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The Effect of Intravenous Taxane-Related Toxicities on Metastatic Breast Cancer Disease Treatment and Healthcare Costs

Breast cancer is one of the most common types of cancer in the United States, affecting approximately 12.8% of women.¹ At the time of initial diagnosis, approximately 6% of breast cancer cases are metastatic.² Five-year survival is approximately 98.9% if diagnosed at the local stage versus 28.1% if the cancer is already metastatic.³ Although it is not known what percentage of women develop metastases later in their disease, some reports suggest that almost 30% of women initially diagnosed with non-metastatic breast cancer will develop metastatic breast cancer (mBC).⁴⁻⁶

THE ROLE OF INTRAVENOUS CHEMOTHERAPY IN THE TREATMENT OF METASTATIC BREAST CANCER

The treatment goal for mBC is to increase overall survival (OS) and to improve quality of life (QOL) by diminishing cancer-related symptoms without increasing toxicity.⁷ New developments in the spectrum of targeted therapies are helping to optimize outcomes, particularly for patients with hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) mutations. As new research and therapies continue to change the treatment spectrum, intravenous (IV) chemotherapy continues to play an important role in treatment, both as initial therapy and adjuvant therapy.⁸

For the treatment of mBC, the safety and efficacy of taxanes have been well established.⁹ Taxanes are antimicrotubular agents, naturally derived from the bark of the Pacific Yew tree,¹⁰ and they work to stabilize microtubules by preventing depolymerization and, consequently, disrupting the microtubule network. This inhibits the cell cycle during mitosis, resulting in the inability of cells to divide, leading to cell death.^{7,8,11,12}

The 3 taxanes in current use for treatment of mBC are paclitaxel, docetaxel, and nanoparticle albumin-bound (nab)-paclitaxel.⁹ For initial therapy of HER2 negative mBC, either a taxane or anthracycline may be used.¹³ Sequential monotherapy has been demonstrated to be more effective than combination therapy, as the toxicities outweigh the benefits.¹⁴ For HER2 positive mBC, taxanes are recommended in combination with pertuzumab plus trastuzumab.¹⁴ Taxanes can also be used alone for triple negative mBC.¹⁴

Taxanes have been shown to act synergistically with targeted therapies by activating toll-like receptor activity and promoting dendritic-cell activity.¹⁵ In the setting of anthracycline toxicity or resistance to anthracycline, taxanes are recommended; they can also be reused in adjuvant therapy.¹³ In patients with recurrent stage IV disease with PD-L1 expression, for example, albumin-bound paclitaxel in combination with atezolizumab has been shown to improve PFS.¹⁴

Factors that affect treatment course include previous treatments with taxanes or other chemotherapeutic agents, HER2 positivity, triple-negative mBC positivity, virulent mBC, and old age.¹⁶ Nab-paclitaxel has been shown to be more effective with fewer toxicities in these populations. In addition to individualizing therapies based on age of the patient, menopausal status, patient

preference, comorbidities, and effectiveness of therapies, toxicities also need to be considered when deciding on or recommending a particular treatment protocol.⁷

Anaphylaxis and severe hypersensitivity reactions are 2 of the most severe toxicities and have occurred in approximately 2% to 4% of patients during clinical trials.^{14,17} Some hypersensitivity reactions are secondary to the solvent; a mixture of dehydrated alcohol and polyoxyethylated castor oil are used for absorption of paclitaxel. Bone marrow suppression, primarily neutropenia,¹⁴ cardiac conduction abnormalities, and hypotension can also occur.¹⁴

Peripheral neuropathy is also a common adverse event (AE) in patients treated with IV chemotherapy. In the IMpassion130 trial (NCT02425891), investigators evaluated the combination of atezolizumab and *nab*-paclitaxel in triple negative mBC and found chemotherapy-induced peripheral neuropathy (CIPN) in approximately 22% of the study participants whether the *nab*-paclitaxel was administered with atezolizumab or placebo.¹⁵ Although generally not severe, neuropathy can affect patient QOL.^{9,18} In a 2016 study evaluating falls in patients with CIPN, the group with CIPN symptoms was more likely to seek medical attention (25%) for a fall than those without those symptoms (7.1%).¹⁹ Most of the visits were to the oncologist's office, followed by the emergency department (ED) and urgent care, all of which contributed to the overall cost of care.¹⁹ Added to this, especially in the elderly population, is the fear of falling, further contributing to a decreased QOL.¹⁹ There is no specific treatment for CIPN; therefore, treatment of symptoms and educating patients regarding fall prevention is important.¹⁹ To prevent or reduce the risk of CIPN, the taxane dose may need to be reduced, which can result in decreased efficacy.^{9,14}

