JBUON 2018; 23(6): 1601-1605
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

A study on the relationship between chemotherapy-induced cognitive impairment and age in patients with breast cancer

Zeyu Liu*, Xiaorong Han*, Chunxiang Tian, Jun Chen, Lei Lei, Qi Liang, Xinlin Lv, Shenli Tang, Ping Ning

Department of Breast Surgery, Chengdu Women's & Children's Central Hospital, Chengdu, China

*These authors contributed equally to this work

Summary

Purpose: *To investigate the correlation of chemotherapy-induced cognitive impairment (CICI) with age in patients with triple-negative breast cancer (TNBC).*

Methods: *A total of 120 breast cancer patients with different ages and receiving chemotherapy were selected as breast cancer group, and another 120 healthy subjects were enrolled as healthy control group. Breast cancer group included 60 TNBC patients (TNBC group) and 60 patients without TNBC (non-TNBC group). Both breast cancer and healthy control group were further divided into young group (n=40), middle-aged group (n=40) and elderly group (n=40). For TNBC group and non-TNBC group, each age group had 20 patients. Then, mini-mental state examination (MMSE), retrospective memory (RM) and prospective memory (PM) questionnaires were performed separately.*

Results: *There were statistically significant differences in MMSE, RM and PM scale scores between breast cancer group and healthy control group (p<0.001). In breast cancer group, the MMSE score was negatively correlated with age (r=-0.614, p<0.001), and the RM scale and PM scale scores were positively related to age (r=0.527, 0.439, p<0.001). The differences in MMSE, RM and PM scale scores were statistically significant between TNBC group and non-TNBC group (p<0.05). Moreover, the scores of MMSE, RM scale and PM scale were statistically significant among the young, middle-aged and elderly group in both TNBC group and non-TNBC group (p<0.001). In young group, there were statistically significantly differences in scores of MMSE, RM scale and PM scale between TNBC group and non-TNBC group (p<0.001). In middle-aged and elderly group, the scores of MMSE, PM scale and RM scale also had statistically significant differences between TNBC group and non-TNBC group (p<0.001). Multivariate logistic regression analyses revealed that TNBC [odds ratio (OR)=3.659, p=0.004] and age (OR =1.128, p<0.001) were risk factors for the occurrence of cognitive impairment in patients with breast cancer.*

Conclusions: *Patients receiving chemotherapy for breast cancer suffer from varying degrees of cognitive impairment. The cognitive impairment in TNBC patients is more severe than that in patients without TNBC, the difference being mainly detected in young patients. In addition, both TNBC and age are risk factors for CICI in breast cancer.*

Key words: *age, breast cancer, chemotherapy-induced cognitive impairment, triple-negative breast cancer*

Introduction

The damages occurring during or after chemotherapy to cognitive function such as memory, attention, execution and information processing speed in cancer patients are called chemotherapy-induced cognitive impairment (CICI) [1-4]. Currently, research on CICI has become one of the hotspots in the field of cancer psychology with the rapid development of cognitive neuropsychology.

Correspondence to: Ping Ning, BM. Department of Breast Surgery, Chengdu Women's & Children's Central Hospital, 1617 Riyue Ave, Qingyang District, Chengdu, 610091, Sichuan, China.
Tel: +86 013980569594, E-mail: 37781380@qq.com
Received: 21/05/2018; Accepted: 07/06/2018

However, the correlation between CICI and age in patients with TNBC has not been reported. Therefore, this study enrolled breast cancer patients with different pathological types and different ages and undergoing chemotherapy as the study subjects, and MMSE, RM and PM questionnaires were used as main tools to investigate and analyze the cognitive function of the above-mentioned patients, so as to verify the associations of CICI in breast cancer with TNBC and age.

Methods

Subjects

A total of 120 breast cancer patients receiving chemotherapy (breast cancer group) treated in Chengdu Women's & Children's Central Hospital from January 2016 to January 2017 were enrolled, including 60 patients with TNBC (TNBC group) and 60 patients without TNBC (non-TNBC group). This study was approved by the ethics committee of Chengdu Women's & Children's Central Hospital.

Exclusion criteria: 1) Advanced cachexia, patients complicated by severe diseases of the heart, liver, kidney, brain and hemopoietic system; 2) patients with history of alcohol or drug dependence, or taking drugs improving cognition; 3) patients with dementia or psychiatric symptoms; or 4) patients with other physical or mental disorders that may lead to cognitive impairment. In addition, another 90 healthy control subjects with matched age, education level and physical condition were selected as the healthy control group. Moreover, these healthy control subjects had no serious physical diseases, no complaint of hypomnesia and normal computed tomography (CT) and magnetic resonance imaging (MRI) of the brain. Both breast cancer group and healthy control group were divided into young group (≤40 years, n=40), middle-aged group (41-65 years, n=40) and elderly group (>65 years, n=40). Each age group in the TNBC group and non-TNBC group included 20 patients. Signed written informed consent was obtained from all participants before the study entry.

