DOI 10.25789/YMJ.2020.69.08

УДК 616.891.6:616.895.4: 618.19:616-006

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# THERAPY OF PATIENTS WITH BREAST CANCER WITH ANXIETY AND DEPRESSIVE DISORDERS

Breast cancer (BC) is one of the leading causes of cancer death worldwide. The problem of mental health and quality of life of such patients is currently particularly relevant. Most patients with breast cancer in the process of adapting to the disease experience certain mental disorders: depressive, anxiety-phobic and psychosomatic disorders.

Purpose. To study the severity of anxiety-depressive disorders in the clinical picture in patients with breast cancer and evaluate the effectiveness of specialized pharmacotherapy using antidepressants in combination with antitumor therapy.

Material and method. The study included 30 patients with a first established diagnosis of breast cancer and 52 patients with a follow-up history of 3-17 years. The main method of work was the clinical, psychopathological, and statistical research methods (a method using contingency tables and the Fechner coefficient, a method using the Chi-square test). To evaluate the effectiveness of psychopharmacotherapy, psychometric data were statistically processed on the basis of statistica 10.

Results. To assess the severity in the clinical picture of anxiety-depressive tendencies and the effectiveness of treatment, special scales were used: hospital scale of anxiety and depression (HADS); general clinical impression scale (CGI) for assessing disease severity (CGI-S "severity") and improvement (CGI-I "improvement"). High antidepressant therapy efficacy indicators were obtained in combination with benzodiazepine drugs and hypnotics in a group of patients with anxiety-depressive nosogenia (15 patients, 88% of respondents with reduction in starting anxiety and depression scores HADS more than 50%, CGI 85%), in the group with chronic hypochondriac dysthymia and cyclotymic endoform depression.

Conclusion. The data obtained in the study confirm the effectiveness of psychopharmacotherapy with antidepressants in breast cancer patients with identified disorders of the anxiety - depressive spectrum.

**Keywords:** breast cancer, anxiety, depressive disorder.

**Introduction.** Breast cancer (BC) is one of the common malignant tumors. With early diagnosis and treatment, the 5-year survival rate of such patients is 89% [3, 5, 7, 11]. Most patients with breast cancer during adaptation to the disease and during complex therapy reveal depressive, anxiety-phobic and psychosomatic disorders, which significantly reduces their quality of life, causes a sense of hopelessness, suicidal thoughts [1, 2, 4, 6, 8, 26]. Depression is one of the most common diagnoses for breast cancer patients (from 5% to 40%), side effects of hormone or chemotherapy (menopause, pain and insomnia) lead to the development of depression.

The use of antidepressants is effective in the treatment of depressive disorders and various somatovegetative symptoms that occur in patients with breast cancer [7, 11, 15]. According to Sanjida S. et al. [7] the appointment of antidepressants for cancer patients was 15.6% for breast cancer patients - 22.6%. The most popular antidepressants in the treatment of somatovegetative disorders in breast cancer patients (asthenia, vasomotor symptoms due to ovariectomy or antiestrogen therapy) [13,26,29] are selective serotonin reuptake inhibitors (SSRIs) [25,27]. The use of SSRIs and SSRIs (serotonin and norepinephrine reuptake inhibitors) significantly reduced the frequency and severity of vasomotor flushing in breast cancer patients by 14-58% compared with placebo therapy [29]. For the treatment of vasomotor "hot flashes", the efficacy of paroxetine, fluoxetine, citalopram in a therapeutic dose of 10-20 mg/day, venlafaxine - 37.5-75 mg/day was noted [29]; sertraline (50 mg/day), duloxetine (60 mg/day) are effective in the treatment of vasomotor disorders, the treatment period was 6-12 weeks [11,14,24]. The effectiveness of antidepressants in the complex treatment of neuropathic pain in breast cancer, anxiety-depressive disorders, including anxiety-phobic disorders, major depressive (MDD) and post-traumatic stress disorders (PTSD) has been shown [13, 14, 17, 19, 25]. The use of antidepressants is diverse according to the indications for the appointment and choice of drugs. The appointment of amitriplillin as an agent for the relief of neuropathic pain (from 25-50 mg/day to 150 mg/day) showed high efficiency (59.6%) during 8 weeks of administration, however, anticholinergic side effects were noted in comparison with the drugs of the SOIZS group (19%) [17]. Paroxetine compared with tricyclic antidepressants is the drug of choice for long-term use [10, 23]. SSRIs due to their better tolerance are the drugs of choice for the treatment of anxiety-depressive disorders in breast cancer patients [7, 9, 11, 27]. The appointment of SSRI antidepressants should be correlated with possible cross-drug interactions at the level of metabolism of the cytochrome P450 system and its subunits CYP2D6 and CYP3A4, especially for patients with breast cancer taking tamoxifen and its analogues [16, 19, 20]. Sertraline, escitalopram, citalopram and venlafaxine have the least cross-drug interaction and are the drugs of choice in the treatment of breast cancer patients. Caution is necessary when prescribing high dosages in patients taking aspirin, non-steroidal anti-inflammatory drugs, warfarin or heparin [27].

