

Presentation and management of docetaxel-related adverse effects in patients with breast cancer

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Abstract: The taxane chemotherapeutic agent docetaxel has been utilized in the management of breast cancer in the adjuvant, neoadjuvant and metastatic setting. Although well tolerated by the majority of patients, docetaxel toxicity may limit the dose which can be administered. Adverse events include infusion reactions, febrile neutropenia, fatigue, fluid retention, pneumonitis, cutaneous and nail toxicity, epiphora and lacrimal duct stenosis, gastrointestinal complications, and neuropathies. In this review, we explore these complications and how they can be effectively managed to improve patient quality of life during and following docetaxel therapy.

Keywords: toxicity, chemotherapy, adverse events

Introduction

Docetaxel (Taxotere®; Sanofi-Aventis Inc., Laval, QC, Canada) is an important antimicrotubule agent used to treat a variety of solid tumors including breast cancer, where docetaxel-containing regimens improve outcomes for patients in the metastatic, adjuvant, and neoadjuvant settings. This paper will provide an overview of the current roles of docetaxel in the treatment of metastatic and early-stage breast cancer as well as management of common side effects in cancer patients.

Efficacy of docetaxel and benefit to risk assessment in breast cancer

The use of adjuvant systemic chemotherapy has contributed greatly to the reduction in cause-specific mortality due to breast cancer in the Western Hemisphere.¹ The decision to use adjuvant chemotherapeutic agents (ie, the administration of cytotoxic treatment following primary surgery) is largely driven by the anticipated risk of breast cancer distant recurrence, as determined by histology of invasive disease, expression of estrogen and/or progesterone receptors, human epidermal growth factor receptor (HER)-2 status, tumor size, nodal status, and age of the patient.^{2,3} In general, adjuvant chemotherapy is considered for patients with hormone-negative breast cancer with tumor size >0.5 cm or with pathological node involvement. For those patients with hormone receptor-positive breast cancer, chemotherapeutic agents are usually administered in the setting of pathologically positive lymph nodes, large tumor size, high tumor grade, and the presence of lymphovascular invasion and/or high recurrence score on gene expression recurrence assays.⁴

The taxanes, docetaxel and paclitaxel, are among the most effective single agents in early breast cancer. Clinically meaningful benefits of taxane incorporation in the adjuvant

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setting were affirmed in the Early Breast Cancer Trialists Collaborative Group 2012 meta-analysis for women with newly diagnosed breast cancer. The addition of taxane to anthracycline resulted in a further reduction in the event rate ratio of recurrence of 0.87, breast cancer mortality of 0.99, and overall mortality of 0.89 when compared with anthracycline alone.⁵ The benefits of taxane incorporation were independent of age, nodal status, tumor size, tumor grade, and hormone receptor status across clinical trials. As a result, anthracycline- and taxane-based chemotherapeutic regimens have become the standard of care in early stage breast cancers. Among the most active adjuvant chemotherapy regimens, the docetaxel-based combinations of docetaxel, doxorubicin, and cyclophosphamide (TAC),⁶⁻⁸ docetaxel with cyclophosphamide,^{9,10} sequential anthracycline (eg, FEC [5-fluorouracil, epirubicin, and cyclophosphamide]) followed by docetaxel monotherapy,¹¹⁻¹⁴ and docetaxel, carboplatin, and trastuzumab¹⁵ are most commonly used.

Similarly, combinations and sequences of anthracycline and taxanes have become the standard of care for preoperative neoadjuvant breast cancer chemotherapy. The value of docetaxel in the preoperative setting was first demonstrated with the Aberdeen study, in which tumor responses and overall survival were improved with sequential anthracycline–docetaxel when compared with continuing anthracycline chemotherapy.^{16,17}

Taxanes also play an important role in the treatment of metastatic breast cancer. The aims of systemic treatment are to palliate symptoms, prolong survival, and maintain quality of life. Even though no prospective randomized controlled clinical trials have shown that systemic chemotherapy improves overall survival versus best supportive care, docetaxel-based trials have demonstrated improved survival outcomes in the setting of metastatic disease when compared with other chemotherapy regimens.¹⁸⁻²⁰ The outcomes for patients with metastatic breast cancer have improved significantly over the last two decades, and this is largely attributed to the availability of novel systemic therapies. A large retrospective study published by the British Columbia Agency Breast Tumor Group revealed that patients who were diagnosed with metastatic breast cancer between 1997 and 2001 had a 45% overall survival rate at 2 years in comparison with those who were diagnosed between 1991 and 1995 with only a 34% survival rate at 2 years.²¹ Chemotherapy is often the treatment choice for patients with visceral metastases associated with end-organ dysfunction, short disease-free interval, and those with rapidly progressive symptomatic disease given the higher likelihood of achieving a response rate.²²