Methods

Participants in both breast cancer group and healthy control group completed the MMSE, RM and PM questionnaires in a quiet and harassment-free environment. The MMSE scale mainly covers time, place, immediate memory, delayed memory, attention & calculation, language and visuospatial capability, with 30 questions in total (1 point for correct answer and 0 point for unknowing or wrong answer in each question). Score ≥26 points shows that cognitive function is normal, and score <26 points means that cognitive function is impaired. For scores of RM and PM, the criteria of Crawford et al. were referred to [5]. As to RM and PM questionnaire survey, both RM and PM include 8 items. Each item is scored based the severity of memory impairment (1 point for mild, 2 points for severe, 3 points for severer and 4 points for severest). The total scores of 8 items are the scores of RM and PM, respectively. The higher the score, the severer the hypomnesia.

Statistics

All statistics were performed using SPSS 19.0 software (IBM, Armonk, NY, USA). The independent-samples t-test was used for the intergroup comparison, and Spearman's correlation analysis was performed for evaluating the relationships. The multivariate logistic regression was used to analyze relevant risk factors. P<0.05 suggested statistical significance.

Results

Comparisons of age, education level and scores of MMSE, RM and PM scales between breast cancer group and healthy control group

There were no statistically significant differences in age and education level between the two groups, but the differences in scores of MMSE, RM and PM scales were statistically significant between the two groups (p<0.001, Table 1). In breast cancer group, age was negatively correlated with the MMSE score (r=-0.614, p<0.001), but positively correlated to the scores of RM scale and PM scale (r=0.527, 0.439, p<0.001), while no obvious correlation between education level and age was detected (p=0.625). In the healthy control group, there was a negative association between MMSE score and age, positive correlations of RM and PM scale scores with age (r=-0.766, 0.721, 0.613, p<0.001) and no

Table 1. Comparisons of indexes between breast cancer group and healthy control group

Indexes	*Breast cancer group mean±SD*	*Healthy control group mean±SD*	*t*	*p*
Age (y)	52.04±8.18	50.44±9.26	0.531	0.310
Education level (y)	11.27±4.35	10.78±6.51	2.184	0.112
MMSE (score)	25.63±4.46	27.91±2.84	-4.728	<0.001
RM (score)	18.12±6.74	12.80±7.32	5.152	<0.001
PM (score)	17.11±5.93	12.16±6.78	3.930	<0.001

MMSE: mini-mental state examination, RM: retrospective memory, PM: prospective memory

distinct relationship between education level and age (p=0.448).

Comparisons of age, education level and scores of MMSE, RM and PM scales between TNBC group and non-TNBC group

Age and education level showed no statistically significant differences between the two groups, but the differences in scores of MMSE, RM and PM scales were statistically significant (p<0.05, Table 2).

Comparisons of MMSE, RM and PM scale scores and education level among different age groups in TNBC group and non-TNBC group

There were statistically significant differences in the MMSE, RM scale and PM scale scores among young group, middle-aged group and elderly group in both groups (p<0.001), but no statistically significant difference was found in terms of education level (Table 3).

Comparisons of scores of MMSE, RM and PM scales and education level between TNBC group and non-TNBC group in each age group

In the young group, the scores of MMSE, RM and PM scales in TNBC group had statistically significant differences compared with those in non-TNBC group (p<0.001), while no statistically significant difference in the education level was detected. In the middle-aged and elderly groups, the differences in scores of MMSE, PM scale and RM scale and education level were not statistically significant between TNBC group and non-TNBC group (Table 4).

Table 2. Comparisons of indexes between TNBC group and non-TNBC group

Indexes	*TNBC group*	*Non-TNBC group*	*t*	*p*
Age (y)	51.57±8.40	53.62±7.59	0.936	0.729
Education level (y)	11.02±4.51	11.47±4.25	1.922	0.414
MMSE (score)	24.16±4.32	26.38±4.61	-7.023	0.003
RM (score)	19.53±5.94	14.19±7.26	2.679	0.006
PM (score)	18.27±7.83	15.54±5.72	3.625	0.002

TNBC: triple negative breast cancer, MMSE: mini-mental state examination, RM: retrospective memory, PM: prospective memory

Table 3. Comparisons of indexes among different age groups in TNBC group and non-TNBC group

