RESEARCH

Analysis of Costs Associated With Administration of Intravenous Single-Drug Therapies in Metastatic Breast Cancer in a U.S. Population

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ABSTRACT

BACKGROUND: An estimated $8.1 billion (in 2004 dollars) is spent annually on total health care costs for the treatment of breast cancer in the United States. Breast cancer has traditionally been treated with intravenous (IV) cancer therapies that entail not only the drug acquisition cost, but additional costs of personnel time, supplies, and equipment used in the preparation and administration of the IV drug. A systematic study of the costs of IV administration in the metastatic breast cancer (MBC) population has not been performed.

OBJECTIVE: To assess the cost components, overall and by payer type and patient age group, for administering a single-agent IV breast cancer drug to women with MBC in the United States.

METHODS: Women diagnosed with MBC (ICD-9-CM codes 174.XX and 196.XX-198.XX) reported any time between January 1, 2003, and May 31, 2006, and receiving single-agent IV breast cancer therapy (including intramuscular fulvestrant) during a visit were identified (using HCPCS and CPT codes) from an administrative claims database supporting 46 general/oncology clinics in the United States. Study drugs were either FDA-approved for breast cancer or recommended for use as preferred single agents per National Comprehensive Cancer Network (NCCN) clinical practice guidelines for breast cancer. Costs were estimated using the contracted allowed payment, which is the amount that the provider is eligible to receive from all parties, including payers and patients. Costs were measured using 2 approaches—average cost per IV-administration visit and average cost per patient per month (PPPM).

RESULTS: Over the 41-month study period (through May 31, 2006), 46,273 patients had a breast cancer diagnosis, of which 8,533 (18.4%) were metastatic; 828 (9.7%) of these patients received 1 of 11 single-agent IV breast cancer drugs over 7,406 visits. Mean (SD) total payments across all drugs and cost components were $2,477 ($1,842) per visit and $4,966 ($3,841) PPPM, of which IV administration costs were 10.2% of per-visit and 11.4% of PPPM costs, and other drugs and services provided during IV administration were 30.8% of per-visit and 32.2% of PPPM costs. In both the per-visit and PPPM analyses, approximately 80% of costs for other drugs and services (approximately 25% of total treatment costs) were attributed to (a) antihypercalcemic agents (e.g., zoledronic acid: 6%-8% of total treatment cost), (b) colony-stimulating factors (CSFs) (e.g., pegfilgrastim, epoetin: 6%-7%), or (c) other anticancer agents being used off-label or for other conditions (e.g., bevacizumab, irinotecan, carboplatin, vincristine: 11%-12%). The remaining 20% of costs for other drugs and services (about 6% of total costs) were attributable primarily to antiemetic agents (e.g., palonosetron, granisetron) and miscellaneous or unclassified products. Non-protein-bound paclitaxel was the most commonly used IV therapy at a mean cost of $2,804 per visit, with IV administration accounting for $353 (12.6%) and other services accounting for $1,237 (44.1%) of total costs per visit. The second most commonly used IV therapy was trastuzumab at a mean cost of $2,526 per visit, with IV administration accounting for $214 (8.5%) and other services accounting for $336 (13.3%) of total costs per visit.

CONCLUSIONS: For patients being administered a single FDA-approved or NCCN-recommended IV drug for treatment of MBC, IV administration costs accounted for approximately 10%-11% of total cost, and the study drugs accounted for 56%-59%. Other drugs and services accounted for 31%-32%, most of which was attributable to antihypercalcemic agents, CSFs, anticancer drugs being used off-label for breast cancer or for other conditions, and antiemetic agents. Although costs of IV administration are 10%-11% of total IV chemotherapy costs for MBC and would clearly be avoided with the use of oral agents, the extent to which other costs would be avoided or incurred with use of oral agents is unknown and requires further research.

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What is already known about this subject

- Breast cancer is the most frequently diagnosed cancer in women and the second most common cause of cancer death in women of all ages in the United States. In 2008, an estimated 250,230 U.S. women will be diagnosed with breast cancer.
- The total annual cost of diagnosing and treating MBC in the United States is an estimated $8.1 billion (in 2004 dollars) for hospital and medical costs, including drug costs and the cost of personnel time and supplies/equipment involved in the preparation, administration, and management of the infused and injectable drugs.
- Limited information exists on the additional costs above the cost of the cancer drug incurred with the administration of IV therapy in patients with MBC. These costs, in addition to the direct drug cost, have been reported to range from 30% across all cancers to 50% in patients with lung cancer.

What this study adds

- Examining 828 patients with MBC with 7,406 visits for treatment with a single IV-administered breast cancer drug over a 41-month time period, the mean total payments across all drugs and cost components were $2,477 per visit and $4,966 PPPM. Costs other than the breast cancer IV drug cost accounted for 41%-43% of total payments, of which 10%-11% was attributable to IV administration and 31%-32% was attributable to *other drugs and services*.
- Approximately 80% of the costs for *other drugs and services* (25% of total MBC treatment cost) were attributable to antihypercalcemic agents (e.g., zoledronic acid, pamidronate), CSFs (e.g., pegfilgrastim, filgrastim, epoetin, darbepoetin), and off-label anticancer drugs. Antiemetics (e.g., palonosetron, granisetron) accounted for about 9% of *other drugs and services*.

In the United States, breast cancer is the most frequently diagnosed cancer in women and ranks second among cancer deaths in women after lung cancer.[1] In 2008, an estimated 250,230 women in the United States will receive a diagnosis of breast cancer—182,460 (72.9%) with invasive/metastatic and 67,770 with in situ cancer—and 40,480 women will die from the disease.[1] An estimated $8.1 billion (in 2004 dollars) in total health care costs is spent annually on the diagnosis and treatment of breast cancer in the United States.[2]

The various options that are available to treat breast cancer can be divided into 2 categories, local treatment or systemic treatment. Local treatment, involving surgery and/or radiation, is directed only at the cancer cells in the breast area. Systemic treatment is the use of medications that travel in the bloodstream to affect or treat cancer cells. Systemic treatments include chemotherapy, hormonal therapy, and targeted therapies (treatments that identify and attack specific cancer cells without harming normal cells) and are often used in combination with surgery or radiation, particularly in early breast cancer.

