

Management of Mood Changes Related to Treatment-Induced Menopause

Ms. R has been a patient in an ambulatory clinic since her diagnosis of breast cancer 14 months ago. At the age of 42, suspicious calcifications were found on routine mammography. Ms. R was found to have multifocal, infiltrating ductal carcinoma with widespread ductal carcinoma in situ of the right breast, node negative. A modified radical mastectomy with immediate reconstruction was followed by six cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF). She began treatment with tamoxifen upon completing her chemotherapy protocol.

Ms. R's diagnosis was preceded by a recent divorce that left her a single mother of three young children. Immediately prior to her diagnosis, she had returned to work part-time and just started to date. Ms. R told her nurse many times over the past 12 months how emotionally challenging and draining the past two years had been; however, her attitude always was strong and positive. During a follow-up appointment, Ms. R expressed overwhelming fatigue and irritability. She stated that the past six months had been extremely challenging both physically and emotionally. She said, "I don't feel like myself anymore."

In addition to fatigue and irritability, Ms. R complained of mood swings, hot flashes with night sweats, and sleep disturbances. She expressed particular frustration with the hot flashes she experienced throughout the past six months. She felt that they had not decreased in intensity or duration; the hot flashes occurred several times a day and caused her to wake several times a night in a complete sweat. On further assessment, Ms. R denied a clinical history of anxiety or depression but stated that she now felt increasingly sad and overwhelmed. Members of her immediate family, including her mother, had a history of untreated depression and anxiety. This concerned Ms. R, and she feared that she was being swept into a "dark tunnel."

Ms. R's medication profile included daily tamoxifen, multivitamins, and ibuprofen as needed. On this clinic visit, Ms. R's physical examination was unremarkable with no evidence of disease recurrence. She became amenorrheic after her second cycle of CMF. Although she felt that she had been forewarned about treatment-induced menopause, she stated that the symptoms now seemed an unfair consequence. She had found that using

Replens® (LDS Consumer Products, Cedar Rapids, IA) managed the vaginal dryness she experienced but the hot flashes seemed intolerable since beginning tamoxifen treatment. As she is fair skinned with red hair, Ms. R joked about feeling like she was "on fire" more often than not. She described the hot flashes as a burning sensation that came over her body in waves and left her feeling "shaky and sweaty." The hot flashes were most disturbing at night and frequently woke her up; she often saturated her clothes and bed linens with perspiration.

Ms. R expressed that her lack of sleep contributed to her irritability with her family. She had bouts of crying, and most mornings described "dragging myself out of bed to try and face another day." Ms. R was openly tearful when confiding her feelings of overwhelming sadness and despair. Wringing her hands, she appeared anxious and distressed.

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Clinical Problem Solving

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Multiple variables, both emotional and physical, appear to influence Ms. R's mood state. What assessment criteria should be focused on?

N. Bush: Taking a detailed history, carrying out a review of systems, and completing a thorough physical examination are critical in making an accurate diagnosis and individualizing Ms. R's treatment plan. Ruling out disease recurrence is important, as well as identifying the physical symptoms that negatively affect Ms. R's quality of life. The healthcare team must include Ms. R's history of cancer and cancer treatment(s), current

medications (both prescribed and over the counter), and her history of presenting symptom(s), including precipitating factors, onset, and duration (St. Marie, 2000). In this case, differential diagnosis also should include mood disturbance versus clinical depression exacerbated by the metabolic and endocrine changes caused by treatment-induced menopause. A careful personal and family history of depression and psychiatric illness should be investigated concurrently with the patient's associated symptoms related to her mood (e.g., sadness, teariness, insomnia, change in appetite and activity level, suicidal tendencies) (St. Marie).

What is the recommended screening for cancer-related depression?

N. Bush: Researchers have recommended that patients with cancer should be screened for episodes of persistent sadness every two weeks. These serial assessments should continue not only during the first month of treatment but, ideally, throughout follow-up to evaluate confounding effects of cancer and its treatment (Lovejoy, Tabor, Matteis, & Lillis, 2000). As in the case of Ms. R, the hormonal and physical symptoms brought on by treatment-induced menopause clearly have confounded her previous stress and the personal loss that she was experiencing even prior to her cancer diagnosis. At the time of her diagnosis, Ms. R recently was divorced and challenged with reorganizing her emotional and financial life. Her social support system had changed dramatically, and she was attempting to begin a new, intimate relationship. The physical and emotional impact of her diagnosis, mastectomy, and chemotherapy treatments were life-changing and became overwhelming because of an accumulation of stressors combined with a depleted level of personal and psychosocial resources. When the continuum of cancer extends over long periods of time and the side effects of

