

# Pharmacoeconomics of paclitaxel-based chemotherapy for treatment of metastatic breast cancer

The continued development of effective chemotherapeutics and biologics for treatment of metastatic breast cancer (MBC) has led to progressive increases in median survival. Prolonged use of these newer therapies, however, results in a significantly increased cost associated with drug treatment, administration, office and emergency room visits, hospitalizations, and management of adverse effects. The advent of targeted therapies such as trastuzumab, particularly in the adjuvant setting, has further added to the high cost of treatment. Even first-line cytotoxic chemotherapy for MBC, which commonly includes a taxane (paclitaxel or docetaxel) and/or an anthracycline, is associated with significant toxicities, such as sensory neuropathy, myelosuppression, and cardiotoxicity. In the case of paclitaxel, significant toxicities also occur due to the Cremophor-EL solvent required for its administration; these toxicities include severe anaphylaxis, acute hypersensitivity reactions, and myelosuppression. Such solvents require the use of special intravenous tubing, premedication with corticosteroids and antihistamines, additional staff time for management of adverse events, and more office visits and hospitalizations that substantially inflate healthcare costs. Pharmacoeconomic analyses reviewed here demonstrate that the cost of first-line therapy for MBC with standard taxanes is substantial as a result of these administration and management issues, as well as drug costs. Use of alternative taxanes, such as albumin-bound nanoparticle paclitaxel, that result in equivalent efficacy but less toxicity than standard paclitaxel may significantly reduce healthcare costs in this patient population.

**M**etastatic breast cancer (MBC) is currently considered a chronic illness, with therapy often spanning years in women who respond to therapy. Palliative treatments include hormones, cytotoxic chemotherapy, and biologics that often provide significant relief of symptoms and may increase time to relapse and survival. New agents such as trastuzumab (Herceptin) and novel chemotherapy regimens have extended survival for many patients with advanced disease. For example, a population-based Canadian study found that new hormonal and chemotherapeutic agents significantly prolonged survival of women with MBC.<sup>1</sup> When cohorts from 1991–1992 were compared with those from 1999–2001, median survival increased from 434 days to 661 days, and 2-year overall survival (OS) improved from 35% to 45%. New treatment modalities therefore have significantly improved outcomes and survival for women with MBC. Many therapies are associated with toxicities, however, that reduce

quality of life (QOL), complicate patient management, and substantially increase healthcare costs.

Among the chemotherapy agents proven to be effective for treatment of MBC, anthracyclines and taxanes form the basis for most front-line regimens.<sup>2,3</sup> Yet long-term survival is poor for most patients who receive such therapy, and resistance to these agents often develops. Toxicity also is a common and clinically significant problem with these drugs. Anthracyclines are associated with dose-dependent cardiotoxicity (eg, at cumulative doxorubicin doses > 460 mg/m<sup>2</sup>), leading to dose reductions and decreased usage.<sup>4</sup> Taxanes (paclitaxel and docetaxel) can cause substantial toxicity, including myelosuppression, alopecia, hypersensitivity, and peripheral neuropathy, which can complicate therapy, limit dose escalation, and diminish QOL.<sup>5</sup>

Because taxanes are hydrophobic, their use requires special solvents such as Cremophor-EL (for paclitaxel) and Tween 80 (for docetaxel [Taxotere]). These solvents can in-

duce severe anaphylaxis, acute hypersensitivity reactions, and myelosuppression.<sup>6,7</sup> Administration of these agents also necessitates use of special intravenous (IV) tubing to avoid leaching of plastic and premedication of patients with corticosteroids and antihistamines to lessen the risk of hypersensitivity reactions to the solvents used in their formulation.

These toxicities can complicate drug therapy, requiring increased usage of medication, additional staff time for management of adverse events, more frequent visits to the physician's office or emergency room (ER), and hospitalizations that can drive up healthcare costs. Frequent dose reductions or discontinuations can lower the efficacy of chemotherapy, leading to the use of additional treatments and further costs. These administration issues and toxicities associated with standard taxane therapy can substantially increase costs for patients with MBC. Alter-

Summary written by Larry J. Rosenberg, PhD; reviewed by Jame Abraham, MD, West Virginia University, Morgantown, WV.

native therapies that are effective but less toxic are needed for treatment of women with MBC to lower the risk of adverse events and reduce the cost of therapy.

### Costs of treating MBC

The skyrocketing price of chemotherapy and, in particular, of newer targeted therapies for breast cancer make cost an important decision factor when evaluating treatment options for patients with advanced disease. Costs associated with MBC care are significant and include the price of drugs and supportive care medications, hospitalizations, office and emergency room visits, home health-care costs, consultations, and any special procedures required.

One recent study assessed the cost of illness for nearly 400 patients with MBC, based upon Medicare program expenditure data.<sup>8</sup> Direct cost data were obtained from Medicare expenditures from a sample of 5% of American women with MBC and compared with a cohort of control patients. Mean total costs for women with MBC over an average of 16.2 months were \$35,164 versus \$4,176 for control patients over a similar period. During the follow-up period, those with MBC averaged 1.7 inpatient admissions per patient, compared with 0.3 admissions/patient for controls, and 14.4 inpatient days per admission for MBC patients versus 1.6 days/admission for controls. Direct costs were inversely proportional to patient age, with older patients having less Medicare costs than younger ones. Since many women with MBC survive and receive treatment for more than 16 months, costs can easily increase well past these estimates for selected patients.