Systemic treatments may also be used alone in more advanced stages when cancer has metastasized to other parts of the body. In the United States, commonly used chemotherapy agents approved by the U.S. Food and Drug Administration (FDA) for metastatic breast cancer (MBC) include taxanes (docetaxel and paclitaxel), anthracyclines (doxorubicin and epirubicin), gemcitabine, and capecitabine (an oral agent). Commonly used endocrine agents are aromatase inhibitors (anastrozole, letrozole, or exemestane) or estrogen modulators (fulvestrant or tamoxifen). Trastuzumab and lapatinib are newer targeted therapies available for patients with breast cancer with tumors that overexpress *ErbB2* (or *HER2*), a growth factor receptor gene, representing approximately 25%-30% of the patient population with breast cancer.[3] The National Comprehensive Cancer Network (NCCN), a not-for-profit alliance of 21 leading cancer centers in the United States, develops guidelines for treatment of many types of cancer and may recommend agents that have not received FDA approval. For example, the NCCN treatment guidelines for breast cancer includes vinorelbine as one of several preferred single agents for recurrent or metastatic breast cancer.[4]

Most patients have traditionally been treated with chemotherapy administered intravenously either alone or in combination and, hence, incur additional costs above the drug acquisition cost. These additional costs include the cost of practitioner time for intravenous (IV) administration and other services that may be provided during the clinic visit, ranging from the management of adverse events associated with the administration to the need for additional supportive care agents, specialized equipment, supplies, and other personnel time. Several oral anticancer drugs (e.g., tamoxifen, capecitabine, lapatinib, sorafenib, sunitinib, and dasatinib) have been approved, and numerous others are in development. Use of oral agents may lead to cost savings for payers by avoiding the cost associated with the IV administration and related costs. Other potential advantages of oral cancer therapies include convenience and ease of administration, which are particularly important when patients require treatment over a prolonged period of time because of advances in cancer management.[5-9]

Most published studies on the economic burden of cancer, including breast cancer, lack sufficient detail to provide a clear understanding of all the cost factors associated with the cancer therapy.[10-13] One published review of the costs of cancer suggests that costs other than cancer drug costs, such as IV administration procedures, other oral and IV drugs, evaluation and management, laboratory services, and radiology, account for 30% of total costs, whereas a study in lung cancer reports these costs to be around 41%.[14-15]

The objective of this study was to assess the cost components, from a payer perspective, of providing IV therapy with a single FDA-approved or NCCN-recommended agent to women with MBC in the United States. This study used a novel provider-payer contract database to categorize MBC claims into the following cost components: IV breast cancer therapies, IV administration, and other supportive services. These costs were examined by IV breast cancer drug, payer type, and patient age group.

Methods

Data Source

Data for this study were obtained from the database of Medical Present Value Inc. (MPV), a contract management company located in Austin, Texas (www.mpv.com). MPV maintains a contract and claims management system that supports 46 general/oncology clinics in the United States and contains information on more than 46,000 patients with breast cancer (identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 174.XX, Table 1). The database contains a complete history of diagnoses (ICD-9-CM codes), procedures, and drug therapies received by the patients within the clinics, as well as patient demographics (e.g., age, gender, and geographic region), insurance type (e.g., managed care, indemnity, Medicare, and Medicaid), and insurance product type (e.g., health maintenance organization and preferred provider organization), including third-party payers for private insurance. For every patient clinic visit, MPV maintains the service dates, total charged, and total contracted payments, with individual services, procedures, and drugs broken out by line item (Current Procedural Terminology, Fourth Edition [CPT-4] and Healthcare Common Procedure Coding System [HCPCS] codes).

Treatment costs were estimated using the contracted allowed payment for a claim, not the practice charges, based on adjudication of the claim by the patient's third-party insurance plan. This contracted payment is defined as the amount that the provider is eligible to receive from all parties, including primary and secondary payers and the patient, based on the contractual agreement with the payer. Because the contracted payment represents the

TABLE 1 ICD-9-CM Codes Used to Identify the Study Cohort

174 Malignant neoplasm of female breast
174.0 Nipple and areola
174.1 Central portion
174.2 Upper-inner quadrant
174.3 Lower-inner quadrant
174.4 Upper-outer quadrant
174.5 Lower-outer quadrant
174.6 Axillary tail
174.8 Other specified sites of female breast
174.9 Breast (female), unspecified
196 Secondary and unspecified malignant neoplasm of lymph nodes
196.0 Lymph nodes of head, face, and neck
196.1 Intrathoracic lymph nodes
196.2 Intra-abdominal lymph nodes
196.3 Lymph nodes of axilla and upper limb
196.5 Lymph nodes of inguinal region and lower limb
196.6 Intrapelvic lymph nodes
196.8 Lymph nodes of multiple sites
196.9 Site unspecified
197 Secondary malignant neoplasm of respiratory and digestive systems
197.0 Lung
197.1 Mediastinum
197.2 Pleura
197.3 Other respiratory organs
197.4 Small intestine, including duodenum
197.5 Large intestine and rectum
197.6 Retroperitoneum and peritoneum
197.7 Liver, specified as secondary
197.8 Other digestive organs and spleen
198 Secondary malignant neoplasm of other specified sites
198.0 Kidney
198.1 Other urinary organs
198.2 Skin
198.3 Brain and spinal cord
198.4 Other parts of nervous system
198.5 Bone and bone marrow
198.6 Ovary
198.7 Adrenal gland
198.8 Other specified sites

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

actual payment to providers from payers, it depicts a more accurate and detailed view of the true economic burden of IV administration to payers than would charges; on average, contracted payments were approximately 51% of provider-submitted charges during the study period.

Based on an Internet search of FDA-approved breast cancer drugs, NCCN clinical practice guidelines, and other sources, 15 drugs were identified (see Appendix) of which 11 therapies were common breast cancer treatments identified and assessed in this study (henceforth referred to as "study drugs"): cyclophosphamide, docetaxel, doxorubicin, fluorouracil, fulvestrant, gemcitabine, non-protein-bound paclitaxel, protein-bound paclitaxel, trastuzumab, vinblastine, and vinorelbine (Table 2). All these drugs are administered intravenously except fulvestrant, which is administered intramuscularly.

