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Benefits of duloxetine may outweigh risks in a patient with hormone-positive breast cancer

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Case Report

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Abstract

Objectives. Duloxetine is the only agent for chemotherapy-induced peripheral neuropathy (CIPN) recommended by the American Society of Clinical Oncology. As a moderate inhibitor of cytochrome P450 isoenzyme 2D6, duloxetine is theorized to decrease the efficacy of tamoxifen, which may be used to treat estrogen receptor–positive breast cancer. A case prompted our team to review the literature to elucidate the risks and benefits of duloxetine use in patients with this cancer.

Methods. We present the case of a patient with estrogen receptor–positive breast cancer who was doing well on duloxetine for CIPN. Due to concern for the possible future need for tamoxifen, she was switched to multiple other agents, including venlafaxine, without success.

Results. Ultimately, the patient was switched back to duloxetine due to persistent CIPN symptoms. The theoretical risk of tamoxifen interaction with duloxetine has not been demonstrated to be clinically significant in the literature.

Significance of results. While emerging evidence suggests venlafaxine may prove an effective alternative, duloxetine remains the agent with the strongest evidence of benefit in patients with CIPN and must remain an option in this patient population.

Introduction

Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) approved by the U.S. Food and Drug Administration (FDA) to treat major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain. Duloxetine is the only agent recommended by the American Society of Clinical Oncology (ASCO) as a treatment option for chemotherapy-induced peripheral neuropathy (CIPN), which may occur in breast cancer patients receiving chemotherapy (Loprinzi et al. 2020). Additionally, within the breast cancer population, duloxetine has shown other benefits, including reduced frequency and severity of hot flashes in breast cancer survivors and reduced musculoskeletal pain associated with aromatase inhibitors in early-stage breast cancer (Biglia et al. 2018; Henry et al. 2018). Given its many uses within the breast cancer population, including those with hormone positivity, duloxetine can be an important tool for many palliative care clinicians. However, duloxetine is also theorized to decrease the efficacy of tamoxifen and has been cautioned against use in the breast cancer population, although recent studies have challenged this belief (Azoulay et al. 2011; Bradbury et al. 2022; Haque et al. 2016; Kelly et al. 2010; National Comprehensive Cancer Network 2024).

Case description

A pre-menopausal woman in her 30s with hypertension and stage IIB infiltrating ductal carcinoma of the breast (estrogen receptor (ER) and progresterone receptor positive), receiving neoadjuvant chemotherapy with doxorubicin, cyclophosphamide, and paclitaxel, presented to our outpatient Supportive Care Center for bilateral numbness, burning, and tingling of her hands and feet that developed after initiating chemotherapy. She was started on duloxetine, a moderate inhibitor of cytochrome P450 isoenzyme 2D6 (CYP2D6), at 30 mg daily for CIPN, with subsequent improvement of her symptoms.

Two weeks after starting duloxetine, she visited the outpatient psychiatry clinic due to ongoing anxiety and depressed mood. Rather than increasing her duloxetine dose to help with her symptoms, it was switched to escitalopram, as it is a weaker CYP2D6 inhibitor than duloxetine and considered more appropriate in combination with tamoxifen, should it be needed in the future. She experienced headaches with escitalopram and discontinued it. She was then given venlafaxine and subsequently gabapentin without improvement in her CIPN symptoms. During this time, she underwent a bilateral mastectomy and received adjuvant radiation therapy. After

completing radiation, she was started on goserelin acetate, a gonadotropin-releasing hormone agonist.

Upon follow-up with our team, she was highly distressed by her ongoing CIPN symptoms and wished to transition back to duloxetine, given its prior benefit. To her understanding, duloxetine had been stopped over concerns for making her cancer worse, but she did not recall the specific risks. We discussed the theoretical risks, including decreased efficacy of tamoxifen and resulting increased risk of recurrence, should tamoxifen be needed in the future. Given her previously experienced benefits and no current need for tamoxifen, we decided to resume duloxetine at 30 mg daily, which was later increased to 60 mg daily. Six months later, tamoxifen was added to her medication regimen by her oncology team. Risks were again discussed, and duloxetine was further increased to 60 mg twice daily. She remains on surveillance and has no evidence of breast cancer recurrence.