Given the extended nature of current therapy for MBC, overall medical care costs can amount to thousands of dollars each month. The rising cost of healthcare in general (particularly insurance costs), coupled with the high

price of many biologics, presents significant economic challenges apart from standard treatment issues. For example, the average cost of trastuzumab therapy was estimated to be \$26,648 (in 2006 Canadian dollars) for MBC and \$47,278 for adjuvant therapy.<sup>9</sup> Despite the growing demand for and use of this agent, some authors have concluded that at a median cost of €44,916 per patient (over \$70,000/patient at the current exchange rate), trastuzumab is not cost-effective for treatment of MBC.<sup>10</sup>

Additionally, most cytotoxic chemotherapy for breast cancer is associated with significant adverse effects that substantially increase healthcare costs. Hassett and colleagues studied medical claims made by over 12,000 individuals with newly diagnosed breast cancer who were covered by private health insurance.<sup>11</sup> Of these patients (age 63 or younger), 4,075 received chemotherapy during the 12 months following diagnosis, whereas 8,164 did not. Those women treated with chemotherapy had a higher incidence of hospitalizations and ER visits compared with the control population for all causes (61% vs 42%;  $P < 0.001$ ) and for chemotherapy-related serious adverse events (16% vs 5%;  $P < 0.001$ ). The cost associated with these adverse effects was significant, estimated at \$1,271/person per year for chemotherapy-related serious adverse events and \$17,617/person per year for ambulatory events. These costs are likely to be even higher for

women with metastatic disease who receive chemotherapy.

### Pharmacoeconomic studies of standard chemotherapy for MBC

Paclitaxel chemotherapy has been found to be an active and cost-effective treatment for many tumors, including ovarian, lung, and breast cancers.<sup>12</sup> Several studies have analyzed the cost-effectiveness of taxanes for treatment of MBC to assess the relative benefit of individual agents or regimens and their relative cost of therapy.

The cost of first-line chemotherapy for MBC following prior anthracycline treatment was evaluated for several monotherapy and doublet regimens.<sup>13</sup> Bhalla and coworkers evaluated costs for paclitaxel and docetaxel monotherapy and for three doublet regimens: docetaxel/capecitabine (Xeloda), gemcitabine (Gemzar)/paclitaxel, and gemcitabine/docetaxel. This analysis was based on a Markov model in which the primary outcome measures were response rate (RR), progression-free survival (PFS), OS, and toxicity. Efficacy data were obtained from phase III trials, and costs were based on data from the British National Formulary and United Kingdom (UK) national databases. When results from the single-agent paclitaxel and docetaxel trials were considered, total direct costs (including chemotherapy cost, premedications, and second- and third-line therapy costs)

### What's new, what's important

Healthcare cost is a national issue debated in both medical and nonmedical forums. In general, cancer treatment is extremely expensive, accounting for about \$72 billion a year in treatment spending.

When we look at the cost of therapeutic intervention, it is important to include the costs of drug treatment, administration, nursing, and management of the side effects related to treatment. A pharmacoeconomic analysis revealed that total costs per treatment cycle—not counting the cost of the medication itself—were sixfold higher for standard paclitaxel (\$85.45) than for *nab*-paclitaxel (\$14.31). This difference is due to the cost of premedication, the cost of nursing time, infusion time, and toxicity management.

— Jame Abraham, MD

were roughly equivalent (£11,527 and £11,042, respectively). Adjusting for quality-adjusted life years (QALY), an overall decrease of £5,650 was evident for the cost of paclitaxel per QALY relative to docetaxel monotherapy, with a decrease of £2,653/life-year (LY).

Jones and colleagues performed a cost-effectiveness analysis of paclitaxel and docetaxel therapy for women with MBC whose disease progressed following treatment with an anthracycline-based regimen.<sup>14</sup> They analyzed UK economic data to assess costs over a 10-year time horizon, analyzing direct medical charges, efficacy, and QALY. Resource use and utility values were acquired from practicing oncologists and published literature, and drug costs were obtained from British formularies. Although docetaxel was more expensive than paclitaxel (£13,500 vs £10,600), it was judged to provide a greater benefit, with a significant increase in LY (2.01 vs 1.48) and QALY (1.18 vs 0.85) compared with single-agent paclitaxel. The discounted incremental cost-effectiveness ratio (ICER) for docetaxel versus paclitaxel was £5,532/LY gained (95% CI £2250–12,700) and £8,741/QALY gained (95% confidence interval [CI], £3,400–£17,300). Thus, compared with every-3-week paclitaxel therapy, docetaxel provided a more cost-effective survival and quality-adjusted survival benefit than paclitaxel in patients with MBC resistant to anthracycline therapy.

Costs were also evaluated for paclitaxel and docetaxel when used for treatment of MBC as second-line or greater therapy in the outpatient setting.<sup>15</sup> Direct medical costs (including costs for medications; hospitalizations: clinic, ER, and office visits; home healthcare; consultations; and special procedures) were evaluated over two to eight courses of therapy. Medicare rates were used to assign costs, and drugs were costed at average wholesale price. This prospective

**TABLE 1**

Average cost of intravenous chemotherapy for late-stage breast cancer

	Total cost	Study drug	Intravenous administration	Other visit-related services*
All drugs	\$2,477	\$1,463	\$252	\$763
Paclitaxel	\$2,804	\$1,214	\$353	\$1,237
Trastuzumab	\$2,526	\$1,976	\$214	\$336

\* Includes other intravenous drugs, specialty drugs, evaluation and management, and supplies and equipment costs  
Adapted from Kruse et al<sup>18</sup>

cost-of-illness analysis included 31 patients who received a total of 156 courses of therapy. Baseline characteristics were comparable for the two treatment groups, except that twice as many patients on docetaxel had received anthracyclines (63% vs 33%). Women who received docetaxel had significantly more grade 3/4 adverse events than those on paclitaxel (29% vs 7%), which necessitated more ER visits and hospitalizations (21% vs 8%). The mean cost per patient was \$14,583 (\$4,298/cycle) for paclitaxel and \$21,038 (\$2,969/cycle) for docetaxel. Response rates were lower with docetaxel than with paclitaxel (16% vs 33%), and docetaxel-treated patients required more antibiotics (53% vs 8%) and growth factor support (62% vs 42%). These factors contributed to a greater average cost per patient for docetaxel (\$21,038) than for paclitaxel (\$14,583). Average cost per cycle was similarly higher with docetaxel than with paclitaxel (\$4,298 vs \$2,869). The authors concluded that in the outpatient setting, docetaxel was more expensive than paclitaxel for MBC therapy, with its greater toxicity requiring more costly treatment.

