

■ Article

Taxanes as a First-Line Systemic Treatment in Metastatic Breast Cancer

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First-line treatment of metastatic breast cancer (MBC) is an important therapeutic setting. Effective treatment of MBC in the initial setting can extend a patient's life and provide significant improvements in quality of life. The taxanes paclitaxel, docetaxel, and *nab*-paclitaxel have been investigated as first-line therapy for MBC requiring chemotherapy in numerous trials. Results from these trials have demonstrated that taxanes are effective treatments in MBC but also have highlighted differences in their toxicity profiles. Those differences must be taken into consideration when deciding the appropriate treatment for each patient. This article explores the differences among the agents in efficacy and safety in the first-line setting for treating MBC. In addition, administration concerns unique to each taxane are discussed.

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Management of metastatic breast cancer (MBC) is complex and requires shared decision making between providers and patients to determine the best treatment option. Treatment for MBC depends on location of recurrence, characteristics of the tumor (e.g., estrogen receptor, progesterone receptor, or HER2 status), and previous treatment (National Comprehensive Cancer Network [NCCN], 2012). The treatment is palliative, and the goals of treatment include improving quality of life and prolongation of life. According to the National Cancer Institute, treatment of MBC usually involves hormone therapy and/or chemotherapy with or without trastuzumab (National Cancer Institute, 2012). Taxanes are commonly used as first-line therapy for MBC when chemotherapy is indicated based on their established survival benefit compared with non-taxane-based therapies in this setting (Ghersis, Wilcken, & Simes, 2005). Three taxanes, paclitaxel, docetaxel, and *nab*-paclitaxel, are currently available for use as single agents or components of multiagent regimens (NCCN, 2012). The clinical efficacy and safety of taxanes in the treatment of MBC

are reviewed in this article, and administration considerations unique to each taxane are discussed.

Paclitaxel

The approval of paclitaxel marked a milestone in the management of MBC because it was the first agent to demonstrate efficacy in the treatment of MBC after **failure of combination therapy** (Nabholtz et al., 1996). Paclitaxel is approved by the U.S. Food and Drug Administration (FDA) for the treatment of breast cancer after failure of combination therapy for metastatic disease or relapse within six months of adjuvant chemotherapy (prior therapy should have included an anthracycline unless contraindicated) (Bristol-Myers Squibb, 2011). Introduction of paclitaxel into first-line treatment regimens for MBC also has resulted in an increase in median overall survival (OS) in this setting (Gennari, Conte, Rosso, Orlandini, & Bruzzi, 2005). Numerous clinical trials have assessed the efficacy and safety of first-line treatment with single-agent paclitaxel for MBC (Bishop et al., 1999; Gradishar et al., 2005; Miller et al., 2007;

Paridaens et al., 2000; Sledge et al., 2003). In these trials, paclitaxel (various doses and schedules) produced overall response rates (ORRs) ranging from 25%–34% and a median OS ranging from 16–25 months. In one early phase III trial, single-agent paclitaxel 200 mg/m² every three weeks was compared with a combination of cyclophosphamide, methotrexate, 5-fluorouracil, and prednisone (a commonly used regimen at that time) in 209 patients with MBC (Bishop et al., 1999). Although no significant differences were observed between the regimens in ORR, median time to progression (TTP), or median OS, a multivariate analysis confirmed that patients treated with single-agent paclitaxel versus combination therapy and those with an Eastern Cooperative Oncology Group performance status of 0, nonvisceral disease, or a diagnosis more than three years before randomization had significantly better survival ($p < 0.05$ for all). In addition, myelotoxicity and gastrointestinal toxicities were more frequent in the combination therapy arm compared with the paclitaxel arm, but paclitaxel produced significantly more peripheral neuropathy, myalgia, arthralgia, and alopecia. The overall quality of life was similar between the treatments (Bishop et al., 1999). Paclitaxel can be administered every three weeks or weekly as initial or subsequent therapy for MBC. In a trial by Seidman et al. (2008), the weekly versus every-three-weeks schedule of paclitaxel was associated with higher ORR (42% versus 29%, $p = 0.0004$), median TTP (9 versus 5 months, $p < 0.0001$), and median OS (24 versus 12 months, $p = 0.009$). However, grade 3 sensory neuropathy was more common with the weekly schedule (24% versus 12%, $p = 0.0003$).