It is important to discuss AEs and toxicities related to the use of cancer chemotherapy with patients prior to and during treatment to determine tolerability and whether or not to continue a particular therapy.

THE ECONOMIC BURDEN OF INTRAVENOUS CHEMOTHERAPY

Costs associated with metastatic breast cancer can be significant. In a 2016 retrospective study comparing treatment costs for breast cancer, investigators reviewed a population from the Truven Healthcare MarketScan commercial claims database, starting with a diagnosis in 2010; they looked back at the year prior and the 24 months after diagnosis.²⁰ Afterwards, the investigators designed a claims-based algorithm for staging.²⁰

According to the study, costs were higher for surgical care for patients diagnosed with stage 0 cancer (\$16,909) than those diagnosed with stage IV cancer (\$7660); patients who were treated with chemotherapy had a higher percentage of the total costs associated with stage IV cancer, while the costs were lower for stage 0.²⁰ The costs for chemotherapy (infused and oral therapy combined) in the first 12 months after the diagnosis were \$5170, \$13,818, \$34,425, and \$35,686 for stages 0, I/II, III, and IV, respectively. Chemotherapy costs comprised the largest portion of the treatment costs in every stage of the disease in months 13 to 24.²⁰ Regarding the total average costs

per patient allowed by an insurance company in the year after diagnosis, the costs were higher based on stage, with the lowest costs at stage 0 and the highest at stage IV. Those costs were \$60,637, \$82,121, \$129,387, and \$134,682 for disease stage 0, I/II, III, and IV, respectively, during the first year after diagnosis. The average costs per patient in the 24 months after diagnosis were \$71,909, \$97,066, \$159,442, and \$182,655 for stage 0, I/II, III, and IV, respectively.²⁰ These findings suggest that earlier diagnosis and better screening for breast cancer, in addition to advances in treatment, can decrease the overall cost, according to the authors.²⁰

In a 2014 study, investigators evaluated the impact of AEs on treatment costs in patients with mBC who were treated with IV chemotherapy. They compared costs over 2 previous 5- to 10-year periods, assessing the prevalence of AEs for all chemotherapy agents and treatments used for mBC. This was followed by an assessment of prevalence and cost of taxanes and capecitabine regimens for first- and second-line treatments for mBC.²¹ Investigators found that the most common AEs were anemia (50.7%), bilirubin elevation (26.4%), leukopenia (24.8%), infection (19.2%), and dyspnea (18.6%).²¹ In the treatment groups that received taxanes, approximately 94% of patients who were treated with first- and second-line treatment had at least 1 AE during their chemotherapy treatments.²¹

Results from the economic analysis showed that AEs resulting from IV chemotherapy were associated with substantial costs. Taxane treatment-related AEs correlated with a 38.7% increase in monthly costs during first-line therapy, and were attributed to hospitalizations and non-chemotherapy drug costs. During second-line treatment with taxanes, AEs correlated with a 69.5% increase in monthly costs, and were attributed to increased pharmacy costs from both chemotherapy and other drugs.²¹ Of note, the investigators observed that costs related to chemotherapy decreased among patients experiencing more than 4 AEs in the first and second-line taxane cohorts; they noted that treatment delay or dose reduction may have affected the decrease in costs.²¹