Indexes	*TNBC group*				*Non-TNBC group*			
	≤40y mean±SD	*41-65y mean±SD*	*> 65y mean±SD*	*p*	*≤40y mean±SD*	*41-65y mean±SD*	*>65y mean±SD*	*p*
MMSE (score)	26.14±2.98	25.52±3.74	22.03±4.92	<0.001	28.42±3.29	27.37±4.65	23.03±4.74	<0.001
RM (score)	18.25±5.98	18.81±4.96	20.24±5.85	<0.001	12.81±7.01	14.16±6.69	16.62±7.78	<0.001
PM (score)	17.36±8.02	18.00±7.28	20.59±7.64	<0.001	14.03±5.53	17.36±8.02	16.26±5.74	<0.001
Education level (y)	12.21±3.35	11.04±3.46	10.52±5.17	0.615	12.32±3.46	11.17±3.48	10.61±5.09	0.268

TNBC: triple negative breast cancer, MMSE: mini-mental state examination, RM: retrospective memory, PM: prospective memory

Table 4. Comparisons of indexes between TNBC group and non-TNBC group in each age group

Indexes	*≤40y*			*41-65y*			*> 65y*		
	TNBC group mean±SD	*Non-TNBC group mean±SD*	*p*	*TNBC group mean±SD*	*Non-TNBC group mean±SD*	*p*	*TNBC group mean±SD*	*Non-TNBC group mean±SD*	*p*
MMSE (score)	26.14±2.98	28.42±3.29	<0.001	25.52±3.74	27.37±4.65	0.079	22.03±4.92	23.03±4.74	0.065
RM (score)	18.25±5.98	12.81±7.01	<0.001	18.81±4.96	14.16±6.69	0.324	20.24±5.85	16.62±7.78	0.716
PM (score)	17.36±8.02	14.03±5.53	<0.001	18.00±7.28	17.36±8.02	0.592	20.59±7.64	16.26±5.74	0.824
Education level (y)	12.21±3.35	11.04±3.46	0.436	11.04±3.46	11.17±3.48	0.618	10.52±5.17	10.61±5.09	0.293

TNBC: triple negative breast cancer, MMSE: mini-mental state examination, RM: retrospective memory, PM: prospective memory

Analyses on risk factors for cognitive impairment in breast cancer patients

Multivariate logistic regression analysis was used, with pathological type (0=non-TNBC and 1=TNBC) and age as independent variables and cognitive impairment (0= without and 1= with) as a dependent variable. The results suggested that TNBC (OR=3.659, p=0.004, 95% CI: 1.325-8.973) and age (OR=1.128, p<0.001, 95%CI: 1.047-1.221) were risk factors for the occurrence of cognitive impairment in patients with breast cancer.

Discussion

At present, studies about CICI in breast cancer mainly focus on hypomnesia or memory loss, and different populations are clearly heterogeneous [1]. Previous studies have manifested that various chemotherapeutic agents (such as cyclophosphamide, fluorouracil and its derivatives and methotrexate) can lead to changes in brain structure and function in specific regions via the blood-brain barrier [2-4]. A study discovered that TNF-α content is significantly elevated in patients undergoing chemotherapy for breast cancer, and the above-mentioned patients with high TNF-α level had more evident hypomnesia, while high level of TNF-α is also associated with reduced prefrontal lobe metabolism [6]. Therefore, it is inferred that chemotherapy is able to result in inflammation of the body and release of inflammatory factors such as TNF-α, causing cognitive impairment.

TNBC refers to breast cancer in which estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (Her-2) are not expressed. Besides, endocrinotherapy and targeted drug treatment against Her-2 are not effective as treatment of TNBC, and the main treatment method for patients with this subtype is systemic chemotherapy that, however, has poor long-term response [7]. This study indicated that TNBC was related to the heterogeneity of CICI in breast cancer, which might be correlated with the protective roles of hormone receptors and Her-2 in the cognitive process. Estrogen and progesterone, having many beneficial effects on the central nervous system (CNS), are involved in the regulation of brain function in learning and memory. CNS is one of the major target organs of estrogen and progesterone [8]. Estrogen and progesterone receptors massively exist in the prefrontal lobe and hippocampus-related memory regions. Estrogen and progesterone bind to the corresponding receptors in the brain, quickly activating signaling cascade and regulating synaptic plasticity, thus adjusting the cognitive function [9,10]. This process plays a key role in the cognitive process. Studies have revealed that the protective effects of estrogen and progesterone on the nervous system are correlated with improvement of cholinergic deficiency, suppression of apoptosis and astrocyte aggregation and increased expression of 5-hydroxy triptamine 2A [11]. Other studies have suggested that after chemotherapy, the overall cognitive function and memory impairment of breast cancer patients with ER and PR double-negative are more significant than those in patients with ER and PR double-positive, proving that cognitive impairment is closely related to hormone receptors. Her-2 is also known as ErbB-2, which belongs to the Her family. Neuregulin-1 (NRG1) is a neurotrophic factor, which plays multiple roles in CNS and functions as neuroprotector. Research speculated that NRG1 signal exerts its function through the ErbB family receptor protein tyrosine kinase, Her-2 is able to bind to NRG1, and the NRG1/ErbB pathway benefits the physiological roles of endothelial cells, oligodendrocytes and neurons and has a neuroprotective function [12,13]. Based on this, it is conjectured that the lack of Her-2 expression in TNBC patients may affect CICI.