In an attempt to improve the efficacy of paclitaxel, Miller et al. (2007) compared paclitaxel (90 mg/m² on days 1, 8, and 15 every four weeks) plus bevacizumab (10 mg/kg on days 1 and 15 every four weeks) with single-agent paclitaxel in 722 chemotherapy-naive patients with MBC. The addition of bevacizumab to paclitaxel versus paclitaxel alone produced a superior progression-free survival (PFS) (11.8 versus 5.9 months, $p < 0.001$) and ORR (37% versus 21%, $p < 0.001$). However, a meta-analysis of five randomized trials found that the addition of bevacizumab to chemotherapy did not yield an improvement in OS compared to chemotherapy alone (Valachis et al., 2010). Based on those findings, the FDA withdrew the approval of bevacizumab for the treatment of MBC (FDA, 2011). Other paclitaxel combination partners recommended by the NCCN (2012) guidelines for patients with MBC include doxorubicin and gemcitabine, pertuzumab plus trastuzumab, or trastuzumab with or without carboplatin for patients with HER2-positive MBC.

Docetaxel

Efforts to identify alternative methods of producing paclitaxel resulted in the development of the semisynthetic taxane docetaxel (Kingston, 2007). The approval of docetaxel in 1996 marked another milestone in the treatment of MBC (FDA, 2012). Docetaxel is FDA approved as a single agent for locally advanced breast cancer or MBC after chemotherapy failure (sanofi-aventis, 2010). Single-agent docetaxel 100 mg/m² every three weeks demonstrated superior response and OS when compared with mitomycin 12 mg/m² every 12 weeks plus vinblastine 6 mg/m² every three weeks in patients with MBC whose disease had progressed despite previous anthracycline-containing therapy (Nabholtz et al.,

1999). Despite the improved efficacy achieved with docetaxel, 93% of patients in the docetaxel arm experienced grade 3 or 4 neutropenia. In addition, a comparison of the every-three-weeks schedule of paclitaxel 175 mg/m² and docetaxel 100 mg/m² in patients with MBC showed that docetaxel provided greater response but was associated with more treatment-related toxicities, including higher rates of grade 3 or 4 neutropenia (93% versus 55%), febrile neutropenia (15% versus 2%), and grade 3 or 4 peripheral edema (7% versus 0.5%) (Jones et al., 2005).

Single-agent docetaxel also has been evaluated in previously untreated patients with MBC (Gradishar et al., 2009, 2012; Miles et al., 2010; sanofi-aventis, 2010; Stemmler et al., 2010). In those trials, docetaxel (various doses and schedules) produced ORRs ranging from 23%–46% and a median OS ranging from 16–32 months. In an early phase III study, 429 previously untreated patients with MBC were treated with docetaxel 75 mg/m² plus doxorubicin 50 mg/m² every three weeks, or with a standard of care regimen consisting of doxorubicin 60 mg/m² plus cyclophosphamide 600 mg/m² every three weeks (Nabholtz et al., 1993). The docetaxel arm produced a significantly better ORR compared with the standard therapy arm (59% versus 47%, $p = 0.009$); however, the median OS was similar between the docetaxel and standard therapy arm (22.5 versus 21.7 months, $p = 0.26$). TTP was longer for patients in the docetaxel versus standard therapy arm (37.3 versus 31.9 weeks, $p = 0.01$). Severe neutropenia was more frequent in the docetaxel arm than the standard therapy arm (97% versus 88%, $p = 0.01$), as was febrile neutropenia (33% versus 10%, $p < 0.001$) and severe infection (8% versus 2%, $p = 0.01$). Despite these findings, quality of life trended in favor of the docetaxel arm.