Study Cohort

The study cohort consisted of female patients diagnosed with MBC. Patients (a) had 1 or more claims with a diagnosis of breast cancer (ICD-9-CM code 174.XX) *and* 1 or more claims with a diagnosis of secondary malignant neoplasms of lymph nodes (ICD-9-CM code 196.XX), respiratory and digestive systems (ICD-9-CM code 197.XX), and/or other specified sites (ICD-9-CM code 198.XX) between January 1, 2003, and May 31, 2006 (Table 1); (b) received at least 1 of the 11 single-agent IV breast cancer treatments (Table 2) during a clinic visit; and (c) had a minimum of 1 month follow-up. Diagnoses could be reported in any position on the claim (e.g., primary, secondary, or tertiary.) A total of 46,273 patients with a diagnosis of breast cancer were identified, of whom 8,533 also had a secondary malignant neoplasm diagnosis. Further restricting the sample to patients receiving a single-agent IV breast cancer drug and minimum follow-up of at least 1 month in the dataset resulted in 828 eligible patients (Figure 1). Patient records were restricted to the starting date of the metastatic diagnosis and were followed until either the end date of the study period or the date on which the patient no longer received care at the clinic or died.

This study focuses only on single-agent visits for IV treatment, defined as visits during which patients received a single FDA-approved or NCCN-recommended breast cancer drug. This decision was made for several reasons. First, single-agent visits comprised a majority (73%) of the IV visits in the data. Second, if visits in which multiple therapies were administered had been used as the unit of analysis, the number of visits for the various unique combination therapies would have been significantly smaller, limiting the interpretability of the results. For example, 18 of the 33 combination therapies identified in the data would have contributed 10 or fewer visits to the dataset, compared with an average of 673 visits for single-agent breast cancer therapy (7,406 total visits divided by 11 breast cancer agents). Third, previous research has shown that costs incurred in addition to breast cancer drug costs are higher for combination therapy than for monotherapy. For example, costs associated with the administration of trastuzumab-based combination therapies were estimated in 1 study to be about 30.3% of total costs (10.9% for IV administration and 19.4% for other visit-related services and drugs provided during IV administration), whereas costs associated with administration of trastuzumab alone were 21.8% of total costs (8.5% for IV administration and 13.3% for other

visit-related services and drugs provided during IV administration).[16] To address the concern of potential bias by focusing on monotherapy, a sensitivity analysis was performed to compare the primary cost categories of monotherapy with the 27% of visits where 2 or more (combination) approved or recommended breast cancer therapies were administered.

Although patients receiving more than 1 FDA-approved or NCCN-recommended regimen were excluded from the study sample, patients receiving an FDA-approved or NCCN-recommended agent coupled with an off-label agent were retained for analysis. This decision was made because off-label use of anticancer agents is prevalent in cancer treatment. A total of 170 (20.5%) patients were using both an FDA-approved or NCCN-recommended treatment and at least 1 off-label anticancer treatment.

Outcome Measures and Analysis

Costs were calculated using 2 approaches: average cost per IV administration visit and average cost per patient per month (PPPM). IV administration visits were selected based on administration of an IV therapy during a clinic visit and identified by the claim ID and date. All services, materials, and drugs identified by the claim line items during these visits were used in the IV therapy administration visit cost analysis. To calculate PPPM costs, therapy duration in months for each patient was calculated using IV study drug start and end dates. Start dates were determined using the filing date of the appropriate J-code claim (Table 2) following a 30-day washout period (i.e., no study drug IV therapy prescribed in prior 30 days). End dates were determined by a 30-day washout period following the last IV therapy claim for a study drug or the end of the study period. Patients could have stopped IV therapy for several reasons, including discontinuation of the therapy, switching to another monotherapy or combination therapy, receiving care in a hospital or another treatment facility, or death. The line items from the visits identified in the IV visit analysis were then aggregated into therapy months based on therapy duration and reported on a PPPM basis.

It is important to note that some of the monotherapy visits were excluded in the PPPM analysis. This pattern occurred when the monotherapy visits of a patient obtaining different drugs overlapped one another. Although these patients could be included in the monotherapy visit analysis because they were receiving only 1 IV breast cancer study drug during each visit, the PPPM calculation would involve combining multiple study drug therapies within the same patient-month. For example, if a patient received drug A for 2 months and then drug B for 2 months, all these visits would be included in both the monotherapy and PPPM analyses. However, if a patient received drug A in months 1-4 and received drug B in months 3 and 4, all these visits would be included in the IV visit analysis since they were single-agent visits, but only drug A for months 1 and 2 would be included in the PPPM analysis because the patient was receiving combination therapy from a duration viewpoint during months 3 and 4. To maintain the

TABLE 2 Breast Cancer Drugs and HCPCS Codes[a]

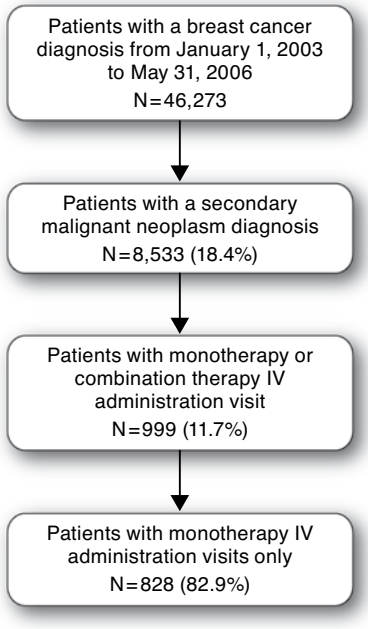
Agent	Common Brand Name(s)	HCPCS Code(s)
Protein-bound paclitaxel	Abraxane	J9264
Doxorubicin[b]	Adriamycin, Rubex	J9000-J9001
Fluorouracil[b]	Adrucil	J9190
Docetaxel	Taxotere	J9170
Non-protein-bound paclitaxel	Taxol	J9265
Vinblastine[b]	Vinblastine	J9360
Trastuzumab	Herceptin	J9355
Gemcitabine	Gemzar	J9201
Fulvestrant (IM)	Faslodex	J9395
Cyclophosphamide[b]	Cytoxan, Neosar	J9070, J9080, and J9090-J9097
Vinorelbine[b]	Navelbine	J9390

[a] *Two additional drugs—epirubicin and thiotepa—met study criteria for inclusion but are not shown in the table because no patients in the study cohort received them.*

[b] *Available generically.*

HCPCS = Health Care Procedure Coding System; IM = intramuscular.