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treatment negatively influence quality of life, the personal and social resources needed for effective coping may be depleted, which contributes to anxiety and depression (Bush, 1998). Healthcare professionals commonly overlook these psychological manifestations because of the focus on somatic symptoms. When depression and physical illness occur together, a patient's symptoms can become more severe, which results in a poorer patient outcome (Ballenger et al., 1999). Healthcare providers must assess and treat all patients' somatic symptoms to determine the impact of these symptoms on patients' mood state and anxiety. For Ms. R, treatment of her hot flashes is imperative. Her hot flashes not only were causing distress and symptoms of anxiety (e.g., She described being "shaky and sweaty."), but also were contributing to her irritability and insomnia.

Is it common for patients with treatment-induced menopause to experience such overwhelming hot flashes as in the case of Ms. R?

T. Young & L. Bosserman: Hot flashes are experienced by an estimated 65% of breast cancer survivors (Carpenter & Lambert, 2000) when estrogen levels are low secondary to chemotherapy, surgical menopause, or the discontinuation of supplemental estrogen because of breast cancer. Hot flashes are described as a sudden sensation of heat or burning starting in the head and neck area passing in waves over the entire body. They are accompanied by profuse sweating, a sensation of pressure in the head (e.g., a headache), and occasionally shaking (e.g., tremors) and palpitations. Although hot flashes may occur at any time of the day, some women may experience them more at night, which causes the women to be awakened from sleep. This may be because of the stress or excess stimuli experienced while dreaming. The exact scientific process leading to hot flashes is not known. Changes in temperature control and hormonal fluctuations likely are responsible for a variety of vasomotor symptoms, including hot flashes (Barton, Loprinzi, & Gostout, 2002). Some women, such as Ms. R, may be affected profoundly by hot flashes. Regardless of the severity, this symptom usually becomes less intense and less frequent over three to six months for most patients. Unfortunately, however, some patients can experience severe hot flashes for years.

In addition to hot flashes, what other symptoms associated with low estrogen levels and treatment-induced menopause may contribute to mood changes?

T. Young & L. Bosserman: Memory impairment, sleeplessness, mood swings (e.g., irritability, weeping), depression, muscle or joint pain, vaginal dryness, lack of libido, and painful intercourse because of vaginal dryness can occur (Barton, Loprinzi, et al., 2002). Like hot flashes, some women never experi-

ence any of these symptoms, whereas others may have a few of these symptoms, which resolve after several months. Some women, including Ms. R, have severe symptoms that drastically reduce their quality of life. Treatments for these symptoms must be individualized, and women should be made to feel comfortable in discussing these issues with their doctors and nurses, especially after breast cancer treatment when many factors need to be taken into account to find the most effective treatment.

What is available to treat Ms. R's disturbing hot flashes, and what is the most recent role of hormone replacement therapy (HRT) for women with a history of breast cancer?

T. Young & L. Bosserman: First and foremost, the role of HRT is controversial; most recent evidence points to HRT being contraindicated in women with a history of breast cancer (Barton, Loprinzi, et al., 2002; Carpenter & Lambert, 2000). Nonhormonal treatments should be the first line of care, including lifestyle changes, nutritional supplements, nonprescription remedies, and prescription medications. Lifestyle changes include exercise, stress reduction, and avoiding diet triggers (e.g., caffeine, alcohol, spicy foods). Nonpharmacologic treatments range from vitamin therapy (e.g., vitamins C and E), herbal remedies (e.g., black cohosh, Remifemin® [GlaxoSmithKline, Research Triangle Park, NC]), and nutritional supplements (e.g., soy protein). However, the safety and efficacy of soy products in relieving menopausal symptoms in women with a history of breast cancer still must be determined by clinical trials (Low & Swain, 2002). In addition, caution must be exercised when using herbal products because of the possibility of interacting with other medications. When intolerable hot flashes or other menopausal symptoms are not relieved by nonhormonal therapies and women's quality of life is impaired, women who have had breast cancer can consent to use soy products, topical estrogen preparations, or hormonal therapies. However, healthcare providers and patients must discuss the possibility of increasing the risk of new or recurrent breast cancer versus the quality-of-life benefits with hormone treatments. In cases in which women choose to use hormone-based therapies, the lowest doses and best routes must be reviewed in detail with each patient individually. Prescription, pharmacologic nonhormonal therapies include agents such as bellerbal-S, megace, anticonvulsants (e.g., neurontin, clonidine), and antidepressants (e.g., Effexor® [Wyeth Laboratories, Philadelphia, PA], Prozac® [Eli Lilly and Company, Indianapolis, IN], other selective serotonin reuptake inhibitors). Healthcare professionals must keep abreast of the latest research and clinical guidelines available to prescribe safe, appropriate, and individualized care for every patient.