In the phase III study by Stemmler et al. (2010), two different regimens of single-agent docetaxel were compared for the first-line treatment of patients with MBC. In this trial, 102 previously untreated patients were randomized to docetaxel 75 mg/m² every three weeks or 30 mg/m² on days 1, 8, and 15 every four weeks. The every-three-weeks arm was associated with a significantly better ORR compared with the weekly schedule (43% versus 23%, $p = 0.039$). The weekly schedule produced a better, although nonsignificant, median OS compared with the every-three-weeks schedule (22.7 versus 15.8 months, $p = 0.24$). The every-three-weeks schedule produced a significantly greater rate of severe leukopenia compared with the weekly schedule (52% versus 4%, $p < 0.0001$), as well as a significantly greater rate of neurotoxicity (4% versus 0%, $p = 0.01$). The NCCN (2012) has recommended docetaxel as a preferred single agent or in combination with doxorubicin or capecitabine for the treatment of MBC.

nab-Paclitaxel

The efficacy of paclitaxel has been demonstrated in numerous trials in MBC; however, some issues exist because of its solvent, Cremophor® EL (now renamed as Kolliphor® EL), including hypersensitivity reactions (HSRs). To improve on the formulation of paclitaxel, nab-paclitaxel was created using albumin in place of a solvent. nab-Paclitaxel is FDA approved for the treatment of breast cancer after failure of combination therapy for metastatic disease or relapse with six months of adjuvant chemotherapy (prior therapy should have included an anthracycline unless contraindicated) (Celgene Corporation, 2012). NCCN (2012) has

- Abdominal pain
- Angioedema
- Bronchospasm
- Dyspnea
- Extremity pain
- Flushing
- Hives
- Hypotension
- Laryngeal stridor
- Pruritus

FIGURE 1. Common Symptoms of Taxane-Related Hypersensitivity Reactions

recommended *nab*-paclitaxel as a single agent in the treatment of MBC. Because *nab*-paclitaxel is a relatively newer taxane, few trials have assessed its efficacy and safety in the first-line setting in MBC. Gradishar et al. (2005) published results from a phase III trial of *nab*-paclitaxel compared with solvent-based paclitaxel in 454 women with MBC. Patients in the trial could have received prior chemotherapy; however, many patients enrolled in the trial were chemotherapy naive. In this clinical trial, *nab*-paclitaxel was given at a dose of 260 mg/m² versus solvent-based paclitaxel 175 mg/m², both every three weeks. Patients in the solvent-based paclitaxel arm received premedication to prevent HSRs, whereas those in the *nab*-paclitaxel arm did not. In patients receiving these agents as first-line therapy, *nab*-paclitaxel demonstrated a higher response rate compared with standard paclitaxel (42% versus 27%, $p = 0.029$). No significant difference in OS was observed between the arms in patients receiving first-line therapy. For the overall population assessed for safety, the incidence of grade 4 neutropenia was significantly higher for solvent-based paclitaxel versus *nab*-paclitaxel (48% versus 9%, $p < 0.001$). In addition, *nab*-paclitaxel produced a higher rate of grade 3 neuropathy compared with solvent-based paclitaxel; however, patients receiving *nab*-paclitaxel experienced a faster time to improvement in neuropathy from grade 3 to grade 2 or lower compared with solvent-based paclitaxel (22 versus 79 days) (Cortes & Saura, 2010). Although the rates of HSRs were low in both arms (*nab*-paclitaxel arm, less than 1%; solvent-based paclitaxel arm, 2%), no severe HSRs occurred in the *nab*-paclitaxel arm despite the fact that no pretreatment was involved (Gradishar et al., 2005). However, severe HSRs did occur in the solvent-based paclitaxel arm, even with those patients being premedicated.

nab-Paclitaxel also has demonstrated improved efficacy and tolerability when compared with docetaxel in the first-line treatment of patients with MBC (Gradishar et al., 2009, 2012). In a randomized, multicenter phase II study that evaluated three *nab*-paclitaxel dosing regimens (300 mg/m² every three weeks, 100 mg/m² weekly, and 150 mg/m² weekly) and docetaxel 100 mg/m² every three weeks in patients with MBC, independent radiologist assessment revealed that all doses of *nab*-paclitaxel produced higher ORRs compared with docetaxel, with the highest response rate being 49% in the 150 mg/m² weekly arm compared with 35% in the docetaxel arm. Final survival results revealed that the 150 mg/m² dose of *nab*-paclitaxel resulted in a 33.8 month median OS compared with 26.6 months in the docetaxel arm (Gradishar et al., 2012). Grade 4 neutropenia was significantly more frequent in the docetaxel arm compared with all of the *nab*-paclitaxel arms, and grade 3 sensory neuropathy was more frequently reported with the 150 mg/m² and 300 mg/m² doses of *nab*-paclitaxel compared with docetaxel. The median

time to improvement from grade 3 neuropathy to grade 2 or less was 20–22 days for the *nab*-paclitaxel arms versus 41 days for the docetaxel arm. The authors concluded that the 150 mg/m² first three of four weeks regimen of *nab*-paclitaxel may allow patients to achieve a clinical response before the emergence of dose-limiting adverse events.