Similar results were found using a population-based comparison of paclitaxel and docetaxel.<sup>16</sup> This retrospective analysis was based on 435 Canadian patients with MBC who were treated with single-agent paclitaxel (n = 190) or docetaxel (n = 245).<sup>17</sup> The two treatment arms were well balanced with respect to MBC prognostic factors. Median OS was statistically longer on the docetaxel

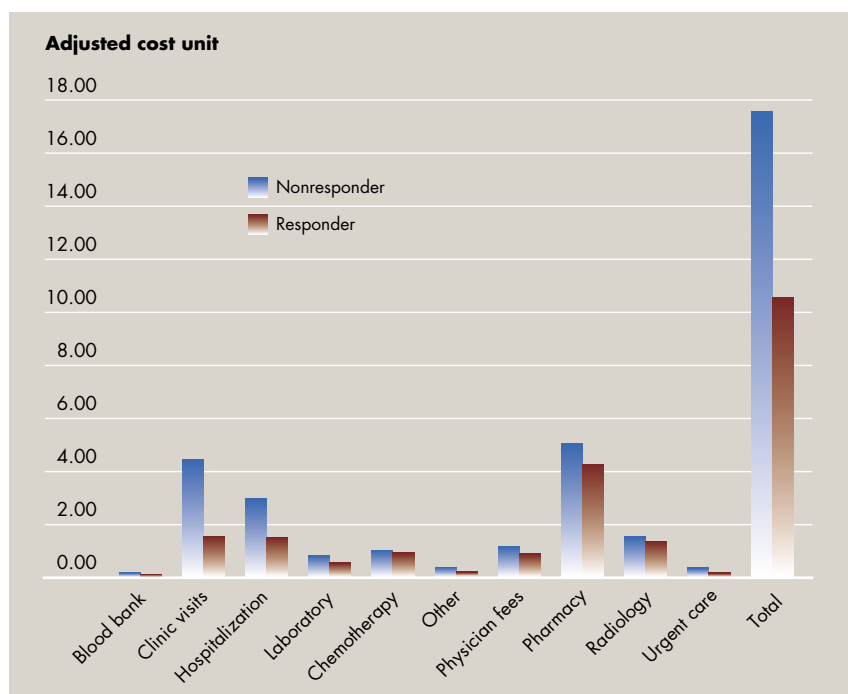
arm than on the paclitaxel arm (10.9 months vs 8.3 months), with a hazard ratio (HR) of 0.76 (95% CI, 0.62–0.92; P = 0.006). The cost per month of survival (in Canadian dollars) was significantly greater for docetaxel (\$865) than for paclitaxel (\$353). The ICER for docetaxel versus paclitaxel was \$30,337/LY gained, corresponding to an incremental cost of \$2,434 for each month of median survival gained. Sensitivity analyses indicated that results were robust, although paclitaxel dominated when the low end of the 95% CI of median OS for docetaxel was compared with the high end of the 95% CI of median OS for paclitaxel. Based on a calculated mean life expectancy at 5 years, these results translated into an estimated cost of \$20,919 per mean LY gained. This population-based study thus confirmed the results of the randomized trial demonstrating superior survival with docetaxel compared with paclitaxel for women with MBC. It also highlighted the not insignificant cost associated with such therapy.

Kruse and colleagues compared various IV monotherapies among women with early- and late-stage breast cancer to analyze the relative contributions of drug, administration, and other visit-related services.<sup>18</sup> Using administrative claims at more than 60 practices, the authors identified 1,393 women with early-stage breast cancer and 828 with late-stage disease. Cost per IV administration visit was determined for 11 IV chemotherapeutic and targeted agents commonly used for treating breast cancer, including the two most

commonly prescribed: paclitaxel and trastuzumab. The average cost of paclitaxel was less than that of trastuzumab or other chemotherapeutic agents (Table 1). However, costs associated with paclitaxel administration were higher, which may reflect the greater number of adverse events associated with this drug, when compared with those of other drugs, and the need for special IV tubing and premedications with paclitaxel. For the entire population, the cost associated with IV administration and other services was significant at 41% of the total healthcare costs.

In contrast with these more indirect modeling approaches, Modi and colleagues prospectively examined the relationship between tumor response to paclitaxel monotherapy, QOL, and cost in women treated with single-agent paclitaxel for refractory MBC.<sup>19</sup> Most patients had received prior chemotherapy (median of two regimens), but no taxane therapy, and had a median Karnofsky performance status of 80. Medical expenditures for each patient were analyzed and converted to cost ratios. QOL scores were measured using the Memorial Symptom Assessment Scale (MSAS)-Global Distress Index and the Functional Assessment of Cancer Therapy-Breast (FACT-B) instruments. Of the 59 enrolled patients, 50 had available data for comparative analyses.

With a median treatment duration of 3.6 months, an overall response rate (ORR) of 24% was observed, and stable disease was noted in an additional 25% of the patients. Significant increases in early QOL scores were more common in responders than in nonresponders (74% vs 30%;  $P = 0.004$ ), presumably due to a reduction in disease burden and symptoms. Monthly hospital costs/patient tended to be lower in responders than in nonresponders, with mean total cost/month ratios of 1.05 and 1.76, respectively ( $P = 0.07$ ; Figure 1). Whereas most charges for responders were



**FIGURE 1** Adjusted monthly cost per patient, by tumor response, in patients treated with single-agent paclitaxel for refractory metastatic breast cancer. Adapted from Modi et al.<sup>19</sup>

for pharmacy costs, charges for nonresponders were incurred primarily for clinic visits, pharmacy costs, and hospitalizations. Patients with lower QOL scores had lower cost/month ratios than patients with higher QOL scores, but this difference was not statistically significant.