A study of the effectiveness of sertraline in all types of depression in patients with breast cancer undergoing chemotherapy for 12 weeks (from 25 mg/day to 100 mg/day). showed improvement:> 50% of the points on the Montgomery-Asberg Depression Rating Scale (MADRS); a significant decrease in fatigue, anhedonia, and suicidal thoughts was

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observed [24,27]. The use of escitalopram (10 mg/day for 2 weeks) in a study in palliative cancer patients, including breast cancer, revealed a significant decrease in anxiety-depressive disorders on the HADS anxiety and depression scale, and hopelessness-helplessness, on the scale of mental adaptation to cancer Mini-MAC [22]. Venlafaxine is one of the SSRIs well tolerated by cancer patients, the least active in the CYP450 system and is the drug of choice for patients taking tamoxifen due to the lack of inhibition of CYP2D6. Venlafaxine reduces vasomotor flushing in patients receiving antiestrogen chemotherapy or undergoing ovariectomy [23, 29]. Duloxetine (30-60 mg/day, 4-12 weeks) is an SSRI approved for the treatment of depression and anxiety, neuropathy and chronic pain in patients with breast cancer [14, 28]. In patients with breast cancer, the indicators improved significantly on each of the scales (HADS, general clinical impression (CGI-S) and the Montgomery-Asberg Depression Assessment (MADRS) [26]. Special attention should be paid to antidepressants with a melatonergic effect. Melatonin significantly reduced the risk of developing depressive symptoms in women with breast cancer during a three-month period at a dose of 6 mg/day after surgery, and affected subjective symptoms: anxiety, general well-being, pain, and drowsiness. In stress disorders, in particular PTSD and anxiety-phobic disorders, SSRIs, SSRIs and mirtazapine are the drugs of choice for cancer patients, in combination with benzodiazepines [12, 13, 25]. Mirtazapine was used to treat major depressive disorder in breast cancer patients for 24 weeks, with a decrease in HAM-D score of> 50% was defined as a positive effect [12, 19].

**Purpose of the study.** To study the severity of anxiety-depressive disorders in the clinical picture in patients with breast cancer and evaluate the effectiveness of specialized pharmacotherapy using antidepressants in combination with antitumor therapy.