This study also showed that with increasing age, MMSE score gradually declined, while scores of RM and PM questionnaires were increased in a gradual way, and age was a risk factor for CICI in breast cancer. Active experiments have indicated that more and more patients undergoing chemotherapy have cognitive impairment and lowered information processing speed with the increase in age, which is consistent with the results of this study [14]. In addition to the above CICI mechanism, aging itself can impact cognitive function by influencing hormone levels, promoting cell senescence and inducing DNA damage. Therefore, chemotherapy and aging may synergistically affect CICI in breast cancer. However, this study suggested that the difference in CICI between TNBC group and non-TNBC group was mainly detected in the young group, which might be related to the younger age at TNBC onset, and the younger the patient, the worse the prognosis. The results suggest that TNBC may play a more important role in CICI in breast cancer than age.

In summary, both TNBC and age are risk factors for CICI in breast cancer. The overall cognitive function and memory impairment in TNBC patients and elderly patients are more severe than those in non-TNBC patients and young patients. This study revealed that CICI in breast cancer patients with different pathological types and ages was discrepant, providing a theoretical basis for

further study on CICI mechanism and individualized treatment of breast cancer.

Conclusions

Varying degrees of cognitive impairment are detected in breast cancer patients undergoing chemotherapy. TNBC patients have severer cognitive impairment in comparison with patients without TNBC. The difference is more likely to be found in young patients. Furthermore, both TNBC and age are risk factors for CICI in breast cancer.

Conflict of interests

The authors declare no conflict of interests.

References

1. Nagykalnai T, Landherr L. The post-treatment cognitive impairment ("chemobrain") in breast cancer patients. Short review. Magy Onkol 2017;61:349-51.
2. Winocur G, Berman H, Nguyen M et al. Neurobiological mechanisms of chemotherapy-induced cognitive impairment in a transgenic model of breast cancer. Neuroscience 2018;369:51-65.
3. Panousis D, Ntasiou P, Grosomanidis D et al. Impact of Oncotype DX on chemotherapy assignment: A retrospective single-center study on female breast cancer patients. JBUON 2017;22:1199-1208.
4. Mandelblatt JS, Stern RA, Luta G et al. Cognitive impairment in older patients with breast cancer before systemic therapy: Is there an interaction between cancer and comorbidity? J Clin Oncol 2014;32:1909-18.
5. Crawford JR, Smith G, Maylor EA, Della SS, Logie RH. The Prospective and Retrospective Memory Questionnaire (PRMQ): Normative data and latent structure in a large non-clinical sample. Memory 2003;11: 261-75.
6. D'Mello C, Le T, Swain MG. Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factoralpha signaling during peripheral organ inflammation. J Neurosci 2009;29:2089-2102.
7. Xu FR, Wang XD, Jiang ZF. New strategy for the endocrinotherapy of breast cancer. Zhonghua Yi XueZaZhi 2018;98:244-7.
8. Baudry M, Bi X, Aguirre C. Progesterone-estrogen interactions in synaptic plasticity and neuroprotection. Neuroscience 2013;239:280-94.
9. Toffoletto S, Lanzenberger R, Gingnell M, Sundstrom-Poromaa I, Comasco E. Emotional and cognitive functional imaging of estrogen and progesterone effects in the female human brain: A systematic review. Psychoneuroendocrinology 2014;50:28-52.
10. Berent-Spillson A, Briceno E, PinskyA et al. Distinct cognitive effects of estrogen and progesterone in menopausal women. Psychoneuroendocrinology 2015;59:25-36.
11. Hu Z, Yang Y, Gao K, Rudd JA, Fang M. Ovarian hormones ameliorate memory impairment, cholinergic deficit, neuronal apoptosis and astrogliosis in a rat model of Alzheimer's disease. ExpTher Med 2016;11:89-97.
12. Gao R, Ji MH, Gao DP et al. Neuroinflammation-Induced downregulation of hippocampacal neuregulin 1-ErbB4 signaling in the parvalbumin interneurons might contribute to cognitive impairment in a mouse model of Sepsis-Associated encephalopathy. Inflammation 2017;40:387-400.
13. Nicodemus KK, Luna A, Vakkalanka R et al. Further evidence for association between ErbB4 and schizophrenia and influence on cognitive intermediate phenotypes in healthy controls. Mol Psychiatry 2006;11:1062-5.
14. Kvale EA, Clay OJ, Ross-Meadows LA et al. Cognitive speed of processing and functional declines in older cancer survivors: An analysis of data from the ACTIVE trial. Eur J Cancer Care 2010;19:110-7.