Docetaxel has comparable activity to anthracycline in the treatment of metastatic breast cancer.²³ Taxanes are often the treatment of choice either as single agents or in combination in patients who are at risk for cardiac complications due to prior anthracycline exposure and those who developed metastases less than 12 months after prior anthracycline-based adjuvant therapy. Even though combinations of anthracycline and taxane generate high response rates, they are associated with a higher toxicity rate, with no clear survival advantage over sequential monotherapy.^{19,24} Consequently, combination regimens are generally reserved for patients with rapidly progressive and/or symptomatic visceral disease. Sequential single-agent chemotherapy is the treatment of choice for most patients with metastatic breast cancer due to a reasonable chance of response, successful symptom palliation, and improved quality of life while minimizing toxicities. For the subgroup of patients with hormone-positive disease, endocrine therapy is often used as the initial treatment of choice for those with soft tissue and bone metastases, while chemotherapy is reserved for those with visceral metastases.²²

For those patients with HER-2-positive metastatic breast cancer, docetaxel has been shown to be synergistic with trastuzumab (the HER-2-directed monoclonal antibody) in preclinical models.²⁵ Docetaxel is commonly combined with trastuzumab, where it has demonstrated important survival advantages in combination^{26,27} and, most recently, with the triplet therapy of docetaxel, trastuzumab, and pertuzumab (a monoclonal antibody that prevents HER family dimerization).²⁸

Dosing schedules

Docetaxel has been used in breast cancer therapy in two dosing schedules which differ in toxicity profiles. The original registration regimen, and the most frequent in clinical practice, is intravenous administration at 3-weekly intervals, with a starting dose of between 60 and 100 mg/m². Weekly intravenous docetaxel schedules are most commonly given day 1, day 8, and day 15 every 28-day cycle, with dosing of 25–35 mg/m². The use of weekly docetaxel schedules is largely restricted to palliation of metastatic disease, where it has been shown to have fewer neutropenic complications than 21-day docetaxel but has somewhat lower anticancer activity and higher rates of skin toxicity and fatigue.^{14,29,30}

Presentation of side effects and management of docetaxel-related adverse events

Docetaxel causes a variety of acute and long-term side effects. Fortunately, most of the common treatment-related

toxicities, such as infusion reactions, febrile neutropenia, fatigue, and fluid retention are resolved between cycles of treatment or reversible upon treatment discontinuation. Prior to therapy administration, patients are screened for adequate renal function, hepatic function, and bone marrow function to ensure these acute side-effects are resolved. However, peripheral neuropathy is a long-term side effect of taxane chemotherapy that may be debilitating for patients well after completion of treatment.

Acute side effects

Infusion reactions

Docetaxel is one of the cytotoxic agents that frequently triggers acute infusion reactions. These reactions typically occur within minutes or hours of drug administration, with characteristic symptoms including “standard” reactions of flushing, itching, dyspnea, fever, hypoxia, and fever, and “classical hypersensitivity” reactions (ie, angioedema, urticaria, wheezing, stridor, anaphylaxis, and cardiorespiratory arrest).³¹ Hypersensitivity reactions tend to be most severe on rechallenge with the drug. Premedication with glucocorticoids and antihistamines prior to infusion can help to reduce and prevent the severity of reactions, and they are routinely administered to patients prior to docetaxel exposure. Even with premedication, approximately 2% of patients will experience potentially life-threatening reactions.^{32,33} While both the taxane and the solvent in which the drug is dissolved (polysorbate 80) can contribute to infusion reactions, the underlying mechanisms of docetaxel-induced infusion reactions still remain unclear.^{34–38} Symptoms associated with standard infusion reactions and hypersensitivity/allergic reactions have been attributed mainly to cytokine release and mast cell/basophil activation, respectively. Initial management of standard infusion reactions includes temporary cessation of drug infusion for 30 minutes, with administration of additional intravenous antihistamines and glucocorticoids. Upon resolution of symptoms, infusion may be restarted at a slower rate. For anaphylaxis, stabilization of the cardiorespiratory system and use of epinephrine are indication, and discontinuation of drug infusion is usually required.