FIGURE 1 Selection of Patients with Metastatic Breast Cancer Receiving IV Monotherapy[a]



[a] *An unknown number of the 8,533 patients with metastatic breast cancer were either treated at other oncology clinics or not treated at all.*

IV=intravenous.

TABLE 3 Study Cohort Characteristics

Characteristic	Metastatic Breast Cancer Patient Cohort	
	Count	%
Overall	828	100.0
Age (Years)		
Younger than 45	145	17.5
45-54	229	27.7
55-64	261	31.5
65-74	129	15.6
75 or older	64	7.7
Geographic Region		
Northeast	5	0.6
Midwest	175	21.1
South	241	29.1
Southwest	134	16.2
West	273	33.0
Payer Type		
Managed Care (HMO, POS, and PPO)	452	54.6
Indemnity	88	10.6
Medicare	194	23.4
Medicaid	27	3.3
Other/Unknown	67	8.1

HMO = health maintenance organization; POS = point of service; PPO = preferred provider organization.

consistency of examining monotherapy across both measures, the PPPM analysis was restricted to therapy durations where patients received only 1 therapy.

We categorized the various billable components into 1 of 3 cost categories: (1) IV breast cancer study drug; (2) administration of all IV medications, including the breast cancer study drug; and (3) other visit-related services and drugs. The IV administration category included all codes and costs associated with the duration of administration (e.g., CPT code 96413 covers chemotherapy administration via intravenous infusion technique up to 1 hour for a single or initial drug). The last category, other visit-related services and drugs, was divided further into 4 categories: (3a) other injectable drugs (e.g., antianemia drugs epoetin and darbepoetin) and concomitant oral drugs (e.g., diphenhydramine, granisetron, and ondansetron), (3b) evaluation and management services, (3c) supplies and equipment, and (3d) miscellaneous administration-related services. Concomitant oral drugs are those which are administered as an initial dose as supportive care at the time of chemotherapy treatment and are billed during that visit. To provide additional detail on the other injectable drugs and concomitant oral drugs administered during these visits, we divided this category into 11 drug categories: antihypercalcemic drugs, colony-stimulating factors (CSFs), anticancer agents (used in an off-label indication or for other conditions), antiemetic agents, saline solution, corticosteroids, heparin, antihistamines, histamine-2 (H2) antagonists, iron, and miscellaneous/unclassified agents. For patients using both a study drug and 1 or more off-label anticancer agents, costs for the off-label drug were placed into the "other visit-related services" category (c-1).

For each of the 3 major cost components—IV study drug, IV administration, and other visit-related costs—drug, payer type, and patient age groups were compared using the Kruskal-Wallis test, a nonparametric one-way analysis of variance.

Results

Study Cohort Characteristics

A total of 828 eligible patients with 7,406 visits for IV therapy for any of the 11 study drugs were identified. Demographic characteristics are presented in Table 3. More than three-quarters (76.7%) of the patients were younger than 65 years of age. Geographically, the patients were more representative of the southern and western United States than of other regions, and few patients were from the northeastern United States. The majority (about 65%) of patients had private insurance (i.e., employer-based, managed care, or indemnity health insurance); 23.4% had Medicare, 3.3% Medicaid, and 8.1% other or unknown insurance type.

Overall Payments for Patients With MBC

Payment amounts overall and by cost category for the per-visit and PPPM analyses are presented in Table 4. The mean (SD) total payments across all drugs and cost categories were $2,477 ($1,842) per visit and $4,966 ($3,841) PPPM. In the per-visit analysis, IV breast cancer drug mean payment amount accounted for 59.0% ($1,463) of the total, with IV administration responsible for 10.2% ($252) and other services provided at the visit accounting for the remaining 30.8% ($763). The PPPM analysis exhibited a breakdown similar to that of the per-visit analysis: $2,800 (56.4%) for IV cancer drug, $568 (11.4%) for IV administration, and $1,598 (32.2%) for other visit-related services and drugs. In both analyses, 99% of costs for the category "other services provided at visit" were attributable to drug costs for other injectable drugs and concomitant oral drugs.

The antihypercalcemic/bone resorption agents such as zoledronic acid and pamidronate comprised the highest-cost drug category in the visit analysis, accounting for 24.7% ($188 per visit) of the cost of other visit-related services, followed by CSFs such as pegfilgrastim, filgrastim, epoetin, and darbepoetin, which accounted for another 20.2% ($154 per visit) of the category. An additional $273 per visit (35.8%) of the other visit-related services cost was attributable to anticancer drugs that may be used off-label or to treat other conditions, including antineoplastic agents (e.g., bevacizumab), platinum agents (e.g., carboplatin), and chemotherapeutic agents (e.g., vincristine).

Other drugs with high prevalence included the supportive care antiemetics (e.g., palonosetron, granisetron; $65.97 per

TABLE 4 *Overall Costs Per Patient With Metastatic Breast Cancer (N=828) by Visit and Month*

		CONTRACTED PAYMENTS ($)				
Per Visit	No. of Visits	Mean	% of Total	% of Other Services Provided at Visit	SD	Median
Total	7406	2,477.32	100	NA	1,842.00	1,998
1. IV study drug		1,462.80	59.0	NA	1,153.00	1,079
2. IV administration (all drugs)		251.74	10.2	NA	217.00	201
3. Other visit-related services and drugs		762.78	30.8	100	1,392.00	160
3a. Other injectable drugs and concomitant oral drugs[a]		754.37	30.5	98.9	1,390.02	149
• Antihypercalcemic agents (e.g., zoledronic acid)		188.33	7.6	24.7	405.61	0
• Colony-stimulating factors (e.g., pegfilgrastim, filgrastim, epoetin, and darbepoetin)		153.80	6.2	20.2	438.74	0
• Antineoplastic agents (bevacizumab)[b]		171.77	6.9	22.5	1,037.16	0
• Platinum agents (e.g., carboplatin and oxaliplatin)[b]		74.49	3.0	9.8	382.78	0
• Chemotherapeutic agents (e.g., irinotecan and vincristine)[b]		26.83	1.1	3.5	203.79	0
• Antiemetic agents (e.g., palonosetron and granisetron)		65.97	2.7	8.6	230.94	0
• Saline solution, dextrose water		11.17	0.5	1.5	14.15	6
• Corticosteroids (e.g., dexamethasone)		4.51	0.2	0.6	20.68	0
• Heparin		3.40	0.1	0.4	14.65	0
• Antihistamine (e.g., diphenhydramine)		0.47	0.0	0.1	1.37	0
• Histamine-2 receptor antagonists (e.g., ranitidine)		0.39	0.0	0.1	1.49	0
• Iron		0.03	0.0	0.0	1.44	0
• Miscellaneous/unclassified agents		53.19	2.1	7.0	341.68	0
3b. Office visit: evaluation and management services[c]		4.31	0.2	0.6	22.61	0
3c. Supplies and equipment[d]		1.87	0.1	0.2	32.52	0
3d. Miscellaneous administration-related services[e]		2.24	0.1	0.3	21.10	0

