Suicidal while receiving treatment for breast cancer

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Mrs. L, age 46, is undergoing treatment for breast cancer. Three weeks into a new regimen, she feels sad and irritable, and has thoughts of suicide. What could be causing these symptoms?

CASE Worsening mood symptoms and suicidal ideation

On a recent visit to the oncology clinic, where she has been receiving treatment for breast cancer for 11 months, Mrs. L, age 46, reports the abrupt onset of sadness, irritability, difficulty sleeping, and negative self-thoughts.

Eleven months ago, Mrs. L was diagnosed with invasive lobular carcinoma of the right breast that was classified as T2N0MX, representing relatively early-stage disease. Shortly after her diagnosis, Mrs. L completed 4 cycles of neoadjuvant chemotherapy with doxorubicin and cyclophosphamide, followed by treatment with trastuzumab. Subsequently, she underwent a right segmental mastectomy with bilateral mastopexy and radiation therapy. Recently, Mrs. L's oncology team prescribed tamoxifen, 20 mg/d, and trastuzumab, 420 mg IV every 3 weeks; however, within 3 weeks after starting tamoxifen, Mrs. L's mood symptoms worsened to the point where she says she is considering suicide—with a plan to use her husband's gun to kill herself.

Mrs. L has no other pertinent medical history and no reported history of psychiatric disease.

The primary oncology team discontinues tamoxifen (after 5 weeks of treatment) and refers Mrs. L to psychiatry for further mood evaluation.

What could be the reason for Mrs. L's depressed mood?

a) cancer
b) tamoxifen and other cancer treatments
c) a previously undiagnosed mood disorder
d) all of the above

The authors' observations

The prevalence of depression is higher in patients with cancer than in the general population.[1] The etiology of depression is often multifactorial.[2] In Mrs. L's case, we hypothesized that the possible cause of her depressive symptoms included concerns about her self-image after mastectomy and the adverse effects of chemotherapy and tamoxifen.

Among these possible causes, estrogen level is particularly important. Estrogen affects the brain in numerous ways, including by modulating different neurotransmitters,[3,4] regulating neuroplasticity, providing neuroprotection by preventing formation of oxidative free radicals and of beta amyloid,

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and possibly avoiding inflammation. From a behavioral standpoint, estrogen acts as an antidepressant while enhancing memory and modulating maternal behavior.[4] Therefore, decreased estrogen levels could result in depression and other neuropsychiatric problems. This is illustrated in Mrs. L's case, where tamoxifen administered after breast cancer treatment coincided with the abrupt onset of depression with suicidal ideation.

Depression in patients receiving tamoxifen might be explained by the fact that tamoxifen is a selective estrogen receptor blocker with dual properties. Specifically, while it has antagonistic action in breast tissue, diminishing the growth-promoting action of estrogen on breast cancer cells, it additionally crosses the blood-brain barrier, so it may block the neuroprotective action of estrogen in the brain.

Clinical Point

Tamoxifen diminishes the growth-promoting action of estrogen on breast cancer cells, but also blocks estrogen's neuroprotective action in the brain

EXAMINATION Improvement in depression but slightly anxious

During her psychiatric examination, Mrs. L is fairly well-groomed and cooperative. Her speech is normal, thought process is organized, and she has fair insight into her medical situation, with fair judgment. She is alert, attentive, and oriented to time, place, as well as person. She confirms that she has no prior psychiatric history, including no prior suicide attempts. She lives with her husband, who has been supportive. Mrs. L has no children, and she continues to work.

Mrs. L reports that per her oncology team's instruction, she has not taken tamoxifen for almost 1 week, and notes improvement in her mood. She describes her mood as "fine now," but appears slightly anxious. She adamantly denies suicidal ideation since stopping tamoxifen; however, she confirms that prior to stopping tamoxifen, she experienced low mood, suicidal thoughts, and a decreased interest in activities. Mrs. L's Patient Health Questionnaire–9 score is 13, indicating moderate depression. She says she is constantly preoccupied with thoughts about the adverse effects of hormone therapy, and specifically about the oncology team's suggestion of a retrial of tamoxifen. Due to her constant worry, she has difficulty relaxing; her Generalized Anxiety Disorder–7 item scale score is 12, indicating moderate anxiety. She has a history of cigarette smoking but stopped after her breast cancer diagnosis. She also reports gaining weight since beginning cancer treatment (body mass index: 28.0 kg/m^2) and experiencing breast pain.