Febrile neutropenia

Myelosuppression is one of the most common treatment-related toxicities following administration of cytotoxic chemotherapy. Patients receiving combination chemotherapy experience a small to moderate reduction in their white cell count most commonly 10–14 days after initial administration. Febrile neutropenia is defined as an oral temperature $>38.5^{\circ}\text{C}$

or two consecutive readings of $>38.0^{\circ}\text{C}$ for 2 hours with an absolute neutrophil count $<0.5 \times 10^9/\text{L}$.³⁹ The condition is associated with significant morbidity and mortality if not managed appropriately. Patients who develop febrile neutropenia are at increased risk of serious infections and often require hospitalization.

In contrast to many chemotherapeutic regimens used in breast cancer therapy, there is a high risk of developing febrile neutropenia with the various docetaxel-containing chemotherapeutic regimens. The cumulative risk of febrile neutropenia ranges from 5%–25% with doxorubicin/cyclophosphamide followed by docetaxel to 21%–24% with adjuvant TAC (docetaxel, doxorubicin, and cyclophosphamide) chemotherapy when these regimens are given without primary prophylaxis with granulocyte colony stimulating factor (G-CSF). The consensus guidelines from the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) recommend the use of G-CSFs as primary prophylaxis if the risk of toxicity is estimated to be 20% or more, with the hope of reducing the incidence of neutropenic fever, duration of neutropenia, infectious complications, and rate of hospitalization.^{40–43} Furthermore, secondary prophylaxis is warranted in patients who have developed febrile neutropenia with previous cycles of chemotherapy, particularly in the curative intent setting of (neo)adjuvant therapy where dose reduction may compromise outcome. In the metastatic setting, dose reduction is often instituted after development of febrile neutropenia to minimize future complications.

Treatment of febrile neutropenia typically involves risk assessment, blood cultures, admission into hospital and administration of broad-spectrum intravenous antibiotics, and close clinical monitoring. Even though the use of G-CSFs has been shown to shorten the duration of neutropenia, fever, and length of hospital stay, no survival benefit has been demonstrated. As a result, ESMO (European Society for Medical Oncology), ASCO, and NCCN guidelines recommend against routine use of G-CSFs for patients with established febrile neutropenia.^{40,41,44} However, use of G-CSFs can be considered for patients with high-risk features such as hospital duration >10 days, profound neutropenia (with <100 cells/ μL), age >65 , multiorgan dysfunction, and hypotension.

Fluid retention

Docetaxel therapy frequently triggers fluid retention presenting as swelling of the extremities, pleural effusions, ascites, and pericardial effusion. One of the proposed

mechanisms underlying this adverse effect is increased permeability of the capillaries resulting in leakage of fluid into the surrounding tissue.⁴⁵ The severity of this reaction is proportional to the cumulative dose of the drug administered. Premedication with glucocorticoid starting 24 hours prior and 48 hours following each docetaxel dose decreases the rate of fluid retention from 20% to 6% and increases the tolerability of this drug among patients.⁴⁶ Studies have indicated that a single dose of dexamethasone, rather than the standard 3 doses, may be sufficient to prevent docetaxel-fluid retention.^{47,48} Patients should be advised to monitor for signs of increased fluid accumulation in their fingers, ankles, and mid-abdominal areas. Treatment with diuretics may provide symptomatic relief and limit the severity of fluid retention.⁴⁹

Cutaneous toxicity

Docetaxel is also known to cause a skin toxicity known as acral erythema. It often starts with a tingling sensation in the palms and soles, followed by tenderness and edema. Occasional desquamation and blistering in the affected area may also occur. The pathogenesis of acral erythema remains unclear. Proposed mechanisms include immunoglobulin E-mediated type 1 reaction and direct toxic effect of chemotherapy on the eccrine sweat glands.⁵⁰ Treatment of acral erythema mainly includes cessation of drug and symptomatic treatment to relieve the painful swelling and erythema. In addition, intravenous docetaxel has also been associated with a specific variant of acral erythema known as erythrodysesthesia plaque that presents as a fixed, solitary plaque proximal to the infusion site without involvement of the palms and soles. The characteristic lesion typically resolves with desquamation followed by hyperpigmentation weeks after the initial insult.^{51,52}

Nail toxicity

Docetaxel can cause a wide range of nail toxicities including subungual and splinter hemorrhages, hyperkeratosis, paronychia, separation of the nail from the nail bed, and cessation of nail growth. The severity of the nail changes correlates with the total number of chemotherapy cycles and the cumulative dose of chemotherapy administered. Studies have indicated that the use of frozen gloves and socks can slow the onset and lower the severity of symptoms in a large proportion of patients by reducing blood flow to the affected areas.^{53,54} The majority of the symptoms resolve spontaneously within 6–12 months after chemotherapy discontinuation.