THE CLINICAL AND ECONOMIC IMPLICATIONS OF INTRAVENOUS TAXANE TREATMENT

At the recent Academy of Managed Care Pharmacy (AMCP) Nexus 2020 virtual meeting, 2 studies further elucidated the clinical and economic burden of traditional chemotherapy in patients with mBC. In the first study, investigators studied the effect of IV paclitaxel or *nab*-paclitaxel on the treatment of adult women diagnosed with mBC over a 5-year period. Investigators identified patients using the MarketScan Commercial and Medicare Supplemental database.²² The women were required to have had continuous medical and pharmacy eligibility for 12 months prior and at least 3 months following the end of the study period.²² The mean age of the women was 54.6 ± 10.9 years, and the average follow-up time was 18.9 months. Eighty-two percent of the women began their treatment with monotherapy, with a mean duration of first-line of therapy (LOT) of 98 ± 62 days (Table 1).²²

Investigators used several factors to determine treatment patterns and outcomes, such as dose reductions of at least 10%,

early discontinuation of therapy (measured by <18 weeks [6 cycles] of chemotherapy), and duration of therapy.²² Therapy was discontinued early in 83.1% of patients and reduced in 42%.²² Of those women in whom the dose was reduced, 55.2% were dose-reduced within the 14-day period following the diagnosis of a toxicity.²²

The most common toxicities after administration of IV paclitaxel or *nab*-paclitaxel occurring in this study were CIPN (47.4%), infection (52.9%), and general symptoms (47.8%), including dysgeusia, edema, fatigue, fever, headache, and epistaxis. Gastrointestinal (GI) upset (38.2%), myelotoxicity (33.6%), neutropenia (21.1%), infusion hypersensitivity (19.4%), and cardiovascular disease (CVD) events (14.3%) also occurred. Most women (78.6%) had at least 1 toxicity during the first LOT; 22.7% had CIPN and 7.0% had an infusion reaction. Patients were more likely to present to the ED or be hospitalized within 14 days of the toxicity if they had cardiovascular disease events (54.2%), general symptoms (34.5%), or GI upset (33.3%).²² New comorbidities (depression [12.3%], liver dysfunction [10.5%], arthritis [9.3%], insomnia [7.4%], and diabetes [4.3%]) also developed in 68.9% of patients following beginning treatment with IV paclitaxel or *nab*-paclitaxel.²²

Utilization of healthcare services in patients who were treated with IV paclitaxel or *nab*-paclitaxel was high, as evidenced by several criteria. Over a 19.2 month period, 40% of the patients had inpatient hospitalizations, and 43% had ED visits;²² patients also had an average of 2 outpatient office visits and 6.4 office services per month, with 1.4 of the office visits and 4.3 of the office services being related to breast cancer.²² These increases in services translated to a significant increase in healthcare costs. The all-cause per patient per month (PPPM) costs were \$11,991; 95% of the costs were medical. The breast cancer-related costs comprised 68.2% of the PPPM for the full post-period (\$8173) and 78% over the first LOT (Figure 1).²² The cost of outpatient services, which included the administration of chemotherapy, was 75.6% of the PPPM costs over the full post-period and 83.2% over the first LOT.²²

A Closer Look at the Impact of CIPN

The second study presented at AMCP Nexus 2020 virtual meeting that examined the economic impact of IV chemotherapy specifically

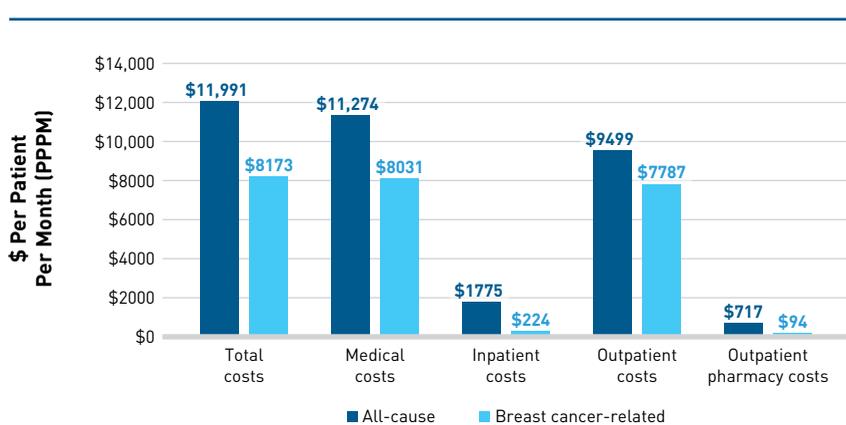
Table 1. The Burden of IV Paclitaxel or IV Nab-Paclitaxel in the Management of Metastatic Breast Cancer, Patient Characteristics²²