#### Cost-utility models

For palliative treatments that are not expected to significantly increase survival, cost-utility analysis provides a means of evaluating the additional cost of new therapies in terms of cost per QALY gained. In the absence of direct comparative clinical and pharmacoeconomic data for paclitaxel and docetaxel, a computer-based cost-utility model was developed to compare these two agents for second-line therapy of anthracycline-resistant MBC.<sup>20</sup> These investigators used a Markov model to assess disease response and toxicities for each treatment. It was assumed that treatment would be administered every 3 weeks for up to 6 cycles. Costs were derived

from published data and the UK national databases, and response rates for each treatment were based on published data from clinical trials and expert opinions. Although the cost associated with docetaxel therapy was slightly higher than that of paclitaxel (£8,233 vs £8,013), the cost-utility of docetaxel was superior to that of paclitaxel, owing to the higher response rate of docetaxel. The incremental cost of docetaxel per QALY gained, equivalent to £7 per additional day of perfect health, was judged to be within acceptable limits for healthcare interventions.

Similar results were found by Yee using cost-utility analysis for the same patient population and therapies.<sup>21</sup> Comparison of paclitaxel and docetaxel monotherapy revealed overall treatment costs to be slightly higher with docetaxel. Compared with paclitaxel, docetaxel therapy resulted in an increase of 0.9 QALY per patient, which translated into a gain of 33 days of perfect health. The ICER associated with docetaxel was \$4,011/

QALY, which is within the acceptable range for such therapy. Docetaxel is therefore more costly per patient than paclitaxel in this model but results in greater health benefits.

This method of analysis was also used to compare second-line chemotherapy with docetaxel, paclitaxel, or vinorelbine in anthracycline-resistant breast cancer.<sup>22</sup> Data analyzed consisted of expenditures for total hospital resources consumed, including direct healthcare costs for chemotherapy, supportive care, laboratory tests, management of adverse effects, and physician fees. Treatment preferences were estimated from a separate cohort of 25 women with breast cancer and 25 oncology healthcare providers, using the time trade-off method.<sup>23</sup> Clinical and economic outcomes were analyzed using a decision model to assess benefit and cost. This study evaluated 88 patients with anthracycline-resistant disease who were treated with second-line paclitaxel ( $n = 34$ ), docetaxel ( $n = 29$ ), or vinorelbine ( $n = 25$ ) over the previous 2 years. Treatment costs per patient (in Canadian dollars) were \$3,259 for vinorelbine, \$6,039 for paclitaxel, and \$10,090 for docetaxel. However, the quality-adjusted PFS benefit was similar for all three treatment groups: 38.0, 37.2, and 33.6 days, respectively. The cost advantage seen with vinorelbine was largely due to its superior toxicity profile compared with that of paclitaxel or docetaxel.

In contrast, another group concluded that docetaxel was more cost-effective than paclitaxel in this setting, based on an analysis of pharmacoeconomic data from French, British, and US studies of docetaxel as second-line therapy for MBC.<sup>24</sup> Since no direct comparative data were available, the authors used model assumptions to compare docetaxel cost-utility with published data on paclitaxel. Docetaxel was associated with 33 and 75 additional days of quality-adjusted health in the UK and US studies, re-

spectively, and 22 additional days of quality-adjusted PFS in the French analysis. The incremental cost-utility of docetaxel versus paclitaxel was estimated to be £2,431/QALY in the UK study (1,994 values) and \$8,615/QALY in the US analysis (1997 costs). In the French study, the additional days of quality-adjusted PFS resulted in a cost savings of 700 French francs (1993 values). Docetaxel was therefore considered to be more cost-effective than paclitaxel for the treatment of MBC, and the incremental cost associated with such gain was considered to be within the accepted range for healthcare interventions.

#### *Taxane-based combination regimens*

The combination of a taxane with other agents has found wide application in the treatment of MBC, resulting in superior outcomes compared with those associated with monotherapy in many trials. The relative cost-benefit of treatment with these doublets is less well studied, however. In a phase III trial, paclitaxel plus gemcitabine has been shown to be effective for first-line treatment of MBC, resulting in significant improvements in ORR, time to progression (TTP), and OS compared with paclitaxel alone.<sup>25,26</sup> The economic benefit of this combination regimen over paclitaxel monotherapy was evaluated using data from this study.<sup>27</sup>

The trial enrolled 529 patients with MBC who had been treated with anthracyclines but had not received prior chemotherapy for metastatic disease. Treatment consisted of paclitaxel (175 mg/m<sup>2</sup>) on day 1 alone or in combination with gemcitabine (1,250 mg/m<sup>2</sup>) on days 1 and 8; cycles were administered every 21 days until disease progression occurred. Compared with single-agent paclitaxel, treatment with the paclitaxel/gemcitabine doublet resulted in improvements in ORR (39.3% vs 25.6%), median TTP (5.4 months vs 3.5 months), median OS (16.5 months vs 15.8 months),

and 1-year survival (70.7% vs 60.9%). Pharmacoeconomic analysis using a Markov model, and assuming chemotherapy was limited to a maximum of 6 cycles, indicated that the combination regimen was associated with an ICER of £38,699/QALY gained and £20,021/LY gained. This high cost is greater than that normally considered for cost-effective chemotherapy from the perspective of the UK National Health Service. The additional toxicity contributed by gemcitabine, together with the increased cost, may outweigh the relatively minor clinical benefit afforded by this combination.