**Research material and methods.** The study was performed in the department of somatogenic psychological pathology (headed by doctor of medical sciences, professor S.V. Ivanov) of the department for the study of borderline mental pathology and psychosomatic disorders (headed by academician of the Russian Academy of Sciences, professor A.B. Smulevich) of Mental Health Research Center (dir. – doctor of medical sciences, professor T. P. Klyushnik) in collaboration with the departments of chemotherapy and combined treatment of malignant tumors (head - doctor of medical sciences,, A.A. Meshcheryakov) and clinical pharmacology and chemotherapy (head - doctor of medical sciences, professor S.A. Tyulyandin), department of chemotherapy (head - doctor of medical sciences A.A. Fedenko), N.N. Blokhin Oncology Scientific Medical Research Center (dir. - corresponding member of the Russian Academy of Sciences, professor I. S. Stilidi). Recruitment of patients in the study sample was carried out on the basis of the departments of the N.N. Blokhin Oncology Scientific Medical Research Center. The study included 82 patients with histologically verified breast cancer. Patients whose condition did not allow a psychopathological examination to be performed to the required extent were excluded from the study. Patients meeting the criteria were included in the study: 1) a verified diagnosis of breast cancer, 2) psychopathological disorders manifesting in connection with the circumstances of the somatic disease (F40 - F48 neurotic stress-related and somatoform disorders according to ICD-10). The study included 30 patients with a first established (6.8 ± 1.2 months from the time of diagnosis) diagnosis of breast cancer who were admitted to the hospital for routine examination and treatment (average age 49.7 ± 4.1 years) and 52 patients (mean age 56.8 ± 6.7 years) with a follow-up history of 3-17 years (mean disease duration 5.7 ± 2.9 years). Patients with higher education prevailed - 50 people. (60.9%), 49 people were married. (59.7%). 20 people worked without reducing the load. (24.3%), with a decrease in load of 25 people. (30.5%), 37 people did not work / were retired. (45.1%). The study was approved by the ethics committee of Mental Health Research Center and N.N. Blokhin Oncology Scientific Medical Research Center.

The main method of work was the clinical - psychopathological and statistical method using contingency tables and the Fechner coefficient, a method using the Chi-square test. A psychopathological assessment was carried out as part of a clinical review involving NCPP staff under the supervision of academician of the Russian Academy of Sciences, professor A.B. Smulevich and doctor of medical sciences, professor S.V. Ivanov. To assess the severity in the clinical picture of anxiety-depressive disorders and the effectiveness of treatment, special scales were used: hospital scale of anxiety and depression (HADS [Zigmond A. S., Snaith R.P., 1983]); general clinical impression scale (CGI [McGuya W., 1976]) for assessing disease severity (CGI-S "severity") and improvement (CGI-I "improvement"). To assess the effectiveness of psychopharmacotherapy, psychometric data were processed statistically based on statistica 10.

**Results and discussion.** The choice of drugs to ensure the treatment of breast cancer patients with anxiety - depressive disorders, the selection of optimal doses and the duration of treatment courses were determined individually depending on the syndromic structure and in accordance with the dynamics of the somatic and mental status of patients, as well as taking into account potential drug interactions in in conditions of polychemotherapy of antitumor drugs. The sample of patients included patients at all stages of breast cancer (I – IV), with the greatest accumulation of patients of stage IV. There were 69 patients in premenopause, of which 49 patients had a hormone-resistant type of tumor, and 18 patients had a hormone-sensitive type of tumor. There were 15 patients in menopause, of which a hormone-resistant type of tumor was observed in 12 patients, a hormone-resistant type in 3 patients. The most popular chemotherapy regimens included such combinations as FAC / CAF (5-Fluorouracil, Adriablastin, Cyclophosphamide in direct and reverse sequence, with different dosages and administration schedule), CA (Doxorubicin-Cyclophosphamide), CVMF (Cyclophosphamide, Vincristine, Methotrexate 5 – Fluorouracil), as well as various combinations of taxanes (Docetaxel, Paclitaxel) and platinum preparations (Cisplatin, Carboplatin) with Doxorubicin, Gemcitabine, Trastuzumab and other chemotherapy drugs.

Possible undesirable cross-pharmacological effects were evaluated by the degree of interaction of specific drugs with the cytochrome P 450 enzyme system. The effectiveness of therapy was evaluated after 6 weeks of treatment (immediate effect), and after 12 weeks (long-term effect). With the early withdrawal of drugs for any reason (the need for surgery, severe somatic condition, patient participation in the study of antitumor drugs according to the protocol, patient self-cancellation), a renewal of depressive and anxious symptoms was observed on average 2–5 days after withdrawal. In case of discontinuation of antidepressant therapy after several months (from 6 to 12 months), drug withdrawal syndrome did not form. Pharmacotherapy tolerance was good. The first signs of clinical

improvement occurred on the 10-14th day of therapy and reached a maximum level by 6-12 weeks of treatment. In this study, not a single case of adverse drug interactions between psychotropic drugs and drugs used for chemotherapy of breast cancer was recorded.