Characteristics of mBC Patients Initiating IV paclitaxel or nab-paclitaxel between Jan. 1, 2014 – Sept. 30, 2018	IV Paclitaxel/ nab-paclitaxel
Number of patients	8890*
Age, mean (SD)	54.6 (10.9)
Insurance, %	
PPO	52.9
HMO	10.1
NCI Comorbidity Index, %:	
0	61.2
1	25.9
2+	12.9
Age at breast cancer diagnosis, mean (SD)	53.9 (10.8)
Age at metastasis diagnosis, mean (SD)	54.3 (10.8)
Most frequent oncology treatment prior to paclitaxel, %:	
Cyclophosphamide	58.9
Doxorubicin	59.7
Monotherapy regimen when initiating paclitaxel, %	82.0
Average follow-up time, months	18.9
Mean duration of first-line therapy, days	98 ± 62

*7714 IV paclitaxel initiators, 1176 nab-paclitaxel initiators

HMO indicates health maintenance organization; IV, intravenous; PPO, preferred provider organization; SD, standard deviation.

Figure 1. Healthcare Costs in Patients With Metastatic Breast Cancer Treated With IV Paclitaxel or IV Nab-Paclitaxel²²



examined the effect of CIPN. As noted previously in this article, CIPN has been shown to substantially add to the healthcare burden of patients with mBC treated with IV chemotherapy.^{18,23} To better understand this impact, investigators examined incremental burden of CIPN in patients with mBC treated with IV paclitaxel or *nab*-paclitaxel using a claims-based analysis of the rate of CIPN in the same population of patients with mBC in the first study.²⁴

Table 2. The Impact of Chemotherapy Induced Peripheral Neuropathy in Metastatic Breast Cancer Treatment With IV Paclitaxel or IV Nab-Paclitaxel, Patient Characteristics²⁴

Key Characteristics	CIPN patients	Non-CIPN patients
Number of patients	1950	1950
Age, mean (SD)	53.7 (10.5)	53.4 (10.9)
Insurance, %		
PPO	53.2	52.8
HMO	9.6	9.6
Follow-up duration, days, mean	639.4	626.3
NCI comorbidity index, %		
0	63.4	65.6
1	26.7	24.4
2+	9.9	10.0
Monotherapy, %	82.9	84.3
Duration of 1st regimen, days, mean (SD)	96 (64)	99 (63)
Early discontinuation of 1st regimen, %	85.2	84.9
Total duration of paclitaxel exposure, days, mean (SD)	114 (109)	112 (92)

CIPN indicates chemotherapy-induced peripheral neuropathy; HMO, health maintenance organization; NCI, National Cancer Institute; PPO, preferred provider organization; SD, standard deviation.

Investigators divided patients into cohorts with and without a diagnosis of CIPN.²⁴ Both cohorts had similar characteristics (Table 2) and treatment patterns.²⁴ Approximately half (46.7%) of the patients with CIPN were diagnosed with CIPN during the first-LOT.²⁴ Approximately 13% of patients in both groups ended their first LOT due to a change in their drug regimen;²⁴ 46.1% of those in the CIPN group had evidence of dose reduction, as compared with 38.2% of the patients in the non-CIPN cohort.²⁴

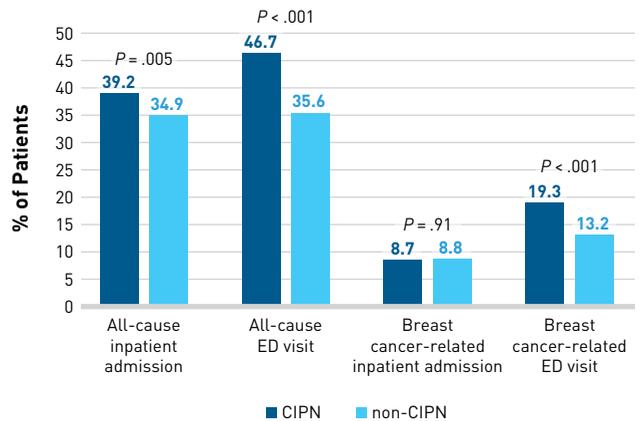
Comorbidities data showed that depression, diabetes, insomnia, liver dysfunction, and nonrheumatoid arthritis occurred more frequently in the patients with CIPN compared with patients in the non-CIPN cohort.²⁴ Patients in the CIPN cohort also had greater all-cause healthcare resource utilization than the non-CIPN cohort, including ED visits (46.7% vs 35.6%), inpatient admissions (39.2% vs 34.9%) (Figure 2a), as well as more outpatient visits and higher use of outpatient services (Figure 2b).²⁴ This increased usage led to \$1012 higher all-cause costs PPPM for patients with CIPN than those in the non-CIPN cohort. The breast cancer care portion of that cost was an additional \$725 PPPM.²⁴