#### *Capecitabine-based regimens*

Capecitabine, an oral prodrug of 5-fluorouracil, has been shown to have significant single-agent activity in MBC and is active in a number of combination regimens.<sup>28</sup> O'Shaughnessy and colleagues conducted a phase III randomized clinical trial comparing single-agent docetaxel with the combination of docetaxel and capecitabine in women with anthracycline-pretreated MBC to compare efficacy, safety, cost, and QOL.<sup>29</sup> Treatment consisted of 21-day cycles of either single-agent docetaxel (100 mg/m<sup>2</sup>) on day 1 or capecitabine (1,250 mg/m<sup>2</sup>) twice daily on days 1–14 combined with docetaxel (75 mg/m<sup>2</sup>) on day 1.

The addition of capecitabine resulted in statistically significant superior efficacy compared with docetaxel monotherapy, with a relative risk of 42% versus 30% for docetaxel alone ( $P = 0.006$ ) and median TTP of 6.1 months versus 4.2 months ( $P = 0.0001$ ).

The combination regimen also resulted in a 3-month increase in median OS (14.5 months vs 11.5 months; HR = 0.774;  $P = 0.01$ ). The incidence of treatment-related adverse events (all grades) and treatment-related hospitalizations was similar between the two treatment arms. More grade 3/4 events occurred in the combination arm (71% vs 49%), primarily due

to an increased incidence of hand-foot syndrome with capecitabine. QOL measures did not significantly differ between the two treatment groups.

Pharmacoeconomic modeling of data from this trial included the incidence and severity of adverse events, management of toxicities, drug costs, and treatment-related hospitalizations. The mean total cost per patient was similar for the two arms, with a cost of approximately \$20,000 for docetaxel and a slightly higher cost for docetaxel/capecitabine (an additional \$983 per patient).<sup>29</sup> The additional cost of the combination regimen, however, was nearly compensated by the cost savings realized through fewer hospitalizations. The authors estimated that the combination regimen was associated with an estimated \$4,500/LY gained (the cost per LY gained with single-agent docetaxel was not reported).

Data from this trial were used to develop a population-based pharmacoeconomic model to evaluate docetaxel/capecitabine compared with docetaxel monotherapy, using data obtained from the Canadian universal healthcare system.<sup>30</sup> This cost-effectiveness analysis revealed that the survival benefit obtained with the combination regimen was associated with an incremental cost (in Canadian dollars) of \$3,691/LY gained, with lower hospitalization costs for the doublet compared with single-agent docetaxel.

Jones and coworkers analyzed published randomized trials of capecitabine, used alone or in combination with docetaxel, in MBC patients pretreated with an anthracycline-containing regimen.<sup>31</sup> Analysis of these studies was limited, however, by the small number of randomized trials and the low quality of the studies. Based on one randomized trial, the addition of docetaxel to capecitabine resulted in superior activity compared with capecitabine alone, with a small decrease in costs and slight improvement in QOL. These observations support

the findings of O'Shaughnessy et al,<sup>29</sup> indicating that the combination of docetaxel and capecitabine is active and cost-effective compared with docetaxel monotherapy for patients with anthracycline-pretreated MBC.

These results with capecitabine-based regimens suggest that use of chemotherapy associated with a lower incidence of severe toxicities should lessen the need for supportive medications and lower overall healthcare costs for women with MBC. This conclusion is supported by a retrospective analysis of medical and pharmacy claims of more than 6 million managed healthcare patients with MBC or metastatic colorectal cancer that compared treatment with capecitabine versus IV chemotherapy.<sup>32</sup> Supportive therapy included antiemetics, analgesics, antibiotics, antidiarrheal agents, leucovorin, and hematopoietic growth factors.

When patients with MBC were considered separately, second-line capecitabine therapy was associated with significantly lower utilization and costs per treatment cycle compared with standard IV chemotherapy. Utilization (odds ratio) ranged from 7.60 to 8.80 for capecitabine compared with prior anthracycline and taxane therapy (regimen 1) or prior treatment with either an anthracycline or a taxane (regimen 2). Third-party costs (mean  $\pm$  standard error) were \$291  $\pm$  \$28 for capecitabine, \$928  $\pm$  \$134 for regimen 1, and \$762  $\pm$  \$58 for regimen 2. Out-of-pocket costs were similar for all three regimens. Utilization of supportive medications was also higher with IV chemotherapy in the first-line MBC setting (odds ratio = 1.76). Based on these results, capecitabine appears to be associated with a lower cost of supportive medications than standard IV chemotherapy for MBC in both the first- and second-line settings.

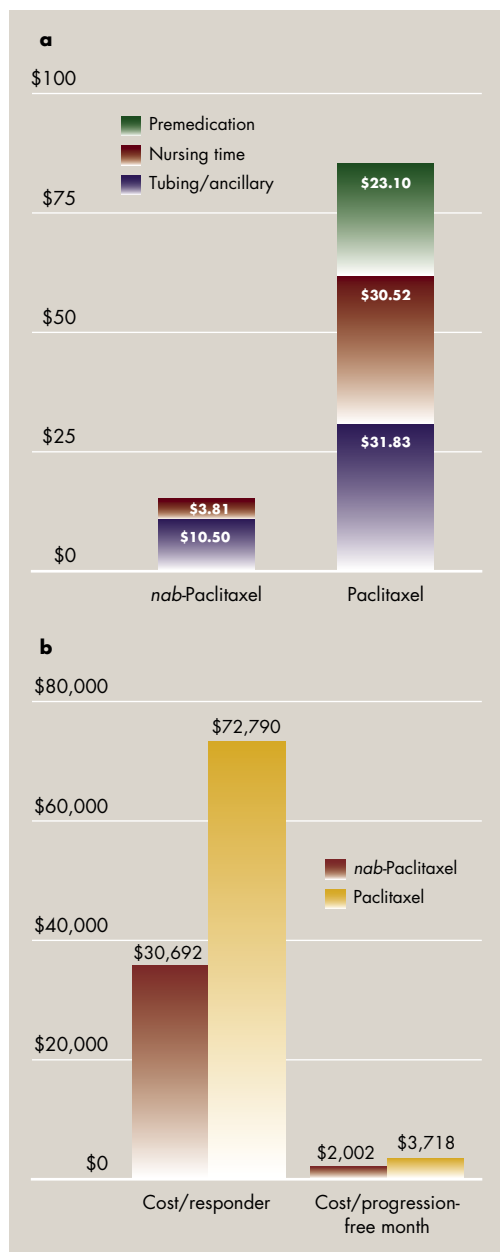
In sum, results of these MBC doublet trials suggest that the addition of