The safety and efficacy of *nab*-paclitaxel in combination with other chemotherapy agents and targeted agents, including trastuzumab and bevacizumab, also have been reported (Conlin et al., 2010; Lobo et al., 2010; Mirtsching et al., 2011; Roy et al., 2009; Rugo et al., 2012). The preliminary results from the phase III Cancer and Leukemia Group B 40502 trial comparing weekly schedules of *nab*-paclitaxel, ixabepilone, and solvent-based paclitaxel given in combination with bevacizumab as first-line therapy for patients with MBC were presented at the 2012 American Society of Clinical Oncology Annual Meeting (Rugo et al., 2012). In that trial, 799 patients were randomized to solvent-based paclitaxel (90 mg/m²), *nab*-paclitaxel (150 mg/m²), or ixabepilone (16 mg/m²); all agents were given weekly for the first three of four weeks. The primary endpoint of the trial was PFS. Preliminary findings indicated that *nab*-paclitaxel demonstrated a similar PFS compared with the solvent-based paclitaxel arm (9.2 versus 10.6 months, $p = 0.12$), whereas ixabepilone was significantly inferior to solvent-based paclitaxel (7.6 versus 10.6 months, $p < 0.0001$). The median OS was 21 months for the ixabepilone arm, 26 months for the solvent-based paclitaxel arm, and 27 months for the *nab*-paclitaxel arm ($p = 0.92$ and $p = 0.1$, respectively, for *nab*-paclitaxel and ixabepilone in comparison with solvent-based paclitaxel). A higher rate of grade 3 or greater sensory neuropathy was noted with the *nab*-paclitaxel arm compared with the solvent-based paclitaxel arm (25% versus 16%, $p = 0.12$). Final analysis of this study is eagerly awaited. Phase II studies of *nab*-paclitaxel plus trastuzumab with and without carboplatin in patients with HER2-overexpressing MBC have reported ORRs of 63% and 52%, respectively, and median PFS of 16.6 and 18.7 months, respectively (Conlin et al., 2010; Mirtsching et al., 2011). In addition, *nab*-paclitaxel in combination with gemcitabine with or without bevacizumab has demonstrated promising efficacy as first-line treatment of MBC (Lobo et al., 2010; Roy et al., 2009).

Preliminary results of the combination of *nab*-paclitaxel and capecitabine as first-line treatment for MBC also have been reported (Schwartzberg, Arena, Mintzer, Epperson, & Walker, 2012). In this phase II trial, 50 patients received capecitabine 825 mg/m² orally twice daily and *nab*-paclitaxel 125 mg/m² weekly for the first two of every four weeks. The ORR, the primary endpoint of the study, was 61%, with 4% and 57% of patients achieving a complete response and partial response, respectively. The median PFS was 10.6 months, and the median OS was 19.9 months. In contrast to studies of paclitaxel plus

Exploration on the Go



The Functional Assessment of Cancer Therapy questionnaires may help oncology nurses assess quality of life in patients receiving taxane therapy. To access, open a barcode scanner on your smartphone, take a photo of the code, and your phone will link automatically. Or visit www.facit.org/FACITOrg/Questionnaires.

capecitabine (Blum et al., 2006; Gradishar et al., 2004), the combination of *nab*-paclitaxel and capecitabine demonstrated a favorable toxicity profile according to Schwartzberg et al. (2012). Of the 50 patients in the study, grade 3 neuropathy was observed in only one patient (2%), and no patients experienced grade 4 neuropathy. Grade 3 or 4 neutropenia was reported in five patients (10%). Four patients (8%) had grade 3 hand-foot syndrome, a common side effect of capecitabine. However, no patients experienced grade 4 hand-foot syndrome.