In addition to hot flashes, what other somatic symptoms are important to assess and treat in patients experiencing treatment-induced menopause, such as Ms. R?

P. Anastasia: A complete history and physical examination related to menopause must be performed. This should include identification and treatment of other possible symptoms negatively affecting mood and quality of life, such as neuronal and vascular functioning, bone strength, and tissue vitality (Barton, Loprinzi, et al., 2002). Again, a thorough history of the cancer diagnosis and treatment is imperative. Although not applicable to Ms. R's case, surgical treatments and radiation therapy (e.g., surgical oophorectomy, pelvic irradiation) are significant risks for premature menopause. Menopause changes tissue, which affects both sexual functioning and urogenital health, and a deficiency in estrogen causes a loss of elasticity and decreased lubrication of vaginal tissues. Dyspareunia, friability of tissues, and a decrease in sexual response is common. As a result of the change in the acidity of the vaginal environment, infection also is a risk (Barton, Loprinzi, et al.). Ms. R stated that Replens was effective in relieving her vaginal dryness. Other treatments may include topical estrogen creams (e.g., premarin cream), tablets, or the new vaginal estrogen ring, if not contraindicated in the patient's individual cancer history because of systemic absorption of estrogen. For example, Vagifem® (Pharmacia, Peapack, NJ) and Estring® (Pharmacia) have the lowest systemic absorption and are safe for patients with breast cancer to use; however, topical estrogen creams are not often recommended. Estring is similar to a diaphragm and is inserted into the vagina by the patient. It releases low levels of estrogen over a long period of time, which are absorbed into the vagina. A new ring should be inserted every three months. A recent report observed an increased number of cases of invasive breast cancer for a subgroup assigned to combined HRT for women who had an intact uterus ("Risks and Benefits of Estrogen Plus Progestin," 2002). Although the study only addresses one combination of estrogen and progesterone (Prempro™, Wyeth Laboratories), prescribing systemic HRT to Ms. R would not be recommended because of her recent diagnosis of breast cancer.

Stress and urge incontinence can occur because of the lack of estrogen causing a decrease in the muscle tone of the urethra and bladder. Medications such as tolterodine (Detrol®, Pharmacia), surgical treatments, or behavioral techniques (e.g., kegel exercises) may be effective in specific cases. Women's sexual history also is important to assess because it has been suggested that vaginal tissue remains healthier because of increased blood flow in women who remain sexually active (Barton, Loprinzi, et al., 2002). Estrogen deficiency will contribute to osteoporosis and the risk of bone fractures, which demands

assessment of bone density and the need for supportive measures, such as calcium (1,500 mg for postmenopausal women), vitamin D (400–800 IU), raloxifene (Evista®, Eli Lilly and Company), and alendronate (Fosamax®, Merck

& Co., Inc., Whitehouse Station, NJ) or risedronate (Actonel®, Proctor & Gamble, Cincinnati, OH). Because Ms. R is taking tamoxifen and because raloxifene is known to cause hot flashes at the same incidence as

tamoxifen, raloxifene is contraindicated. Raloxifene is approved for osteoporosis but may have some protective effects on contralateral breast cancer. Studies are ongoing to determine raloxifene's effect in breast cancer.

Clinical Highlights: Depression Related to Menopause

Definition: Diagnostic criteria for major depression are defined by clusters of symptoms identified in the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1994; Lovejoy, Tabor, & Deloney, 2000). Identifying depression in patients experiencing cancer is challenging (Massie & Popkin, 1998). In patients with cancer undergoing treatment, nonsomatic symptoms provide a more accurate index of depression (Lovejoy, Tabor, & Deloney). Treatment-induced estrogen deficiency and menopause can contribute to symptoms common to depression: negative mood swings, irritability, weeping, sleep disturbances, hopelessness, guilt, worthlessness, and low self-esteem (Barton, Loprinzi, & Gostout, 2002; Lovejoy, Tabor, & Deloney).