agents that significantly increase toxicity (eg, gemcitabine) may not be economically feasible, particularly given the modest increase in efficacy. Conversely, use of agents that improve outcomes without significantly increasing toxicity and the concomitant need for costly supportive medications, hospitalizations, and additional office visits may be a more cost-effective approach to treating MBC. Although capecitabine demonstrates good clinical activity in this setting, the significant toxicities associated with its use, such as hand-foot syndrome and diarrhea, can limit its use and further escalate costs for management of adverse effects.

### Pharmacoeconomic studies of nab-paclitaxel for MBC

To obviate the toxicities associated with the administration of Cremophor-based paclitaxel and improve upon the efficacy of standard paclitaxel, a novel nanoparticle albumin-bound paclitaxel formulation (*nab*-paclitaxel; Abraxane) was developed. *nab*-Paclitaxel does not require solubilization in Cremophor-EL or Tween 80, thus reducing toxicity from such solvents and the need for premedications to prevent hypersensitivity reactions. Tumor uptake and penetration of *nab*-paclitaxel also are enhanced by albumin receptor-mediated (gp60) endothelial transcytosis, effectively targeting tumors.<sup>33,34</sup> At equitoxic doses, *nab*-paclitaxel produces more complete tumor regressions, longer doubling times, increased time to recurrence, and prolonged survival compared with standard paclitaxel.

*nab*-Paclitaxel has good clinical antitumor activity in patients with MBC and a better toxicity profile than that of solvent-based paclitaxel. In a phase II MBC trial, treatment with *nab*-paclitaxel (300 mg/m<sup>2</sup>) produced an ORR of 48% for all patients and 64% for those who had not received first-line therapy.<sup>35</sup> Overall TTP was 26.6 weeks, with a medi-



**FIGURE 2** Pharmacoeconomic analysis of *nab*-paclitaxel versus standard paclitaxel for metastatic breast cancer. Adapted from Gradishar et al.<sup>37</sup>

an OS of 63.6 weeks. The incidence of myelosuppression and neuropathy was less than that seen in previous trials of standard paclitaxel.

These results have been substantiated by an international randomized phase III trial that compared the efficacy, safety, and cost of *nab*-paclitaxel with those of standard paclitaxel in the treatment of MBC.<sup>36</sup> *nab*-Pacli-

taxel (260 mg/m<sup>2</sup>) was administered IV over 30 minutes every 3 weeks without premedication, and standard paclitaxel (175 mg/m<sup>2</sup>) was infused IV over 3 hours every 3 weeks with premedication. Most (86%) of the 460 women enrolled had received prior chemotherapy, and more than 75% had more than three metastatic lesions and visceral disease. Disease progression had occurred in 59% of the patients who had received first-line chemotherapy for MBC. Results demonstrated a significantly greater relative risk with *nab*-paclitaxel compared with standard paclitaxel (33% vs 19%; *P* = 0.001); TTP also was superior with *nab*-paclitaxel (23.0 weeks vs 16.9 weeks with standard paclitaxel; *P* = 0.006). Median survival for all patients was longer in the *nab*-paclitaxel arm than in the standard paclitaxel arm (65.0 weeks vs 55.7 weeks; *P* = 0.374), and this difference was statistically significant for those who received treatment with *nab*-paclitaxel as second-line therapy or greater (56.4 weeks vs 46.7 weeks; HR = 0.73; *P* = 0.024). The toxicity profile with *nab*-paclitaxel was improved compared with standard paclitaxel, with less grade 4 neutropenia (9% vs 22%). More grade 3 sensory neuropathy occurred in the *nab*-paclitaxel arm (10% vs 2%) but was easily managed and resolved rapidly.

Gradishar and colleagues also evaluated the cost-effectiveness of these two regimens in this trial.<sup>37</sup> Their decision analytic model was designed to assess the impact of these results from a provider and a payer perspective. The model included costs associated with drug treatment (total cost per course, premedication and administration costs per cycle, incremental cost per responder, and cost per progression-free month), toxicity management, and treatment failure (Table 2). Drug acquisition costs were not included since, at the time of this study, *nab*-paclitaxel was not yet commercially available. Cost data

were derived from clinical outcomes; the costs of premedication, drug administration, and associated nursing time (assuming that the supervision of a registered nurse was required over 33% of the infusion time); special IV tubing and ancillary costs; adverse-event management; and treatment failures. Clinical data were obtained from the phase III trial. The frequency and cost of toxicities in the model were based on values obtained from peer-reviewed literature and standards of care.

Pharmacoeconomic analysis (Figure 2a) revealed that total costs per cycle were approximately sixfold higher for standard paclitaxel (\$85.45) than for *nab*-paclitaxel (\$14.31).<sup>37</sup> The increase in cost per cycle with paclitaxel therapy was largely due to the need for premedication (\$23.10) and the significant increase in cost for nursing time (\$30.52 for paclitaxel vs \$3.81 for *nab*-paclitaxel). Cost per responder was \$30,692 with *nab*-paclitaxel versus \$72,790 with standard paclitaxel, a difference of \$42,098 (Figure 2b). Cost savings were particularly evident when toxicity management per course of therapy was considered (\$4,935 with *nab*-paclitaxel vs \$7,228 with standard paclitaxel), reflecting the lower toxicity and reduced need for premedication with *nab*-paclitaxel. The cost per progression-free month was \$3,718 for standard paclitaxel versus \$2,002 for *nab*-paclitaxel. Results of this analysis demonstrated that, compared with standard paclitaxel, *nab*-paclitaxel was less costly and more effective and has the potential to generate considerable cost savings for payers and providers in the treatment of MBC. This benefit was particularly true for *nab*-paclitaxel responders, who realized a cost savings of more than \$42,000 (\$30,692 vs \$72,790).