Discussion

Tamoxifen is a selective ER modulator and an FDA-approved first-line option to treat pre- or post-menopausal women with ER-positive breast cancer, as well as to reduce the risk of primary breast cancer in certain high-risk patients. Tamoxifen requires CYP2D6 to be metabolized into its active form, endoxifen (Kelly et al. 2010). Selective serotonin reuptake inhibitors (SSRIs) and SNRIs inhibit CYP2D6 to varying degrees, potentially decreasing conversion of tamoxifen to its active form and thus resulting in decreased efficacy of tamoxifen and increased risk of breast cancer recurrence or rate of progression. For instance, the SSRI paroxetine, a strong CYP2D6 inhibitor, when co-administered with tamoxifen in a small prospective study, resulted in decreased serum levels of endoxifen (Stearns et al. 2003). Thus, the National Comprehensive Cancer Network advises caution when using SSRIs and SNRIs classified as strong or moderate CYP2D6 inhibitors in patients taking tamoxifen, recommending alternate agents whenever possible (National Comprehensive Cancer Network 2024).

Alternative agents, which were tried in our patient, have demonstrated variable efficacy. Gabapentin has proven benefit in conditions including postherpetic neuralgia and painful diabetic neuropathy; however, high doses are necessary for adequate effects and may be difficult to tolerate due to the adverse effect of sedation (Wiffen et al. 2017). Also, a small crossover randomized controlled trial (RCT) comparing gabapentin with placebo failed to demonstrate any benefit in CIPN (Rao et al. 2007). Furthermore, many cancer patients are also taking opioids, increasing the risk of opioid-related death when opioids are combined with gabapentin (Gomes et al. 2017). Escitalopram is a mild CYP2D6 inhibitor and has demonstrated benefit for vasomotor symptoms and depression in breast cancer survivors (Biglia et al. 2018); however, there is no evidence that SSRIs improve symptoms of CIPN.

Venlafaxine, another SNRI and a mild CYP2D6 inhibitor, has some emerging evidence for benefit in treating neuropathic pain (Aiyer et al. 2017). The evidence for its use in relieving CIPN-related symptoms specifically is more limited. An early RCT comparing venlafaxine to placebo found mixed results but may have utilized too low a dose of venlafaxine to have seen benefit (Tasmuth et al. 2002). A more recent RCT looking at venlafaxine for prevention of oxaliplatin-induced acute neurotoxicity found it reduced both short- and long-term risk of neuropathic symptoms (Durand et al. 2012). While reaching statistical significance for the primary end point, this RCT failed to reach the targeted accrual of patients and was terminated early, potentially introducing bias. A retrospective case–control study in cancer patients with CIPN found venlafaxine to have a significant reduction in neuropathic symptoms in as little as 3 weeks (Kus et al. 2016). A Cochrane review did not find compelling evidence for venlafaxine use for any type of neuropathic pain due to study limitations, high risk of bias, and availability of effective alternative agents (Gallagher et al. 2015).

Duloxetine, a moderate CYP2D6 inhibitor, remains the only agent recommended by ASCO to treat CIPN-related symptoms (Loprinzi et al. 2020). The first RCT comparing duloxetine and placebo for symptoms of CIPN demonstrated a greater improvement in average pain level with duloxetine after 5 weeks, although the absolute decrease was small (1.06 decrease in pain score with duloxetine versus 0.34 with placebo) (Smith et al. 2013). Since this trial, duloxetine's efficacy has been demonstrated in at least 4 more RCTs (Wang et al. 2022). More recent studies have sought to compare the efficacy of duloxetine versus venlafaxine. A recent double-blinded RCT of 88 patients suggests that venlafaxine is non-inferior to duloxetine at decreasing neuropathic pain within a breast cancer population with taxane-induced peripheral neuropathy (Radkhah et al. 2024). This study had significant limitations, including a small sample size through a single center and a high attrition rate without clear use of intention-to-treat analysis. An earlier RCT including 110 cancer patients (a majority having breast cancer) with CIPN found that both duloxetine and venlafaxine resulted in decreased grade of neuropathic pain compared to placebo, with duloxetine resulting in a greater reduction compared with venlafaxine (Farshchian et al. 2018). In this study, venlafaxine was associated with potentially lower rates of hypertension compared with duloxetine, which may have been an important consideration in our patient, who had this comorbidity. This study was limited by a small sample size, exclusion of patients receiving tamoxifen, and inclusion of a mix of cancer types and chemotherapeutic agents.