Incidence: Symptoms of depression occur across a continuum that can range from sadness to a major affective disorder, and mood changes in patients experiencing a life-threatening illness, such as cancer, can make the diagnosis challenging (Massie & Popkin, 1998). Symptoms of treatment-induced menopause can adversely affect a woman's quality of life and mood state (Barton et al., 2002), yet no clinical trials have studied the differential diagnosis of depression in this specific group of patients. A lower prevalence of depression has been reported in patients experiencing cancer compared to the general population when the symptoms of depression are defined more narrowly (Massie & Popkin). General medical disorders, such as cancer and its treatment, may result in clinical depression, and most patients with cancer do suffer major depressive episodes (U.S. Department of Health and Human Services, 1993). Vasomotor symptoms, such as temperature control and hormonal fluctuations, have been found to adversely affect mood and quality of life in more than half of all women experiencing menopause (Barton et al.). These symptoms have been more dramatic for women who experience a cessation of menses because of adjuvant therapy for breast cancer than for women who undergo a natural menopause (Low & Swain, 2002).

Pathophysiology: Lovejoy, Tabor, and Deloney (2000) provided a comprehensive synopsis of the neurobiology of cancer-related depression. Inherently, depressive disorders are caused by imbalances between the receptors and neurotransmitters that are re-

sponsible for firing impulses throughout mood-sensitive areas of the brain. A diminished catecholaminergic and serotonergic neurotransmission in the limbic system, basal ganglia, and hypothalamus has been theorized, with an upset of the neurotransmitter-neuroreceptor ratios that induce depression (Lovejoy, Tabor, & Deloney; St. Marie, 2000).

Clinical findings: Assessment of a mood disorder in patients experiencing cancer must include a thorough evaluation of medical, endocrine, and neurologic factors (Massie & Popkin, 1998). Risk factors for depression include personal or family history, severity of illness, concurrent stressful life events, socioeconomic pressures, a tendency toward pessimism, alcohol or substance abuse, poorly controlled pain, or treatment- or medication-induced physiologic changes (Albright & Valente, 1998). Symptoms of depression in patients with treatment-induced menopause can range from a major depressive episode (e.g., insomnia, fatigue, change in appetite, psychomotor agitation) to symptoms of dysthymia (e.g., chronic fatigue, feelings of helplessness, worthlessness, irritability, anger, poor concentration) to symptoms of atypical depression (e.g., lethargy, fatigue, panic attacks, hypersomnia) (St. Marie, 2000).

Specific menopausal symptoms that may contribute to depressed mood should be assessed. These include hot flashes, night sweats, insomnia, fatigue, anxiety, irritability, decreased cognition, and sexual dysfunction (Cormier, 2000).

Differential diagnosis: In patients experiencing cancer, organic factors underlying a depressive syndrome must be evaluated (Massie & Popkin, 1998) and treated accordingly. In patients experiencing treatment-induced menopause, differential diagnosis must include estrogen deficiency, metabolic or thyroid dysfunction, uncontrolled symptoms (e.g., nausea, pain, insomnia), personal or family history (e.g., bipolar mood disorder), psychosocial stressors, or metastatic disease (Cormier, 2000; St. Marie, 2000). Clinical tools and questionnaires are readily available to clinicians in assessing depression in the context of cancer-related symptoms (Roth & Holland, 1994).

Treatment: In the case of menopause-induced depression, attempting to treat symptoms such as hot flashes is the initial priority. Practical interventions (e.g., diet, exercise, stress-reducing activities) should be investigated. Cognitive-behavioral therapies (Lovejoy, Tabor, Matteis, & Lillis, 2000) and psy-

chopharmacologic interventions, such as the selective serotonin reuptake inhibitors, may prove effective in treating both estrogen-deficiency symptoms (e.g., hot flashes) and associated mood changes and depression (Barton et al., 2002; Lovejoy, Tabor, & Deloney, 2000).

Albright, A.V., & Valente, S.M. (1998). Depression and suicide. In R. Carroll-Johnson, L. Gorman, & N.J. Bush (Eds.), *Psychosocial nursing care: Along the cancer continuum* (pp. 153–169). Pittsburgh, PA: Oncology Nursing Society.

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Weight-bearing exercises and a nonsmoking lifestyle also protect against osteoporosis.