Mrs. L's vital signs are normal. Results of her laboratory workup reveal a thyroid-stimulating hormone level of 1.40 µU/mL (reference range: 0.27 to 4.20 µU/mL); a follicle-stimulating hormone (FSH) level of 78.4 mIU/mL (postmenopausal reference range: 25.8 to 134.8 mIU/mL); and an estradiol level of <12.0 pg/mL (postmenopausal range: <55 pg/mL).

The authors' observations

Studies investigating the effects of tamoxifen on mood have produced varying results (***Table,***[5-16] ***page 50***). Some researchers have found a significant relationship between depression and tamoxifen in patients with breast cancer. In a case-control study, 42 postmenopausal women with breast cancer who received tamoxifen reported statistically significant elevated depression scores.[5] Similarly, in a prospective trial that assessed mood symptoms in 21 pre- and postmenopausal women who developed estrogen deficiency during breast cancer treatment (including treatment with tamoxifen and chemotherapy), 38% of patients met the criteria for major depressive disorder (MDD) in the first 6 months of treatment. Sixty-six percent of these patients were postmenopausal, and 38% were premenopausal. Twenty-five percent of the premenopausal women who experienced MDD symptoms had been treated with tamoxifen and chemotherapy.[6]

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In a larger prospective trial (N = 257), an oncologist assessed mood symptoms in 2 groups of patients with breast cancer: individuals who received tamoxifen, and those who did not receive tamoxifen.[7] They found that 15% of patients who received tamoxifen experienced depression, compared with 3% of patients who did not receive tamoxifen; this difference was statistically significant.[7] Overall, 31% of the patients had "significant depression" and 27% discontinued tamoxifen because of adverse effects.[7] There have been 2 case reports of tamoxifen use and severe depression in patients with no prior psychiatry history[8,9] and 3 case reports of tamoxifen use and severe depression in patients who had a psychiatric history.[10-12]

One study that examined 24 men with breast cancer found that 62.5% of these patients experienced adverse effects related to tamoxifen, and 25% discontinued tamoxifen because of its adverse effects.[13] Among the various adverse effects related to tamoxifen, mood alteration was reported in 20.8% of cases, and depressed feelings were reported in 16.6%.[13]

Despite this evidence, other studies have not found an association between tamoxifen and depressed mood in patients with breast cancer. One group of researchers who assessed various symptoms self-reported by postmenopausal women who were breast cancer survivors found that the depression scores were not significant.[14] A retrospective cohort study assessed the onset of depression in patients with breast cancer with positive hormone receptor status (who received tamoxifen) vs negative hormone receptor status (who did not receive tamoxifen). These researchers did not find a statistically significant hazard ratio for "new-onset depression."[15] Unfortunately, the criteria for "new-onset depression" used in this study was the diagnosis of depression or use of an antidepressant given or ordered by a clinician, which is not a sensitive assessment of depressed mood.[15]

A multicenter randomized, placebo-controlled trial (the National Surgical Adjuvant Breast and Bowel Project) assessed the incidence of negative health outcomes, including depression, in a secondary outcome analysis.[16] These researchers did not find a statistically significant association between tamoxifen and depression. However, in this study, assessment of depression was based on self-report using the Center of Epidemiologic Studies Depression (CES-D) scale, which does not clinically categorize depression. Furthermore, these researchers strongly recommended screening for mood disorders in routine clinical practice. In this study, 3 women completed suicide, 2 of whom were in the tamoxifen arm.[16]

Which antidepressant(s) might interfere with the metabolism of tamoxifen?

a) bupropion
b) duloxetine
c) fluoxetine
d) paroxetine
e) all of the above

The authors' observations

Tamoxifen is a prodrug that converts to the active metabolite, endoxifen, via cytochrome P450 2D6 (CYP2D6) activity. Antidepressants with strong 2D6-inhibiting properties, such as fluoxetine, duloxetine, bupropion, and paroxetine, should be avoided in patients receiving tamoxifen because they interfere with the formation of the active metabolite and could reduce the effectiveness of tamoxifen and its ability to reduce the risk of cancer recurrence.[17] Antidepressants can help treat psychological distress, especially depression, which is common in patients with cancer, and vasomotor symptoms, which may impair quality of life and adherence to long-term endocrine therapy. Because tamoxifen can decrease cancer recurrence and associated mortality,[18] adherence with treatment is crucial.