Continued on next page

visit), saline products (used for dilution or reconstitution of the IV product; $11.17 per visit), and other supportive care concomitant oral drugs, such as dexamethasone sodium phosphate (e.g., to avoid the occurrence of severe hypersensitivity reactions in patients receiving non-protein-bound paclitaxel; $4.51 per visit), diphenhydramine hydrochloride (to avoid severe hypersensitivity reactions; $0.47 per visit), and H2 antagonists (e.g., ranitidine; $0.39 per visit).

The remaining other visit-related costs were services and equipment provided during the IV administration visit. The most frequently billed procedures in the evaluation and management services category were physician assessments for chemotherapy administration or side-effects related to chemotherapy, including nausea and/or vomiting, fatigue, and pain ($4.31 per visit). During these visits, the most common supplies and equipment used were IV needles, sterile water, dressing pads, and infusion supplies ($1.87 per visit). Finally, the miscellaneous administration-related services category primarily included fluid collection and laboratories such as metabolic panels and red and white blood cell counts ($2.24 per visit). A similar pattern for these cost categories was observed in the PPPM analysis.

Payments by IV Cancer Drug

Payments in total and for each of the 11 breast cancer drugs (including intramuscular [IM] fulvestrant) and 3 cost categories, by visit and PPPM, are presented in Table 5. Among the 828 patients, the most commonly used drugs included non-protein-bound paclitaxel (31.5% of patients) and trastuzumab (25.6%), whereas the least commonly used drugs included protein-bound paclitaxel (2.3%) and cyclophosphamide (2.1%).

Average total contracted payments significantly differed by drug in the per-visit ($P<0.001$) and PPPM ($P<0.001$) analyses. The highest total payments per visit were observed for protein-bound paclitaxel ($4,347) and doxorubicin ($3,145). The lowest total payments were observed for vinorelbine ($1,270) and cyclophosphamide ($1,532). In the PPPM cost analysis, protein-bound paclitaxel and fluorouracil had the highest average total PPPM costs ($12,441 and $6,920, respectively), whereas IM fulvestrant and cyclophosphamide had the lowest average total costs ($2,560 and $1,751, respectively). Examining IV breast cancer drug costs alone, the most expensive treatments per visit and PPPM were protein-bound paclitaxel, docetaxel, and trastuzumab, whereas fluorouracil and cyclophosphamide were the least expensive.

TABLE 4 Overall Costs Per Patient With Metastatic Breast Cancer (N = 828) by Visit and Month
(continued from previous page)

PPPM	No. of Therapy-Months[f]	Mean	% of Total	% of Other Services Provided at Visit	SD	Median
Total	3646	4,965.97	100	NA	3,841.00	4250
1. IV study drug		2,800.31	56.4	NA	2,399.00	2595
2. IV administration (all drugs)		567.80	11.4	NA	562.00	427
3. Other visit-related services and drugs		1,597.87	32.2	100	2,597.00	756
3a. Other injectable drugs and concomitant oral drugs[a]		1,577.27	31.8	98.7	2,593.04	745
• Antihypercalcemic agents (e.g., zoledronic acid)		319.42	6.4	20.0	586.41	0
• Colony-stimulating factors (e.g., pegfilgrastim, filgrastim, epoetin, darbepoetin)		363.19	7.3	22.7	853.10	0
• Antineoplastic agents (bevacizumab)[b]		362.51	7.3	22.7	1,925.71	0
• Platinum agents (e.g., carboplatin, oxaliplatin)[b]		172.12	3.5	10.8	703.18	0
• Chemotherapeutic agents (e.g., irinotecan, vincristine)[b]		41.06	0.8	2.6	381.34	0
• Antiemetic agents (e.g., palonosetron, granisetron)		159.28	3.2	10.0	435.90	0
• Saline solution, dextrose water		21.60	0.4	1.4	30.56	10
• Corticosteroids (e.g., dexamethasone)		11.48	0.2	0.7	44.51	1
• Heparin		6.58	0.1	0.4	31.35	0
• Antihistamine (e.g., diphenhydramine)		1.07	0.0	0.1	2.95	0
• Histamine-2 receptor antagonists (e.g., ranitidine)		1.03	0.0	0.1	3.83	0
• Iron		0.05	0.0	0.0	1.56	0
• Miscellaneous/unclassified agents		117.34	2.4	7.3	503.38	0
3b. Office visit: evaluation and management services[c]		11.37	0.2	0.7	74.19	0
3c. Supplies and equipment[d]		3.67	0.1	0.2	21.45	0
3d. Miscellaneous administration-related services[e]		5.56	0.1	0.3	38.06	0

[a] *Includes other injectable drugs administered and oral drugs administered as an initial dose for supportive care at the time of chemotherapy treatment during the breast cancer IV administration visit.*

[b] *Breast cancer chemotherapy therapy was restricted to FDA-approved or National Comprehensive Cancer Network guideline-recommended agents. These anticancer agents were not indicated for breast cancer during study period.*

[c] *Primarily includes physician assessments for chemotherapy administration or side effects related to chemotherapy including nausea and/or vomiting, fatigue, and pain; these codes include G9021-G9024 (chemotherapy assessment for nausea and vomiting) and G9029-G9032 (chemotherapy assessment for lack of energy [fatigue]). Side effects related to chemotherapy accounted for about 60% of total costs in this category.*

[d] *Includes non-coring needles, sterile water, dressing pads, and infusion supplies.*

[e] *Includes fluid collection and laboratories such as blood collection by venipuncture, metabolic panels, red and white blood cell count, and lactate dehydrogenase.*

[f] *Patients receiving administrations of 2 or more different drugs at separate visits during the same month were included in the per-visit analysis (monotherapy during visit) but excluded from PPPM analysis (multiple drugs received during the month).*

Source: Medical Present Value Inc., Phynance database, Austin, Texas (www.mpv.com).