Cardiac functioning, including assessing family risk factors, is another important assessment to perform. The risk of cardiac disease increases after menopause because of estrogen deficiency, which causes changes in lipid profiles (Barton, Loprinzi, et al., 2002). Ms. R should have a baseline cardiac panel to evaluate her cholesterol and lipid panels. She may need to begin taking a cholesterol-lowering drug if hypercholesterolemia is identified and not controlled with diet and exercise. Lastly and most applicable to Ms. R, preliminary evidence points to changes in neuronal and cognitive functioning in women undergoing menopause. In addition, women with breast cancer undergoing chemotherapy have reported cognitive impairment known as "chemobrain" months to years after completing treatment. Chemobrain has been described as the difficulties in short-term memory and concentration often reported by women (Barton, Loprinzi, et al.). Long-term stress, such as the experience of cancer and its treatment, has been known to contribute to depression (Lovejoy, Tabor, & Deloney, 2000; Massie & Popkin, 1998). Initial treatments recommended for mood disorders and cognitive dysfunction are practical and include avoiding substance abuse (e.g., alcohol, smoking), initiating a healthy lifestyle (e.g., nutritional diet, exercise), and carrying out other stress-reducing activities (e.g., relaxation techniques, support group membership, cognitive activities such as reading). Cognitive exercises (e.g., crossword puzzles, card and board games) have been found to be helpful in keeping the mind alert.

In Ms. R's presentation of somatic symptoms and mood disorder, what treatment plan most likely would be initiated?

N. Bush: After a thorough history, review of symptoms, and physical examination, the healthcare team determined that Ms. R was not only suffering from negative menopausal symptoms but also from many symptoms related to a differential diagnosis of depression: irritability, sadness, teariness, insomnia, and difficulty getting up in the morning. Her statements were very reflective of her negative mood state (e.g., "being swept into a dark tunnel"). Depression can manifest in many different forms in patients with cancer (Lovejoy, Tabor, & Deloney, 2000; Massie & Popkin, 1998; St. Marie, 2000). Symptoms may support a diagnosis classified in the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1994), including the following most common: (a) adjustment disorder with depressed mood, (b) situational depression, (c) depression with anxiety, (d) atypical depression, or (e) major depressive episode. In addition to a thorough clinical work-up, many valuable tools are available to assist healthcare professionals in

making accurate diagnoses and developing treatment plans (Lovejoy, Tabor, & Deloney; Lovejoy, Tabor, Matteis, et al., 2000; Massie & Popkin; "NCCN Practice Guidelines," 1999; St. Marie). For Ms. R, treating her most disturbing menopausal symptoms and those related to depression are most important. Initially, Ms. R was treated for hot flashes with bellergal-S, one tablet twice daily. This medication combines ergotamine tartrate, levorotatory belladonna alkaloids, and phenobarbital. Bellergal-S must be used with caution because of its sedative and addictive properties. Also, in this case, the drug's sedative qualities had the risk of potentiating Ms. R's symptoms of sadness; however, it had the opposite benefit and decreased her anxiety and helped with her insomnia. Other important interventions were advised, including beginning a moderate exercise program, utilizing relaxation techniques, and being referred to a breast cancer support group. Practical tips to thwart off the hot flashes also were offered (i.e., drink adequate amounts of water; dress in light, cotton layers of clothing; and avoid triggers, such as spicy foods, alcohol, and caffeine) (Cormier, 2000). Ms. R was followed closely for the next month with only minimal improvement in her symptoms of depression. She continued to struggle with her feelings of sadness, and she found it difficult to motivate herself to attend a support group or routinely exercise. In addition, she found herself unable to eat. Although the bellergal-S helped with her insomnia and anxiety, she felt somewhat sedated during the daytime hours. As a result, her treatment plan was changed and she was started on an antidepressant that has demonstrated effectiveness for the control of hot flashes (Barton, La Vasseur, et al., 2002). Venlafaxine (Effexor XR) was prescribed at a starting dose of 37.5 mg orally each day for one week then titrated to 75 mg per day for a three-week period. The lower dose initially was prescribed to minimize any untoward side effects, such as mild nausea, poor appetite, sedation, and dry mouth. The patient was educated regarding possible side effects; she also was informed that a minimum of four to six weeks would be necessary for effective management of her mood and hot flashes. This is important for patient compliance: Medication must be continued long enough to experience benefit. Doses of venlafaxine can be increased to 150 mg per day if needed; in cases where patients develop worsening insomnia, nightmares, or increased depression, increasing the dose to 150 mg every morning will help resolve these symptoms. These symptoms may result from insufficient norepinephrine or epinephrine levels.

Ms. R was referred to individual psychotherapy for assistance with psychoeducational and cognitive-behavioral interventions. The healthcare team hoped that with appropriate pharmacologic and symptom control and psychological support, Ms. R would begin to feel

the emotional energy to engage in positive activities, such as relaxation techniques, exercise, and support group membership.

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