continued

Clinical Point

Avoid the use of antidepressants with strong 2D6-inhibiting properties in patients receiving tamoxifen

Clinical Point

Antidepressants with strong 2D6-inhibiting properties could reduce tamoxifen's ability to reduce the risk of cancer recurrence

Table

Studies of tamoxifen and depression

Study	Design	Measures of depression/medication administered
Shariff et al[5] (1995)	Case-control study Postmenopausal women (N = 42) Assessed at baseline and 8 months after tamoxifen treatment	State-Trait Anxiety Inventory Institute for Personality and Ability Testing Depression Scale State-Trait Anger Expression Inventory Functional Living Index–Cancer Millon Clinical Multiaxial Inventory II
Duffy et al[6] (1999)	Prospective cohort study Both pre- and postmenopausal women (N = 21)	Structured Clinical Interview for the Diagnostic Statistical Manual
Cathcart et al[7] (1993)	Prospective trial Both pre- and postmenopausal women (N = 257)	Serial evaluations of cancer status and mood symptoms by an oncologist
Lin and Thompson[8] (2001)	Case report Female, age 51, no history of depression	Beck Depression Inventory Sertraline administered
Pluss et al[9] (1984)	Case report Female, age 69, no history of depression	No scales Temporal association considered
Bourque et al[10] (2009)	Case report Female, age 34, with history of depression	DSM-IV-TR criteria No scales Venlafaxine administered
De Berardis et al[11] (2014)	Case report Female, age 42, with history of adjustment disorder	Hamilton Depression Rating Scale Snaith–Hamilton Pleasure Scale Agomelatine administered
Ito et al[12] (2006)	Case report Female, age 63, with family history of depression	Hamilton Depression Rating Scale Milnacipran administered
Anelli et al[13] (1994)	Descriptive study Male patients with breast cancer (N = 24)	Telephone interview during tamoxifen treatment. To avoid confounding by other adjuvant treatments, the interview was done 8 weeks after chemotherapy or radiation therapy. None of the patients were receiving any kind of chemotherapy at the time of the evaluation
Love et al[14] (1991)	Randomized toxicity placebo-controlled trial Postmenopausal women (N = 140)	Self-report of various symptoms
Lee et al[15] (2007)	Retrospective cohort study Women with genetic mutation (N = 2,943)	No instrument used to measure depression New diagnosis of depression or start of antidepressant treatment was used as a tool to assess depressed mood
Day et al[16] (2001)	Multicenter randomized controlled trial (N = 11,064)	Center of Epidemiological Studies–Depression

Outcomes
Depression scores were higher during tamoxifen therapy and statistically significant
Thirty-eight percent of patients were diagnosed with major depressive disorder in the first 6 months of treatment
Temporal association between depressed mood and initiation of tamoxifen. Fifteen percent of patients in tamoxifen group developed depression
After tamoxifen treatment, the patient developed depression. Patient wanted to restart tamoxifen, so sertraline was initiated for prophylaxis. Depression improved and remained stable with antidepressant plus tamoxifen regimen
Cerebellar symptoms and depression improved after tamoxifen was discontinued
Depressed mood with suicidal ideation with 2 trials of tamoxifen. Antidepressant added and maintained for third trial of tamoxifen
Depression improved with agomelatine. Tamoxifen was continued with antidepressant. No recurrence of breast cancer reported
Depression improved after discontinuing tamoxifen. Antidepressant was maintained after stopping tamoxifen
Mood alteration reported in 20.8% and depression noted in 16.6% of patients
Study did not find statistical significance for depression scores, but found statistical significance for anxiety symptoms
Study did not find a statistically significant association between tamoxifen and new-onset depression
Study did not find a statistically significant association between tamoxifen and depression; however, the authors recommended screening for and treatment of depression

TREATMENT Starting an antidepressant

The psychiatry team initiates venlafaxine, 37.5 mg/d, to treat Mrs. L's anxiety and help prevent the recurrence of severe depression. They prescribe venlafaxine because they anticipate that, based on Mrs. L's age, the oncology team might reconsider treatment with tamoxifen. Venlafaxine is preferred because it has a favorable pharmacodynamic profile and does not interfere with the metabolism of tamoxifen, as is the case with many selective serotonin reuptake inhibitors.[17]

Although Mrs. L's depression had abated once she stopped receiving tamoxifen, she continues to experience anxiety and tearfulness, primarily due to fear of adverse effects of hormone therapy, and due to family as well as work stressors. Therefore, venlafaxine is gradually titrated up to 150 mg/d.