IV = intravenous; NA = not applicable; PPPM = per patient per month.

Although IV breast cancer drug cost variation was expected, we observed that the costs associated with administration and with other visit-related services and drugs also varied significantly between agents ($P < 0.001$). Costs associated with IV administration ranged from $110 to $496 per visit across drugs, representing 6.3% to 21.3% of total costs, and from $114 to $1,057 PPPM across drugs, representing 6.5% to 33.7% of total costs. Costs associated with other visit-related services and drugs also varied significantly across therapies ($P < 0.001$), showing greater variation than did costs associated with IV administration. These costs varied from $336 to $2,573 per visit and $602 to $5,164 PPPM across drugs. These costs as a percentage of total costs ranged from 13.3% (trastuzumab) to 85.9% (vinblastine) on a per-visit basis and from 13.5% (trastuzumab) to 74.6% (fluorouracil) on a PPPM basis.

Payment by Payer Type and Patient Age

Significant differences in costs for study drug, IV administration, and other visit-related services and drugs were observed across payer types in both the per-visit ($P < 0.001$) and PPPM ($P < 0.001$) analyses (Figure 2). The overall mean payment per visit (PPPM) was $2,924 ($6,092) for managed care; $2,672 ($5,192) for indemnity; $1,582 ($3,007) for Medicare; $1,594 ($3,565) for

TABLE 5 Costs by Drug Per Patient With Metastatic Breast Cancer—Per Visit and Per Month

Drug[b]	Patients (n)[c]	Visits (n)	Total Mean Costs ($)	Total %	Study Drug Mean Costs ($)	Study Drug %	IV Administration Mean Costs ($)	IV Administration %	Other Visit-Related Services[a] Mean Costs ($)	Other Visit-Related Services[a] %
Per Visit										
All Study Drugs	828	7406	2,477.32	100.0	1,462.80	59.0	251.74	10.2	762.78	30.8
Protein-bound paclitaxel	19	94	4,346.72	100.0	3,044.46	70.0	361.29	8.3	940.97	21.6
Doxorubicin	72	288	3,145.11	100.0	1,944.22	61.8	274.99	8.7	925.90	29.4
Fluorouracil	28	186	3,100.79	100.0	32.10	1.0	495.57	16.0	2,573.13	83.0
Docetaxel	151	761	3,042.66	100.0	2,080.27	68.4	204.88	6.7	757.51	24.9
Non-protein-bound paclitaxel	261	1450	2,803.64	100.0	1,213.84	43.3	352.97	12.6	1,236.83	44.1
Vinblastine	1	2	2,620.60	100.0	205.20	7.8	164.50	6.3	2,250.90	85.9
Trastuzumab	212	2416	2,526.41	100.0	1,976.27	78.2	213.66	8.5	336.48	13.3
Gemcitabine	137	973	2,249.60	100.0	1,116.12	49.6	289.11	12.9	844.37	37.5
Fulvestrant	119	517	1,660.29	100.0	917.49	55.3	110.37	6.6	632.43	38.1
Cyclophosphamide	17	21	1,531.68	100.0	94.33	6.2	326.17	21.3	1,111.19	72.5
Vinorelbine	103	698	1,270.38	100.0	431.03	33.9	185.71	14.6	653.64	51.5

Drug[b]	Patients (n)[c]	Therapy Months (n)	Total Mean Costs ($)	Total %	Study Drug Mean Costs ($)	Study Drug %	IV Administration Mean Costs ($)	IV Administration %	Other Visit-Related Services[a] Mean Costs ($)	Other Visit-Related Services[a] %
PPPM										
All Study Drugs	776	3646	4,965.97	100.0	2,800.31	56.4	567.80	11.4	1,597.87	32.2
Protein-bound paclitaxel	17	34	12,441.07	100.0	8,205.76	66.0	1057.15	8.5	3,178.17	25.5
Fluorouracil	27	89	6,919.59	100.0	755.49	10.9	1000.39	14.5	5,163.70	74.6
Non-protein-bound paclitaxel	241	679	6,323.25	100.0	2,944.86	46.6	856.41	13.5	2,521.98	39.9
Trastuzumab	174	1040	5,256.34	100.0	4,089.50	77.8	457.71	8.7	709.13	13.5
Docetaxel	137	426	5,090.27	100.0	3,606.53	70.9	373.96	7.3	1,109.78	21.8
Gemcitabine	117	378	4,883.22	100.0	2,596.41	53.2	690.72	14.1	1,596.09	32.7
Doxorubicin	66	258	3,734.52	100.0	2,194.48	58.8	372.25	10.0	1,167.79	31.3
Vinorelbine	87	234	3,712.88	100.0	1,377.73	37.1	581.98	15.7	1753.17	47.2
Cyclophosphamide	10	11	2,559.83	100.0	172.78	6.7	863.74	33.7	1523.31	59.5
Fulvestrant	109	497	1,750.87	100.0	1,035.05	59.1	113.55	6.5	602.27	34.4
Vinblastine	0	0	–	–	–	–	–	–	–	–

[a] *Includes other injectable drugs and concomitant oral drugs (e.g., antihypercalcemic agents, colony-stimulating factors, anticancer agents, and antiemetic agents), evaluation and management services, supplies and equipment, and miscellaneous administration-related services.*