In the group of patients with newly diagnosed breast cancer (6.8 ± 1.2 months from the time of diagnosis), anxiety-depressive disorders according to clinical examination and psychometric scales were recorded in 17 of 30 patients (56.6%). The average HADS hospital score for these patients was 18–20 points on the anxiety scale (18.2 ± 1.22) and 16–20 points on the depression scale (17.93 ± 1.38), which corresponds to "severe disturbances" (table 1). According to the CGI-S clinical impression scale, the average total score was 4.6, which corresponds to a shift in the degree of impairment to the value of "acute impairment"

In the follow-up group of patients with a breast cancer duration of 3-17 years, chronic hypochondriac dysthymia requiring drug exposure was recorded in 23 patients. In 9 patients, cyclotymic endoform depression was registered against the background of disease progression after prolonged (from 1 year to 7 years) breast cancer remission. The total number of patients requiring psychopharmacotherapy in this group was 32 people. (61.5%). The average HADS score for these patients was 14–16 points on the anxiety scale (15.3 ± 0.76) and 16–18 points on the depression scale (17 ± 0.79) (table 1). The total total score on the CGI-S scale was 4.4, which corresponds to the average value between "clear violations" and "acute violations". The total number of patients in both groups in need of correction by antidepressants was 49 out of 82 patients (59.7%). The choice of drugs was carried out depending on the prevalence of one or another symptomatology in the clinical picture: in the case of a predominance of alarming symptoms, drugs with anti-anxiety and/or sedative effect were prescribed, such as paroxetine (10 - 40 mg/day), mirtazapine (15 - 45 mg/day), amitriptyline (50 - 100 mg/day). In the case of a predominance of melancholy affect with signs of apathy, drugs with a psychostimulating (SSRI group) and / or "double" action (SSRI) were prescribed: sertraline (up to 100 mg/day), venlafaxine (up to 150 mg/day), duloxetine (up to 120 mg/day). In order to stop anxiety and insomnia in patients, in addition to antidepressant therapy, anxiolytic drugs (diazepam, alprazolam, clonazepam) or hypnotics (zopiclone, zolpidem tartate) were prescribed.

In the group of breast cancer patients with anxiety-depressive disorders, a good response to antidepressant therapy was observed after 7-10 days in most patients (15), 88% of responders with a reduction in starting points on the HADS clinical scale of more than 50% (7.86 ± 0, 81 on the anxiety scale and 7.2 ± 1.06 on the depression scale, which corresponds to a subclinical level), on the CGI scale of 85% (table 1). The average total score on the CGI-I scale (to assess improvement) at the last visit was 1.5, which is the average value between grades 1 - "very pronounced improvement" and 2 - "pronounced improvement"). Complete reduction of anxiety - depressive disorders was observed in 2 patients with initial stages of breast cancer (I-II). In most cases (75%), a tangible therapeutic effect developed even when prescribing low starting dosages that did not reach those recommended by the treatment protocol. In a number of signs of improvement, patients noted a significant decrease in anxiety symptoms, normalization of sleep, appetite, decreased depression, restoration of affective background by the 6-th week of treatment.

The stabilization of the clinical effect was observed by the 12-th week of psychopharmacotherapy. In 86% of patients, background manifestations of anxiety that did not reach the clinical level remained due to the features of the diagnosis and prognosis of the underlying disease during subsequent follow-up. In order to consolidate the achieved remission and further improve the condition, the patients underwent maintenance therapy with a partial reduction in dosages, or with the cancellation of psychotropic drugs for 6-12 months, depending on the initial severity and dynamics of the anxiety - depressive symptoms.