## Conclusion

Treatment for MBC can span many years in patients who respond to

**TABLE 2**

Pharmacoeconomic analysis of data from a phase III trial comparing *nab*-paclitaxel with standard paclitaxel

Parameter	<i>nab</i> -Paclitaxel	Standard paclitaxel	Difference
Premedication cost/cycle	\$0	\$23	– \$23
Administration cost/cycle	\$14	\$62	– \$48
Toxicity management cost/course	\$4,935	\$7,228	– \$2,293
Toxicity failure cost/course	\$5,108	\$6,175	– \$1,067
Total cost/course	\$10,128	\$13,830	– \$3,702
Cost/responder	\$30,692	\$72,790	– \$42,098
Cost/progression-free month	\$2,002	\$3,718	– \$1,716

Adapted from Gradishar et al<sup>37</sup>

therapy, resulting in significant cumulative expense when the costs of drugs, drug administration, adverse-effect management, and personnel time are considered. Consequently, pharmacoeconomic studies that can aid in the decision-making process regarding choice of therapy are useful for both patients and physicians. Cost-utility analyses that consider the potential impact on patient QOL, as well as traditional measures such as efficacy and toxicity, can help determine the effectiveness of palliative therapies. This is becoming more important as healthcare costs become more constrained and the price of biologic therapies such as trastuzumab substantially increases the total healthcare expense for treatment of MBC.

The comparative studies and cost-utility analyses presented here suggest that single-agent docetaxel may be more cost-effective than paclitaxel, based on healthcare costs and clinical benefit. Agents that provide comparable efficacy with reduced toxicity can significantly lower treatment costs, including the need for hospitalizations, office and ER visits, and supportive care medications. Conversely, the use of gemcitabine-based regimens that add toxicity with little increase in efficacy may not be economically sound. These findings indicate that alternatives to standard taxane therapy that produce less toxicity and reduce the need for supportive-care

measures can significantly decrease overall healthcare costs. Capecitabine has been shown to provide good activity, with fewer of the toxicities related to taxane therapy, but can cause significant diarrhea and peripheral neuropathy that can limit therapy and escalate treatment costs.

Clinical trials of *nab*-paclitaxel have demonstrated that treatment with this agent, in both the first- and second-line settings, results in good efficacy in women with MBC. Based on a pharmacoeconomic analysis, the drug costs related to the use of standard paclitaxel were sixfold higher than those associated with *nab*-paclitaxel therapy, and the cost per responder was 2.4-fold higher than with *nab*-paclitaxel, due, in part, to the reduced need for premedication with *nab*-paclitaxel and the lower toxicity of this agent. The low incidence of infusion-associated reactions and the fewer adverse events encountered with *nab*-paclitaxel reduce administration (“chair”) time and staff needs, thus lowering costs compared with standard paclitaxel. This agent thus may provide clinical benefit equivalent to the taxanes but with less toxicity, resulting in significant cost savings.

Further pharmacoeconomic analyses of MBC treatments, including novel targeted therapies and new agents and regimens, are needed to formally analyze the cost savings relative to the current standard of care.

Studies that correlate outcomes with QOL would help relate treatment costs to QOL in both responders and nonresponders.

When used with methods that can identify those patients more likely to respond to a given therapy, such as early radiological response or pharmacogenomic markers, such an approach could significantly lower overall healthcare costs and minimize the risk of adverse events and QOL impairment in nonresponders.

## References

1. Chia SKL, Speers C, Kang A, et al. The impact of new chemotherapeutic and hormonal agents on the survival of women with metastatic breast cancer (MBC) in a population based cohort. *Proc Am Soc Clin Oncol* 2003;22:22.
2. Hortobagyi GN. Treatment of breast cancer. *N Engl J Med* 1998;339:974–984.
3. Valero V, Hortobagyi GN. Are anthracycline-taxane regimens the new standard of care in the treatment of metastatic breast cancer? *J Clin Oncol* 2003;1:959–962.
4. Ng R, Green MD. Managing cardiotoxicity in anthracycline-treated breast cancers. *Expert Opin Drug Saf* 2007;6:315–321.
5. Lee JJ, Swain SM. Peripheral neuropathy induced by microtubule-stabilizing agents. *J Clin Oncol* 2006;24:1633–1642.
6. Weiss RB, Donehower RC, Wiernik PH, et al. Hypersensitivity reactions from Taxol. *J Clin Oncol* 1990;8:1263–1268.
7. Gelderblom H, Verweij J, Nooter K, et al. Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation. *Eur J Cancer* 2001;37:1590–1598.
8. Rao S, Kubisiak J, Gildea D. Cost of illness associated with metastatic breast cancer. *Breast Cancer Res Treat* 2004;83:25–32.
9. Drucker A, Virik K, Skedgel C, Rayson D, Sellon M, Younis T. The cost burden of trastuzumab and bevacizumab monoclonal antibody therapy in solid tumors: can we afford it? *J Clin Oncol* 2006;24(18S):6044.
10. Norum J, Risberg T, Olsen JA. A monoclonal antibody against HER-2 (trastuzumab) for metastatic breast cancer: a model-based cost effectiveness analysis. *J Clin Oncol* 2005;23(16S):732.
11. Hassett MJ, O'Malley AJ, Pakes JR, Newhouse JP, Earle CC. Frequency and cost of chemotherapy-related serious adverse effects in a population sample of women with breast cancer. *J Natl Cancer Inst* 2006;98:1108–1117.
12. Bishop JF, Macarounas-Kirchman K. The pharmacoeconomics of cancer therapies. *Semin Oncol* 1997;24(suppl 19):S106–S111.
13. Bhalla S, Hibbert C, Chetty M, et al. An evaluation of clinical and cost-effectiveness of combination chemotherapy with gem-

citabine plus paclitaxel for treatment of metastatic breast cancer (MBC) in the UK from a National Health Service perspective. Presented at the 29<sup>th</sup> Annual San Antonio Breast Cancer Symposium; December 14–17, 2006; San Antonio, Tex. Abstract 5057.