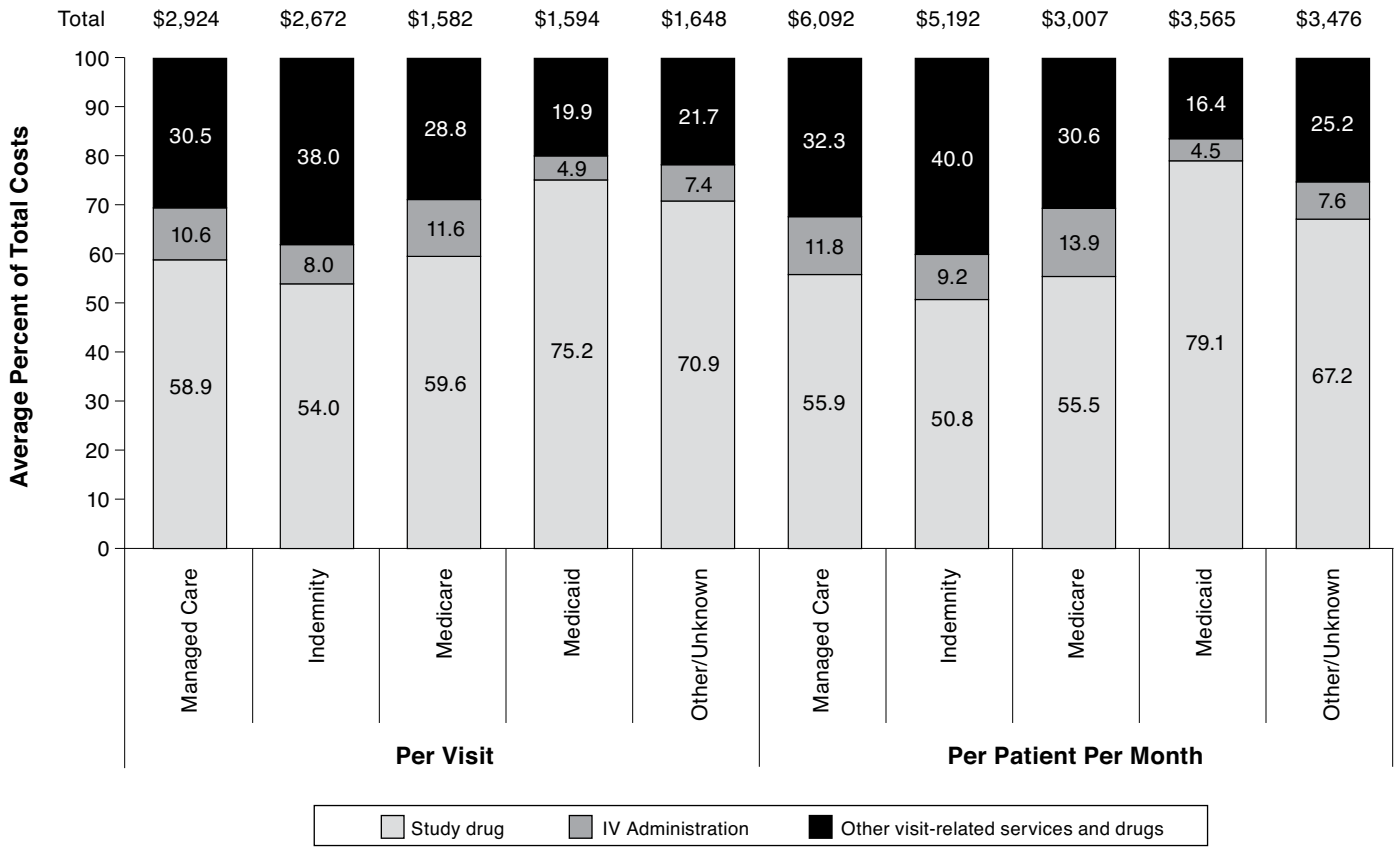
[b] *Comparisons by study drug on costs for study drug, IV administration, and other services were statistically significant in both the IV-visit analysis ($P < 0.001$) and the PPPM analysis ($P < 0.001$) using a Kruskal-Wallis test. Vinblastine was excluded due to low number of visits. Pairwise comparisons were performed using Dunn's nonparametric multiple comparison test.*

[c] *Numbers in cells do not sum to total because some patients used more than 1 drug during the study period.*

Statistical Test Results for Per-Visit Pairwise Comparisons: *Cost of study drug — All pairwise comparisons were significant at $P < 0.05$ except for cyclophosphamide vs. fluorouracil, cyclophosphamide vs. vinorelbine, and gemcitabine vs. non-protein-bound paclitaxel. Administrative costs — All pairwise comparisons were significant at $P < 0.05$ except for protein-bound paclitaxel vs. cyclophosphamide, protein-bound paclitaxel vs. fluorouracil, protein-bound paclitaxel vs. non-protein-bound paclitaxel, cyclophosphamide vs. docetaxel, cyclophosphamide vs. doxorubicin, cyclophosphamide vs. fluorouracil, cyclophosphamide vs. gemcitabine, cyclophosphamide vs. non-protein-bound paclitaxel, cyclophosphamide vs. trastuzumab, cyclophosphamide vs. vinorelbine, docetaxel vs. trastuzumab, docetaxel vs. vinorelbine, and doxorubicin vs. gemcitabine. Other visit-related services — All pairwise comparisons significant at $P < 0.05$ except for protein-bound paclitaxel vs. cyclophosphamide, protein-bound paclitaxel vs. docetaxel, protein-bound paclitaxel vs. doxorubicin, protein-bound paclitaxel vs. fulvestrant, protein-bound paclitaxel vs. non-protein-bound paclitaxel, protein-bound paclitaxel vs. vinorelbine, cyclophosphamide vs. docetaxel, cyclophosphamide vs. doxorubicin, cyclophosphamide vs. fulvestrant, cyclophosphamide vs. gemcitabine, cyclophosphamide vs. non-protein-bound paclitaxel, cyclophosphamide vs. trastuzumab, cyclophosphamide vs. vinorelbine, docetaxel vs. vinorelbine, doxorubicin vs. fluorouracil, doxorubicin vs. gemcitabine, doxorubicin vs. non-protein-bound paclitaxel, fulvestrant vs. vinorelbine, and gemcitabine vs. non-protein-bound paclitaxel.*

IV = intravenous; MBC = metastatic breast cancer; PPPM = per patient per month.