CONCLUSIONS

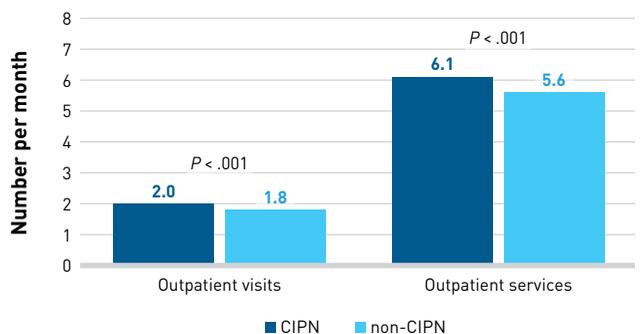
For patients with mBC, chemotherapy is a considered a standard therapy, both for initial LOT and in combination with other chemotherapeutics and/or hormonal or targeted therapies. Taxanes are 1

Figure 2. Inpatient Admission or ED Visit During Follow-Up in Patients With Metastatic Breast Cancer With CIPN Treated With IV Paclitaxel or IV Nab-Paclitaxel²⁴

2A. ED Visits and Admissions



2B. Outpatient Visits and Services



CIPN indicates chemotherapy-induced peripheral neuropathy; ED, emergency department

of the primary classes of chemotherapeutics utilized in treatment of mBC and include paclitaxel and nab-paclitaxel. However, patients treated with this class of medications commonly experience toxicities, such as CIPN, which can lead to dose reduction and/or discontinuation. These toxicities can affect treatment outcomes while also increasing healthcare resource utilization and overall costs.

Findings presented at the recent AMCP Nexus 2020 virtual meeting further reinforce that patients treated with intravenous paclitaxel or nab-paclitaxel are high utilizers of healthcare services. Total all-cause cost of care for these patients is high as well, and breast cancer-related monthly resource use and costs were substantial. Therefore, given the burdens associated with IV chemotherapy, the investigators suggested that treatments with increased tolerability and reduced dosing complexity could potentially improve treatment outcomes while reducing costs. ●

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Thought Leader Perspectives: The Trajectory of Chemotherapy in Metastatic Breast Cancer: A Q&A with John Fox, MD, MHA



JOHN FOX, MD, MHA

Medical Director, Managed Care
OneOncology

AJMC®: Given the heterogeneity of metastatic breast cancer with designations such as human epidermal growth factor receptor 2 [HER2]-positive and triple-negative breast cancer [TNBC], how much of a concern is the cost of care?

John Fox, MD: Until recently, high-cost monoclonal antibody treatments had been primarily reserved for patients with HER2-positive disease with trastuzumab, pertuzumab, and ado-trastuzumab emtansine. With the advent of CDK4/6 inhibitors and targeted therapies for PIK3CA mutations in [HR-positive], HER2-negative disease, and immunotherapy for triple-negative disease, costs for treating all types of metastatic disease are increasing. This is especially true when agents are used in combination (eg, TNBC with atezolizumab and albumin-bound paclitaxel). Given

the rising costs, incidence, and prevalence of breast cancer, overcoming the high costs of these therapies requires a renewed focus on early detection.

AJMC®: Although targeted therapies are available, chemotherapy remains the backbone of metastatic breast cancer (mBC) treatment. What do you consider some of the biggest limitations of chemotherapy use?

