients after receiving chemotherapy. Therefore, the conclusions drawn by our study have high credibility and may offer guidance regarding clinical decision-making.

The possible reason for these conclusions is that psychological distress in the form of depression and anxiety can cause immune dysfunction. Psychological distress is considered to dysregulate immune function in several ways, including the exacerbation of chronic inflammation, the suppression of protective immunity, and the enhancement of immunosuppressive mechanisms[26–29]. Activation of the HPA axis, which is well recognized in individuals with depression, inhibits immune system activity by releasing cortisol and disrupts the immune microenvironment[30, 31]. Therefore, breast cancer patients experiencing depression are more prone to myelosuppression during chemotherapy. In addition, depression, anxiety, or a combination of both is associated with increased recurrence and mortality in patients with breast cancer[11]. Hence, oncologists should try to identify patients with depression before and during chemotherapy and take measures when necessary to relieve psychological distress and improve the compliance and tolerance of patients.

Some retrospective studies have been conducted to explore the role of psychological distress in chemotherapy-induced nausea and vomiting, and the results suggest that anxiety plays a role in the perception, frequency, intensity and severity of nausea and other chemotherapy-induced side effects[32]. In our study, univariate analysis showed that depression and anxiety were not associated with gastrointestinal events. This result is different from the results of previous studies[33, 34]. The reason may be because in the present study, the patients received preventive antiemetic treatment before chemotherapy, which reduced the incidence of gastrointestinal adverse events to a nonsignificant level. This also suggests that preventive antiemetic treatment can relieve nausea and vomiting in patients. In addition, there was no statistically significant association between psychological status and elevated transaminases, anemia and alopecia. This indicates that depression and anxiety in breast cancer patients does not affect the incidence of such adverse events.

In this work, we demonstrated, for the first time, that depression status is an independent factor associated with myelosuppression induced by chemotherapy in Chinese breast cancer patients. Unlike previous reports in the literature, this work dynamically monitored the depression and anxiety status of breast cancer patients throughout the course of chemotherapy. Patients with depression were found to be more likely to develop grade two or higher myelosuppression during chemotherapy. These findings indicate that oncologists should make efforts to monitor the depression status of breast cancer patients during chemotherapy. Nevertheless, proper psychological care is still necessary after screening[35]. Before starting chemotherapy, it is necessary for oncologists to consider not only the patient's tumor development and disease experience but also their psychological status, including depression, anxiety and other psychological symptoms[36, 37]. Moreover, oncologists and nurses should perform intervention measures when patients with severe psychological symptoms are identified to ensure that they can successfully complete chemotherapy, which is of great significance for preventing tumor recurrence and improving patient prognosis.

As intended, this study assessed the psychological status of breast cancer patients being monitored at the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital and identified factors associated with chemotherapy-induced myelosuppression, which will help oncologists and nurses offer better support to breast cancer patients. Nevertheless, some limitations should be noted. First, this study was conducted at a single institute. Second, the population size was relatively insufficient. Additional studies should be conducted on larger populations to increase the validity of our conclusions in the future. Third, a potentially minor limitation is that our study was merely an observational study, and no interventions were performed for the patients. Perhaps psychological interventions could reduce the incidence or grade of chemotherapy-induced myelosuppression. Further investigations into the effect of psychological interventions on the adverse events induced by chemotherapy are warranted in the future.

In conclusion, we demonstrated in this exploratory study that the depression status of breast cancer patients was correlated with the incidence of grade two or higher myelosuppression throughout the course of chemotherapy, and populations with prechemotherapy depression were more likely to develop myelosuppression. These findings suggest that oncologists should focus more attention on monitoring the depression status of breast cancer patients during chemotherapy, which might help to improve the management of adverse events, ensure the safety of patients, and improve tolerance to chemotherapy.

Abbreviations

HADS Hospital Anxiety and Depression Scale

HPA Hypothalamic-pituitary-adrenal

CTCAE Common Terminology Criteria for Adverse Events

5HT3 5-hydroxytryptamine receptors

NK-1 Neurokinin-1

AST Aspartate aminotransferase

ALT Alanine aminotransferase

GCS-F Granulocyte colony stimulating factor

Declarations

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Conflicts of interest: The authors declare that they have no conflicts of interest.

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Code availability: Not applicable

Authors' contributions: Conception and design: FM, DL, BL. Development of methodology: MA, DL, BL. Acquisition and management of data: DL, BL, LZ, XYS, MY. Analysis and interpretation of data: FM, DL, BL. Writing, review and/or revision of the manuscript: FM, DL, BL, LZ, XYS, MY. Study supervision: FM.

Ethics approval: The study was approved by the Institutional Review Board of the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital.

Consent to participate: All participants provided informed consent.

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