In the follow-up group of breast cancer patients with chronic hypochondriac dysthymia and cyclothymic endoform depression, the high effectiveness of specialized pharmacotherapy has been established. The proportion of patients with a reduction in psychopathological symptom complexes (anxiety-phobic, asthenic, somatoform, affective disorders, post-castration vegetative symptoms) more than 50% on the HADS scale was 93.7% (30 people, 8.5 ± 1.61 on the anxiety scale and 6 , 77 ± 1.08 on the depression scale), a significant clinical improvement on the CGI-I scale of 90.6% (29 people, the average total score is 2). A significant effect of the therapy was associated with the combined use of pharmacological agents of a psychotropic effect - benzodiazepines and antidepressants of the SSRIs group, SSRIs, tri- and tetracyclic antidepressants. Clinical improvement occurred on days 10-14, with further gradual reduction of anxiety and depressive symptoms. In 46% (n = 15), anxiety-phobic and somatoform disorders prevailed in the clinical picture. The following psychotropic drugs were used to stop the disorders: alprazolam / lorazepam (0.5-1 mg/day) + paroxetine 20-40 mg/day, amitriptyline 50-75 mg/day, fluvoxamine 50-100 mg/day, mirtazapine 15-45 mg/day, sertraline up to 100 mg/day, venlafaxine up to 150 mg/day). In 53% (n = 17), affective and asthenic disorders predominated. In order to correct them, effective therapy using antidepressants of the IOPSSi group was used: venlafaxine 75 mg/day, duloxetine 60 mg/day. To stop concomitant insomnia in both groups of patients, benzodiazepine drugs (clonazepam, phenazepam) or hypnotics (zolpidem tartrate, zopiclone) were used. In 71% (n = 23) patients, against the background of an anxious depressive state, somatovegetative postcastration (climacteric) phenomena associated with the use of antiestrogen hormone therapy intensified. Hypoestrogenia states, expressed in autonomic dysfunction (hot flashes, increased blood pressure, heart attacks, dizziness, sweating), completely or significantly stopped against the

**The dynamics of the severity of anxiety and depression on the HADS scale before and after treatment in patients with anxiety-depressive nosogenia, chronic hypochondriac dysthymia and cyclothymic endoform depression**

| Disorder | Subscales HADS | HADS rate Before and after psychopharmacotherapy | |
|---|---|---|---|
| | | before | after |
| Anxious- depressive reaction | anxious | 18.2±1.22 | 7.86±0.81 |
| | depressive | 17. 93 ±1.38 | 7.2±1.06 |
| Chronic hypohondrical dysthymia, endogenoform cyclothymic depression | anxious | 15.3±0.76 | 8.5±1.61 |
| | depressive | 17±0.79 | 6.77±1.08 |

background of combined therapy with SSRI antidepressants and anti-anxiety drugs.

In most cases, clinical improvement occurred on the 10-14th day with a further gradual reduction of anxiety and depressive symptoms to a sub-syndromic level. The affective background was normalized, there was an improvement in sleep and appetite, fears associated with cancer and a quick adverse outcome were deactivated. At the same time, the phenomena of symptomatic and reactive lability (exacerbation of psychopathological disorders under the influence of somatogenic and psychogenic factors) persisted. In these cases, prolonged use of the minimum doses of psychotropic drugs used was recommended.

**Conclusion.** The data obtained confirm the effectiveness of antidepressant therapy in patients with breast cancer with anxiety - depressive disorders. High efficacy of antidepressant therapy in combination with benzodiazepine drugs and hypnotics has been shown (15 patients, 88% of responders with a reduction in starting anxiety and depression scores by HADS of more than 50%, on a CGI scale of 85%), in the group with chronic hypochondria dysthymia and cyclotymic endoform depression (the proportion of patients with a complete reduction in psychopathological symptom complexes (anxiety - phobic, asthenic, somatovegetative, affective disorders) - amounted to 93.7% (30 patients), according to the CGI-I scale of 90.6% (29 patients). In patients with anxiety-depressive disorders of the asthenic and somatovegetative spectrum, it is advisable to prescribe modern selective serotonin and noradrenergic antidepressants with good tolerance and safety. The drugs and their doses were selected individually taking into account tolerance and drug interactions, according to the principle "benefit ratio exceeds the possible risk for the patient" The results of the study can help optimize specialized care for cancer patients. and the medical and diagnostic stage in an oncological hospital and on an outpatient basis during the subsequent stages of therapy. Patients with breast cancer are psychologically vulnerable for many reasons, including stress due to cancer diagnosis, debilitating treatment, and concomitant chronic pain. Further development of anxiety-depressive disorders without specialized therapy may jeopardize adherence to the treatment regimen and adversely affect the prognosis and survival of patients.