Administration Considerations

Several considerations exist when the treatment plan for paclitaxel therapy is developed. First, paclitaxel has been associated with HSRs, which have been shown to occur in as many as 20% of patients despite premedication (Gonzalez, Saez, Rodilla, Yges, & Toledano, 2000; Weiss et al., 1990); anaphylaxis and severe HSRs occur in about 2%–4% of patients treated with paclitaxel (Bristol-Myers Squibb, 2011). About 50% of these reactions occur within the first few minutes after the first dose of paclitaxel, and reactions are more frequent with

shorter infusion times (Gonzalez et al., 2000). As seen in Figure 1, symptoms manifested during taxane-induced HSRs include flushing, pruritus, and hives to more severe symptoms such as dyspnea, hypotension, angioedema, and generalized urticaria (Bristol-Myers Squibb, 2011). Those reactions may be directly related to the Cremophor EL in the paclitaxel preparation because Cremophor EL has been shown to induce HSRs (Sparreboom, Baker, & Verweij, 2005; Weiss et al., 1990). Patients experiencing a severe HSR should not be rechallenged (Bristol-Myers Squibb, 2011). Because of the potential for HSRs, using premedication prior to administration of paclitaxel is routine (Bristol-Myers Squibb, 2011). Commonly used premedications include dexamethasone, a histamine 1 receptor antagonist such as diphenhydramine, a histamine 2 receptor antagonist such as cimetidine and ranitidine, or an antiemetic of the prescriber's choice (Bristol-Myers Squibb, 2011). In addition to HSRs, common toxicities of paclitaxel therapy are neutropenia, neuropathy, leukopenia, anemia, infections, bleeding, hypotension, nausea, vomiting, diarrhea, mucositis, and alopecia (Bristol-Myers Squibb, 2011). Paclitaxel should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm³ (Bristol-Myers Squibb, 2011). Another important treatment consideration with paclitaxel administration is the use of appropriate tubing and containers. Glass, polyolefin, or polypropylene containers and polyethylene-lined administration sets must be used (Bristol-Myers Squibb, 2011). The use of polyvinyl chloride (PVC) containers or tubing when paclitaxel is administered is not recommended because leaching of the plasticizer diethylhexaphthalate from the PVC into the infusion fluid can occur (Bristol-Myers Squibb, 2011). An inline filter of no more than 0.22 μ m must be used as well; no significant leaching of diethylhexaphthalate has been observed with filters that incorporate short inlet and outlet PVC-coated tubing (Bristol-Myers Squibb, 2011).

Docetaxel is associated with HSRs as well (sanofi-aventis, 2010); several studies have demonstrated that as many as 21% of patients treated with docetaxel had HSRs (patients may or may not have been premedicated in these studies), with as many as 10% developing severe HSRs (sanofi-aventis, 2010; Syrigou et al., 2011). Interestingly, one study found that patients were more likely to develop HSRs during second- or third-line therapy (Syrigou et al., 2011); however, healthcare providers must remain vigilant in quickly identifying HSR symptoms with first-line therapy. Premedication with a three-day course of corticosteroids is required prior to infusion with docetaxel to prevent HSRs (sanofi-aventis, 2010). Severe fluid retention also has been noted with docetaxel therapy (sanofi-aventis, 2010). Premedication with corticosteroids is recommended to reduce the incidence and severity of fluid retention (sanofi-aventis, 2010). Liver function tests should be performed prior to each treatment cycle, and docetaxel should not be administered in patients with certain elevations in bilirubin or liver enzyme levels (see specifics in the prescribing information prior to administration). Other common toxicities associated with docetaxel therapy are infections, leukopenia, neutropenia, constipation, anorexia, nail disorders, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia (sanofi-aventis, 2010).

The preparation of *nab*-paclitaxel requires more time compared with the other taxanes because of the mixing procedure as