John Fox, MD: I'm not an oncologist and I don't treat breast cancer, but it is well known that the primary limitations are drug-induced toxicities. With paclitaxel, for example, mucositis, nausea, vomiting, and diarrhea are common, as are hematologic abnormalities including anemia, thrombocytopenia, and severe neutropenia. The latter requires the use of white cell colony stimulating factors to avoid febrile neutropenia, opportunistic infections, and the subsequent need for hospitalization. The toxicities of chemotherapy present challenges not only to patients and caregivers but also to oncologists, who may need to modify dosing to manage these toxicities.

AJMC®: Do you consider these limitations to be significant challenges?

John Fox, MD: These limitations are certainly challenging to the extent that they can result in costly, avoidable emergency department visits and hospitalization. Furthermore, dose reduction and/or interval prolongation may reduce response rates and thus progression-free and overall survival.

AJMC®: With all the different therapeutics available, are you evaluating therapies and measuring outcomes for each one? If so, how?

John Fox, MD: Health plan pharmacy and therapeutics committees are certainly evaluating new therapies as part of their routine work. There is still considerable variability between different plans in their willingness to adopt selected, preferred agents and in their willingness to implement incentive-based pathways programs. Plans attempt to ensure that patients and providers have access to cost-effective alternatives for chemotherapy-induced nausea and vomiting as well as neutropenia prophylaxis.

Measuring outcomes is particularly challenging using claims-based data. Progression-free survival can be estimated based on some simplifying of temporal assumptions such as reasons for changing therapy. Overall survival is especially difficult because payers do not have accurate date-of-death information unless they have access to state-specific vital records data. Utilization metrics are easier to come by, but small numbers, lack of detail on [disease] stage and line of therapy, and drug-specific indication bias make it difficult to draw statistically valid conclusions related to drug-specific outcomes.

AJMC®: As oncologists become more accountable for the treatments they prescribe for patients, how do insurers collect information regarding evaluating therapies and measuring outcomes used to support clinical decision-making and clinical pathways?

John Fox, MD: I am not aware of any health insurers that are actively collecting information [on] real world data, evaluating alternative therapies, and [assessing] their respective outcomes. If oncology benefits managers are doing so, I'm not aware that that evidence has been published. With that said, as oncologists take more accountability for the total cost of care and clinical outcomes,

we should give them latitude to make the best choices for patients as long as those choices are consistent with best evidence and [National Comprehensive Cancer Network] guidelines.

AJMC®: Do clinicians see chemotherapy-induced peripheral neuropathy (CIPN) as a significant concern?

John Fox, MD: [CIPN] does not rank highly compared to other toxicities such as dehydration or febrile neutropenia that can result in additional health care resource [use] such as hospitalization. Certainly, CIPN can lead to dose reductions and medication discontinuation, requiring the selection of alternate agents. While neuropathy may not be reversible, it's not really on our radar screen simply because it doesn't result in significant long-term costs.

AJMC®: Are you looking forward to the development of innovations that can serve as intravenous [IV] chemotherapy alternatives in the patient population with mBC?

John Fox, MD: Recent approvals for oral decitabine for [myelodysplastic syndromes] and oral azacitidine for [acute myeloid leukemia] are welcome [additions] for patients who are otherwise on oral therapeutic regimens or cannot tolerate IV therapies. Approval of oral therapies that can be used in combination with hormonal therapies as an alternative to chemotherapy would be welcomed by patients and providers alike. With that said, oral therapies, especially for Medicare beneficiaries, carry significant financial toxicity, so balancing chemotherapy toxicity against financial toxicity is important. This is especially true for Medicare beneficiaries, who have a 5% cost share during their catastrophic coverage phase.

AJMC®: If alternatives enter the market, how will this affect the traditional place of chemotherapy in the treatment landscape?

John Fox, MD: Every drug or drug combination has a benefit-risk profile. As new drugs come to market with improved benefit-risk ratios, one would anticipate that they would be rapidly adopted. This is especially true of a drug or drug combination that improves clinical outcomes such as survival and reduces the toxicities. For drugs that don't improve clinical outcomes, reduce toxicities, and increase cost, providers and payers will have to carefully consider how to integrate these into their clinical pathways. •