Recent studies have questioned whether the theoretical risk of decreased tamoxifen efficacy posed by CYP2D6 inhibitors' effects translates to meaningful clinical outcomes. An early retrospective cohort study demonstrated that the SSRI paroxetine, a strong CYP2D6 inhibitor, when used with tamoxifen, was associated with an increased risk of death from breast cancer (Kelly et al. 2010). However, subsequent large-population studies that looked at a broader set of CYP2D6 inhibitors (not only SSRIs or SNRIs) have not shown increased risk of breast cancer recurrence (Azoulay et al. 2011; Haque et al. 2016). A recent systematic review did not find any significant negative clinical impact with the concurrent use of antidepressants and tamoxifen, including strong CYP2D6 inhibitors such as paroxetine and fluoxetine (Bradbury et al. 2022). A critique of this systematic review further vetting the studies found similar results, although the letter cautioned against practice change given that effective, lower-risk alternative treatment options are available for many indications, such as depression and vasomotor symptoms (de Oliveira et al. 2023).

Similar complex clinical findings have been demonstrated in studies of CYP2D6 genotype and tamoxifen efficacy. One recent RCT stratifying patients by CYP2D6 genotype demonstrated higher endoxifen concentrations in patients receiving higher doses of tamoxifen who had lower CYP2D6 activity, but this did not affect progression-free survival (Tamura et al. 2020). Another study found an increased risk of breast cancer–specific mortality among both poor and ultrarapid CYP2D6 metabolizers (He et al. 2020). These studies further demonstrate that while serum endoxifen levels are impacted by CYP2D6, this effect does not clearly translate

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to negative clinical impacts on breast cancer outcomes. A systematic review did not find sufficient evidence to recommend CYP2D6 genotype testing to inform tamoxifen treatment planning (Lum et al. 2013). We did not consider CYP2D6 genotype testing in our patient, although this could be an interesting area of future research to further elucidate the effects of CYP2D6 inhibitors on tamoxifen efficacy.

The heightened vigilance over the use of SSRIs and SNRIs with potentially significant CYP2D6 inhibition in hormone-positive breast cancer needs to be reconsidered based on the recently available evidence. Until guidelines are updated, when considering initiation of these classes of medications in patients with ER-positive breast cancer, it is reasonable to avoid strong CYP2D6 inhibitors such as fluoxetine and paroxetine in favor of mild or moderate CYP2D6 inhibitors for certain indications. For mood or vasomotor symptoms, an SSRI in the mild CYP2D6 category is likely to be effective. Given their evidence of use in menopausal vasomotor symptoms, paroxetine and venlafaxine may be more commonly prescribed for vasomotor symptoms induced by tamoxifen and aromatase inhibitors (Crandall et al. 2023). In the case of CIPN, evidence for preferential use of venlafaxine, with less CYP2D6 interaction and possibly lower hypertension risk, is increasing. More prospective, well-powered studies are needed to confirm these preliminary findings.

In the case of our patient, the possibility of future tamoxifen use resulted in the discontinuation of duloxetine and the worsening of her CIPN-related symptoms despite trialing of alternative agents, including venlafaxine. Although the use of duloxetine with tamoxifen is cautioned against in some guidelines, recent evidence demonstrates that concomitant duloxetine with tamoxifen is not associated with increased risk of recurrence or death in breast cancer survivors. While evidence is emerging for venlafaxine as an efficacious, reasonable alternative, duloxetine remains the most evidence-based first-line agent for symptoms related to CIPN. As always, risks and benefits should be thoroughly discussed with patients through individualized conversations considering patient preferences, concomitant vasomotor or mood symptoms, and risk of cancer recurrence. When symptoms of CIPN are significantly impacting quality of life, we must be able to use duloxetine as the preferred agent in our ER-positive breast cancer patients.

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