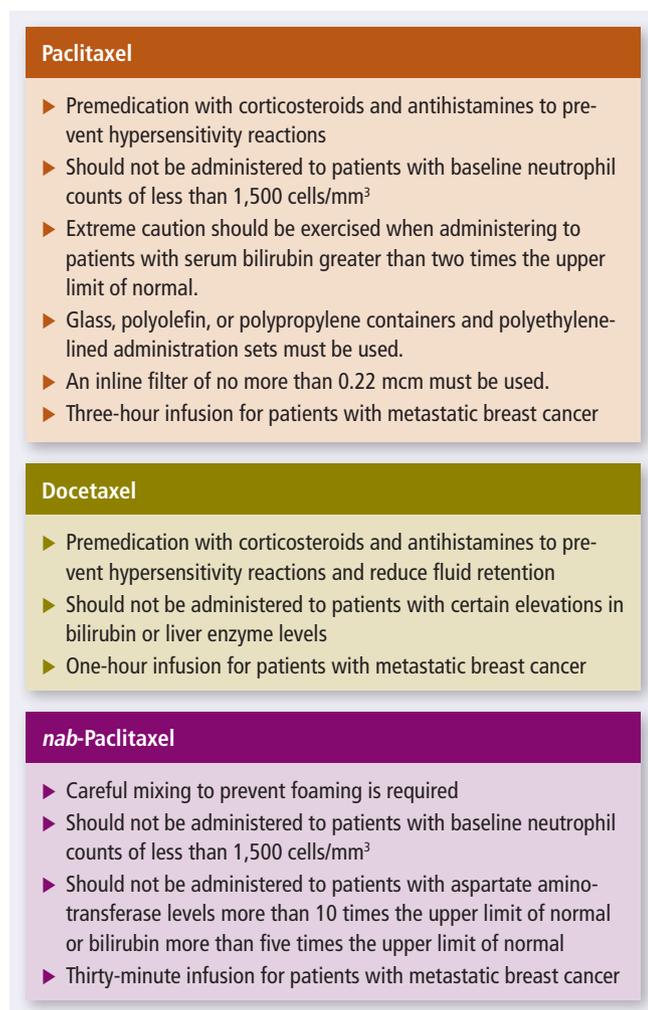


FIGURE 2. Key Administrative Concerns for Paclitaxel, Docetaxel, and *nab*-Paclitaxel

Note. Based on information from Bristol-Myers Squibb, 2011; Celgene Corporation, 2012; sanofi-aventis, 2010.

described in the prescribing information (Celgene Corporation, 2012). Briefly, the normal saline solution must be slowly injected (more than one minute) into the vial containing the lyophilized *nab*-paclitaxel powder, and the flow of the normal saline must be directed toward the inside wall of the vial (Celgene Corporation, 2012). Next, the vial must sit for a minimum of five minutes, and then the solution must be gently swirled for at least two minutes. The goal of this preparation technique is to prevent foaming; however, if foaming does occur, the solution must sit for at least 15 minutes until the foam subsides (Celgene Corporation, 2012). No special tubing is required for administering *nab*-paclitaxel, and using an inline filter is not recommended. Also, because *nab*-paclitaxel is free of Cremophor EL, premedication is not required (Celgene Corporation, 2012). As is the case with paclitaxel, patients experiencing severe HSRs to *nab*-paclitaxel should not be rechallenged. *nab*-Paclitaxel should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm³ (Celgene Corporation, 2012). The most common toxicities with *nab*-paclitaxel include alopecia, neutropenia, sensory neuropathy, abnormal electrocardiogram, fatigue or asthenia, myalgia or arthralgia, aspartate aminotransferase elevation, alkaline phosphatase elevation, anemia, nausea, infection, and diarrhea (Celgene Corporation, 2012). The key administrative concerns for each taxane can be seen in Figure 2.

Conclusion

The use of taxanes in the first-line treatment of MBC has led to improved outcomes but, often, significant toxicities. Because taxane-based chemotherapy suppresses the immune system, hematologic toxicities such as neutropenia and anemia often occur. Those toxicities can be managed with treatment; however,

Implications for Practice

- ▶ Understanding the efficacy and safety profiles of taxanes in the first-line setting will help nurses provide accurate and helpful education to patients with metastatic breast cancer.
- ▶ Paclitaxel and docetaxel have administrative considerations, such as requirements for premedication and special IV administration sets, that *nab*-paclitaxel does not have.
- ▶ Appropriate documentation per institutional policy is essential for providing consent for treatment, maintaining a record of side effects and extravasation, and offering post-treatment care.

nurses should be aware of their signs and symptoms. Signs of chemotherapy-induced anemia include fatigue and dyspnea on exertion (Groopman & Itri, 1999). Fatigue, fever, and impairment in daily functioning also are symptoms of chemotherapy-induced neutropenia, and the presence of neutropenia increases the risk of infection (Crawford, Dale, & Lyman, 2004; Ropka & Padilla, 2007). Unfortunately, fatigue is one of the most frequently reported symptoms in patients receiving chemotherapy (Groopman & Itri, 1999). Implementation of a quality-of-life assessment tool, such as the neutropenia or anemia/fatigue subscales of the Functional Assessment of Cancer Therapy (FACT) tool may assist healthcare providers in identifying and distinguishing between these toxicities. Example questions from the FACT-Neutropenia questionnaire can be seen in Figure 3.