14. Jones SE, Benedict A, Cameron D, Jourdan S. Cost-effectiveness of docetaxel compared to paclitaxel in metastatic breast cancer: a UK health economic analysis. *J Clin Oncol* 2007;25(18S):1081.

15. Klementich F, Hauser R, Koeller J. Cost-of-illness evaluation in metastatic breast cancer for women receiving taxane therapy. *Proc Am Soc Clin Oncol* 2001;20:2582.

16. Vu TT, Ellard S, Olivotto I, et al. Survival and cost-effectiveness of docetaxel (D) and paclitaxel (P) in patients with metastatic breast cancer (MBC): a population-based evaluation. *J Clin Oncol* 2006;24(18S):6117.

17. Jones SE, Erban J, Overmoyer B, et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J Clin Oncol* 2005;23:5542–5551.

18. Kruse GB, Amonkar MM, Skonieczny D, Smith GL. Costs of administration of intravenous (IV) therapies in early versus late stage breast cancer in a US population. *J Clin Oncol* 2007;25(18S):6588.

19. Modi S, Panageas KS, Duck ET, et al. Prospective exploratory analysis of the association between tumor response, quality of life, and expenditures among patients receiving paclitaxel monotherapy for refractory metastatic breast cancer. *J Clin Oncol* 2002;20:3665–3673.

20. Hutton J, Brown R, Borowitz M, Abrams K, Rothman M, Shakespeare A. A new decision model for cost-utility comparisons of chemotherapy in recurrent metastatic breast cancer. *Pharmacoeconomics* 1996;9(suppl 2):8–22.

21. Yee GC. Cost-utility analysis of taxane

therapy. *Am J Health Syst Pharm* 1997;54(suppl 2):S11–S15.

22. Leung PP, Tannock IF, Oza AM, Puodziunas A, Dranitsaris G. Cost-utility analysis of chemotherapy using paclitaxel, docetaxel, or vinorelbine for patients with anthracycline-resistant breast cancer. *J Clin Oncol* 1999;17:3082–3090.

23. Torrance GW, Thomas WH, Sackett DL. A utility maximization model for evaluation of health care programs. *Health Serv Res* 1972;7:118–133.

24. Lamb HM, Wiseman LR. Docetaxel: a pharmacoeconomic review of its use in the treatment of metastatic breast cancer. *Pharmacoeconomics* 1998;14:447–459.

25. O'Shaughnessy J, Nag S, Calderillo-Riuz G, et al. Gemcitabine plus paclitaxel (GT) versus paclitaxel (T) as first-line treatment for anthracycline pre-treated metastatic breast cancer (MBC): interim results of a global phase III study. *Proc Am Soc Clin Oncol* 2003;22:25.

26. Albain K, Nag S, Calderillo-Riuz G, et al. Global phase III study of gemcitabine plus paclitaxel (GT) vs. paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): first report of overall survival. *Proc Am Soc Clin Oncol* 2004;23:510.

27. Takeda AL, Jones J, Loveman E, Tan SC, Clegg AJ. The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation. *Health Technol Assess* 2007;11:iii, ix–xi, 1–62.

28. Tripathy D. Capecitabine in combination with novel targeted agents in the management of metastatic breast cancer: underlying rationale and results of clinical trials. *Oncologist* 2007;12:375–389.

29. O'Shaughnessy J, Twelves C, Aapro M. Treatment for anthracycline-pretreated metastatic breast cancer. *Oncologist* 2002;7(suppl

6):4–12.

30. Verma S, Illersich AL. Population-based pharmacoeconomic model for adopting capecitabine/docetaxel combination treatment for anthracycline-pretreated metastatic breast cancer. *Oncologist* 2003;8:232–240.

31. Jones L, Hawkins N, Westwood M, Wright K, Richardson G, Riemsma R. Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda) for locally advanced and/or metastatic breast cancer. *Health Technol Assess* 2004;8:iii, xiii–xvi, 1–143.

32. Dugan U, Baran RW, Barron J, et al. Utilization and costs of supportive medications among patients with metastatic breast (mBC) or colorectal cancer (mCRC). *J Clin Oncol* 2004;22(14S):6099.

33. Foote M. Using nanotechnology to improve the characteristics of antineoplastic drugs: improved characteristics of *nab*-paclitaxel compared with solvent-based paclitaxel. *Biotechnol Annu Rev* 2007;13:345–357.

34. Stinchcombe TE. Nanoparticle albumin-bound paclitaxel: a novel Cremophor-EL-free formulation of paclitaxel. *Nanomed* 2007;2:415–423.

35. Ibrahim NK, Samuels B, Page R, et al. Multicenter phase II trial of ABI-007, an albumin-bound paclitaxel, in women with metastatic breast cancer. *J Clin Oncol* 2005;23:6019–6026.

36. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol* 2005;23:7794–7803.

37. Gradishar W, Wolinsky S, Vishalpuria T, et al. Cost-effectiveness of nanoparticle albumin-bound (*nab*) paclitaxel (ABX) vs Cremophor-based paclitaxel (CP) in the treatment of metastatic breast cancer (MBC). *J Clin Oncol* 2004;22(14S):635.