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# RESULTS OF STUDY OF PARAMETERS OF BIOCHEMICAL AND ANTIOXIDANT STATUS IN PATIENTS WITH OVARIAN CANCER DURING POLYCHEMOTHERAPY

DOI 10.25789/YMJ.2020.69.09

УДК 618.11-006.04-089.163:615.272.03

The use of chemotherapeutic drugs causes an increase in the formation of free radicals and a change in antioxidant status. As a result, side effects are observed. On the basis of the Oncology Dispensary Ministry of Health of the Khabarovsk Territory (Komsomolsk-on-Amur) there was conducted a controlled randomized open study of parameters of biochemical and antioxidant status in patients with ovarian cancer: 30 patients received chemotherapy (a experimental group); the control group consisted of 20 healthy women, comparable in age. Biochemical status was evaluated by the levels of total protein, albumin, bilirubin and the activity of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase in the blood of patients. Antioxidant status was evaluated by the levels of lipid hydroperoxides, conjugated dienes, and malondialdehyde and by the activity of the main components of the antioxidant system (ceruloplasmin, vitamin E) in the blood of patients. The administration of chemotherapeutic drugs to patients significantly increased the plasma levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, of lipid hydroperoxides by 50%, conjugated dienes by 51%, and malondialdehyde by 46% compared with the women in the control group. An analysis of the effect of chemotherapy on the activity of the antioxidant system components established that the blood concentrations of ceruloplasmin and vitamin E were 55 and 39%, respectively, lower than those in the control group. Thus, the incorporation of antioxidants into the treatment of patients with ovarian cancer should be considered pathogenetically justified, clinically reasonable, and promising.

**Keywords:** ovarian cancer, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lipid peroxidation, antioxidant system, patients.

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An urgent problem of modern gynecological oncology is an increase in the frequency of malignant ovarian tumors, the bulk of which are stage III-IV processes [2, 10]. Ovarian cancer is the most sensitive tumor to the therapeutic effect of cytotoxic drugs, however, the possibilities of specific therapy are limited due to toxic complications and pronounced metabolic dysfunctions at the level of the whole organism, which largely depend on the activation of lipid peroxidation (LP) [1, 15]. The action of peroxide products under these conditions is manifested in an increase in the membrane ion permeability, dissociation of oxidative phosphorylation, disruption of the structure and function of mitochondria, ribosomes, and a decrease in the activity of membrane-bound enzymes [9]. In addition, according to published data, platinum preparations, used mainly in the treatment regimen for patients with ovarian cancer, are antitumor agents that potentially cause the development of hepatotoxicity [3]. Therefore, there is a need to develop new science-based approaches and pathogenetically substantiated optimization of therapy in patients with ovarian cancer [14].

The purpose of the study was to study the parameters of biochemical and antioxidant status in patients with ovarian cancer during polychemotherapy (PCT).

**Material and methods.** A prospective, controlled, open, randomized trial was conducted in accordance with the “Rules for Qualitative Clinical Trials (GCP)” (OST No. 42–511–99 of December 29, 1998), with the provisions of the Helsinki Declaration and Guidelines for Good Clinical Practice developed at the International Conference on harmonization of technical requirements for the registration of pharmaceutical products intended for humans (ICH-GCP - International Conference on Harmonization of Technical Requirements for Human Use) and with the permission of the ethical committee of Amur State Medical Academy.

The control group consisted of 20 practically healthy women, comparable in age. The experimental group included 30 patients who are being treated in the oncology clinic of the Ministry of Health of the Khabarovsk Territory (Komsomolsk-on-Amur). Criteria for inclusion in the study: women over 18 years old; verified process (proven morphologically); stage III ovarian cancer; the absence of serious impaired renal, liver and hematopoietic function; adequate indicators of the cardiovascular and respiratory systems;