Another important side effect of taxane therapy is neuropathy. Chemotherapy-induced neuropathy can tremendously affect

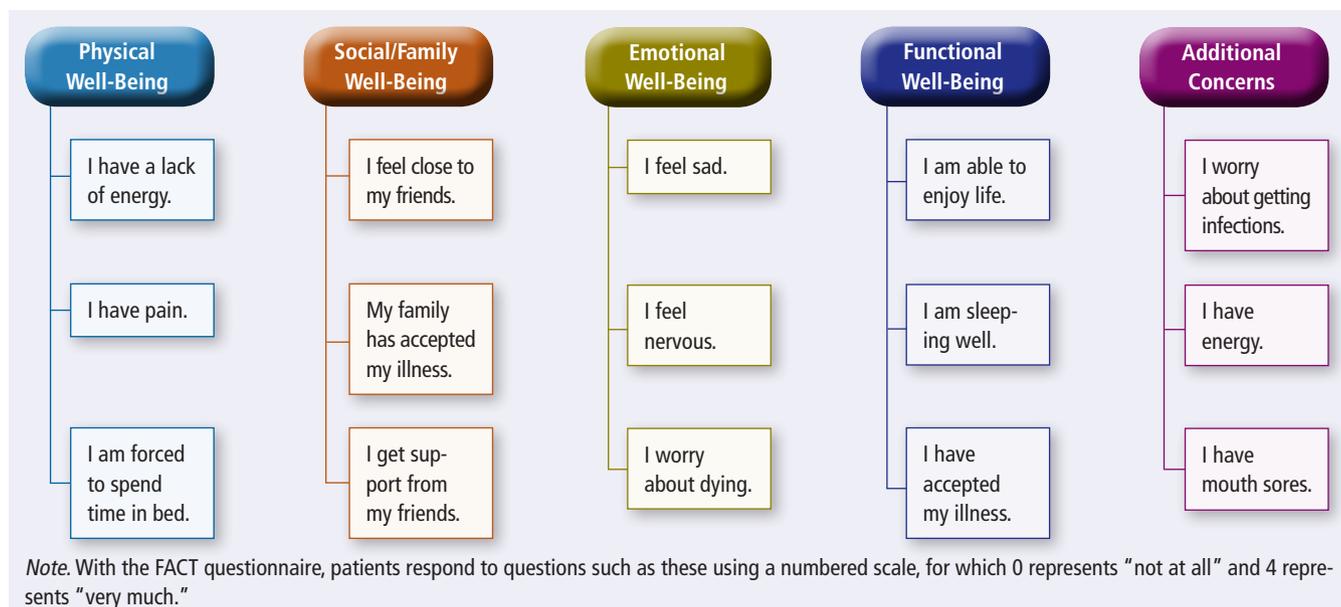


FIGURE 3. Example Questions From the Functional Assessment of Cancer Therapy (FACT)-Neutropenia Scale

Note. From "Functional Assessment of Cancer Therapy (FACT)-Neutropenia Scale Version 4," by FACIT.org, 2010. Retrieved from <http://www.facit.org/FACITOrg/Questionnaires>. To view the full scale and other FACT scales, visit <http://www.facit.org/FACITOrg/Questionnaires>. Permission for use can be obtained from <http://www.facit.org>.

quality of life, as well as treatment outcomes (Lema, Foley, & Hausheer, 2010); however, measures can be taken to reduce the severity of the neuropathy if identified early enough. This supplement includes an article by Ellen M. Lavoie Smith, PhD, ANP-BC, AOCN®, that provides important considerations and practical applications for nurses on methods for assessing and managing taxane-related neuropathy.

Because nurses play an integral role in the administration process, they must fully understand the differences among the administration concerns of each taxane. Being aware of potential infusion reactions with each of the taxanes, including those that may be related to the solvents that are used for formulation, also is important. Nurses should take the time to fully educate themselves on these issues to ensure that patients receive the best possible care.

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