Pneumonitis

Docetaxel has been rarely reported to cause acute, bilateral interstitial lung disease that can occur during, within a few hours, or up to weeks after initial administration. Symptoms include exertional dyspnea, dry cough, malaise, and fever.⁵⁵ The mechanism behind interstitial pneumonitis is not well understood at the present time. Some researchers believe that it is predominantly a lymphocyte-mediated immune reaction.³³ In contrast to paclitaxel, the incidence of pulmonary toxicity is proportional to the total dose of docetaxel administered. In a Phase III trial of women with advanced breast cancer, a statistically significant higher rate of pulmonary toxicity was observed with higher docetaxel doses (100 mg/m² in comparison with 60 mg/m²).⁵⁶ Moreover, a higher incidence of pneumonitis was seen in patients receiving weekly versus every 3 weeks docetaxel regimen.⁵⁷ The rate of pulmonary toxicity is also higher when docetaxel is given in combination with gemcitabine or radiation.^{58–60} Patients with preexisting lung disease are at a higher risk of developing pulmonary complications with docetaxel treatment. Therefore, taxane treatment is relatively contraindicated in patients with preexisting lung disease.⁶¹ Fortunately, most cases resolve with supportive care and discontinuation of taxane therapy. For patients with clinical signs of oxygen desaturation or impending respiratory failure, an empiric trial of glucocorticoids may be warranted.

Fatigue

Most patients receiving docetaxel chemotherapy will experience fatigue during the course of their treatment. Research indicates that continuous exercise may help to delay the onset of fatigue and optimize physical function.^{62,63} To date, no studies have been conducted on the management of docetaxel-related fatigue. Other common causes of asthenia such as depression, pain, anemia, and hypothyroidism must also be considered and treated accordingly.

Epiphora and lacrimal duct stenosis

Epiphora (excessive tearing) is a frequent complaint of breast cancer patients receiving docetaxel. Although most patients treated with short courses of adjuvant docetaxel find this is a self-limited problem that resolves soon after completion of docetaxel chemotherapy, it is particularly frequent and severe in those receiving prolonged docetaxel therapy in the metastatic setting and those treated with weekly docetaxel. In some cases, canalicular fibrosis requiring surgical stenting has been identified.^{64–66}

Gastrointestinal complications

Cases of gastrointestinal perforation, and dehydration as a consequence of enterocolitis, colitis, and neutropenic enterocolitis have been reported in breast cancer patients receiving docetaxel. Patients receiving this agent should be carefully evaluated if severe diarrhea or new onset abdominal pain occurs, and surgical consultation is warranted in patients with severe enterocolitis or demonstrated perforation.^{67,68}

Long term side effects

Neuropathies

Two of the most common long-term side effects of docetaxel chemotherapy are sensory and motor peripheral neuropathy. Fortunately, the incidence of both of these is much less than paclitaxel. Grade 3 and 4 neuropathy is only observed in less than 10% of patients receiving docetaxel therapy.^{69,70} Major clinical symptoms include numbness and tingling of the hands and feet, with loss of reflexes. The incidence of neuropathy is dependent upon the total dose of the drug administered. In the Phase III clinical trial of metastatic breast cancer patients treated with docetaxel, neuropathy of grade 2 or greater began at a dosage of 371 mg/m².⁷¹ The mainstay of treatment includes prompt recognition of onset of symptoms with subsequent delay of therapy or dose reduction. Unfortunately, none of the pharmaceutical agents have demonstrated efficacy in the prevention and treatment of taxane-induced neuropathy. Anticonvulsants such as gabapentin may be useful in providing symptomatic relief.⁷²

Conclusion

Docetaxel is an effective chemotherapeutic agent for the treatment of breast cancer in the adjuvant, neoadjuvant, and metastatic settings. Its widespread use has contributed to improvements in breast cancer-specific survival seen in many developed countries. Even though the drug can cause a wide range of toxicities, most of them are treatable with supportive care and cessation of the chemotherapeutic agent. The decision to initiate chemotherapy should always be made in partnership with the patient, who should be fully informed about the potential side effects of the treatment.

Disclosure

The authors have no conflicts of interest to disclose.

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