The oncology team proposes a trial of leuprolide, a gonadotropin-releasing hormone agonist that downregulates pituitary receptors, subsequently suppressing female reproductive hormones, which in turn stops the ovaries from producing estrogen so there is a minimal amount of estrogen to promote the growth of estrogen–receptor-positive breast cancer. Mrs. L declines this agent because she is concerned that she will gain weight. Instead, Mrs. L expresses interest in undergoing an oophorectomy to reduce her estrogen level. In the meantime, based on her reproductive hormone levels (FSH and estradiol levels) which are indicative of postmenopausal status, the oncology team prescribes the aromatase inhibitor (AI) exemestane 25 mg/d. The AI helps to decrease the amount of estrogen the body makes peripherally, which is the main source of estrogen in postmenopausal women.

The authors' observations

Estrogen originates in the ovaries in premenopausal women; it is also produced by peripheral conversion of androgens to estrogen in adipose tissues and muscle in

Clinical Point

Venlafaxine does not interfere with the metabolism of tamoxifen

Related Resource

- Agarwala P. Tailoring depression treatment for women with breast cancer. Current Psychiatry. 2010;9(11):39-40,45-46,48-49.

Drug Brand Names

Agomelatine • Valdoxan	Leuprolide • Eligard, Lupron
Bupropion • Wellbutrin, Zyban	Milnacipran • Savella
Cyclophosphamide • Cytoxan	Paroxetine • Paxil
Doxorubicin • Adriamycin	Sertraline • Zoloft
Duloxetine • Cymbalta	Tamoxifen • Soltamox
Exemestane • Aromasin	Trastuzumab • Herceptin
Fluoxetine • Prozac	Venlafaxine • Effexor

Clinical Point

The results of studies assessing the adverse psychiatric effects of aromatase inhibitors are mixed

postmenopausal women.[19] Aromatase inhibitors block the enzyme aromatase that converts androgen to estrogen, which leads to estrogen deficiency in postmenopausal women and possibly to neuropsychiatric effects.[19]

The results of studies assessing the adverse psychiatric effects of AIs are mixed. When the results of studies evaluating tamoxifen are compared with those evaluating AIs, overall patients who received AIs had less severe or less frequent mood symptoms. One possible explanation could be that AIs are relatively new compared with tamoxifen. Second, AIs are more commonly used in postmenopausal women with breast cancer, and these patients' overall estrogen level is significantly lower than that of premenopausal women with breast cancer. Therefore, the degree of hormone fluctuation is less intense in postmenopausal breast cancer survivors.

OUTCOME

After starting exemestane, and while still receiving venlafaxine, Mrs. L no longer experiences severe depressive symptoms. After 8 months, venlafaxine is discontinued. She continues to deny depressive symptoms but has intermittent anxiety, which she is able to manage without psychiatric medication. She continues to remain adherent with ongoing exemestane treatment, with no evidence of disease progression or recurrence.

The authors' observations

For patients with estrogen-positive breast cancer, the decision to discontinue tamoxifen because of unacceptable adverse effects is an important one because it may increase the risk of cancer recurrence. Psychiatrists have an important role in supporting the patient through this process, helping patients understand alternatives, and working with the oncology team to formulate a plan that is acceptable to everyone.

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Bottom Line

For patients with estrogen–positive breast cancer, anti-estrogen treatment can reduce the risk of cancer recurrence. However, it can cause adverse effects, including depression, that might impair quality of life and treatment adherence. For patients with severe depression, stopping estrogen blockers may be warranted. Initiating an antidepressant that does not interfere with the metabolism of tamoxifen may help treat depression and vasomotor symptoms.

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