FIGURE 2 Costs by Payer Type[a]



[a]*Significant differences by payer type were found in costs for study drug, IV administration, and other services in the visit analysis (P<0.001) and the PPPM analysis (P<0.001) using a Kruskal-Wallis test. Pairwise comparisons were performed using Dunn's nonparametric multiple comparison test.*

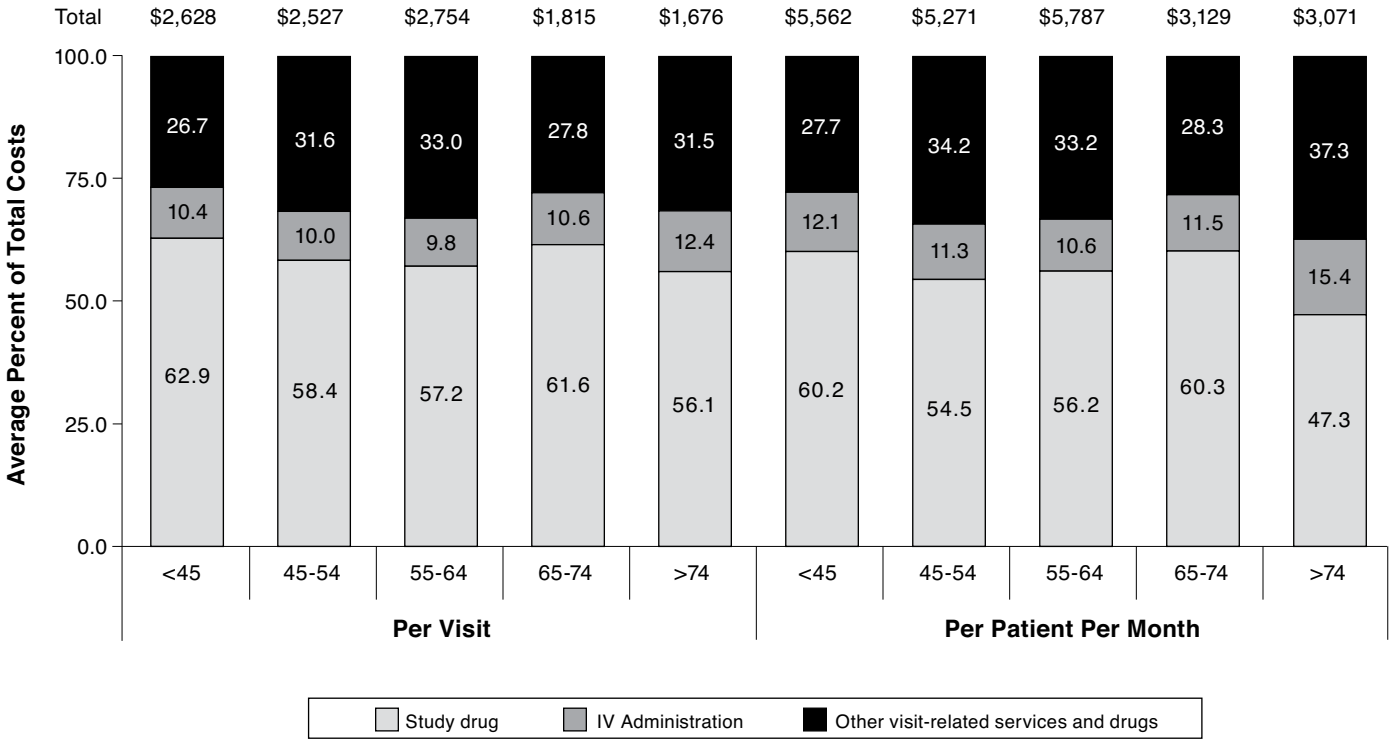
Statistical Test Results for Pairwise Comparisons of Per-Visit Costs: *Cost of study drug — All pairwise comparisons significant at P<0.05 except for Medicare vs. Medicaid and Medicaid vs. other/unknown. IV administration — All pairwise comparisons significant at P<0.05 except for Medicaid vs. other/unknown. Other visit-related services — All pairwise comparisons significant at P<0.05 except for managed care and Medicare vs. other/unknown.*

IV=intravenous; PPPM=per patient per month.

Medicaid; and $1,646 ($3,476) for the other/unknown category of patients. When comparing the additional costs beyond the breast cancer study drug as a percentage of total payments, Medicaid had the lowest cost of IV administration visit at $77 per visit (4.9% of total costs) and $160 PPPM (4.5% of total costs), whereas managed care patients had the highest cost of IV administration at $310 per visit (10.6% of total costs) and $718 PPPM (11.8% of total costs). Similar to IV administration costs, Medicaid patients had the lowest cost of other visit-related services and drugs at $318 per visit (19.9% of total costs) and $586 PPPM (16.4% of total costs). However, patients covered by indemnity insurance had the highest costs for other visit-related services and drugs at $1,015 per visit (38.0% of total costs) and $2,075 PPPM (40.0% of total costs).

There were also significant differences in payments to providers by patient age group for study drug, IV administration, and other visit-related services and drugs in both the per-visit ($P<0.001$) and PPPM ($P<0.001$) analyses (Figure 3). Patients aged 65 years or older (Medicare-eligible patients) had the lowest average total costs per visit and PPPM, reflecting the lower payments by Medicare. In contrast to the analysis by payer type, little age-related variation was observed for costs associated with IV administration and other visit-related services and drugs, which ranged, respectively, from 10%-12% and 27%-33% of

FIGURE 3 Costs by Patient Age Group[a]



[a]*Significant differences by age group were found in costs for study drug, IV administration, and other services in the visit analysis (P<0.001) and the PPPM analysis (P<0.001) using a Kruskal-Wallis test. Pairwise comparisons were performed using Dunn's nonparametric multiple comparison test*

Statistical Test Results for Per-Visit Pairwise Comparisons: *Cost of study drug — All pairwise comparisons significant at P<0.05 except for groups aged (years) 45-54 vs. 55-64. Administrative costs — All pairwise comparisons significant at P<0.05 except for groups aged (years) less than 45 vs. 45-54, less than 45 vs. 55-64, 45-54 vs. 55-64, 45-54 vs. older than 75, and 65-74 vs. older than 75. Other visit-related services — All pairwise comparisons significant at P<0.05 except for groups aged (years) less than 45 vs. 45-54, less than 45 vs. 65-74, less than 45 vs. older than 75, 45-54 vs. 55-64, 45-54 vs. 65-74, 45-54 vs. older than 75, and 65-74 vs. older than 75.*

IV=intravenous, PPPM=per patient per month.

total per-visit costs.

In the sensitivity analysis limited to patients taking 2 or more study drugs (combination therapy), results were similar to those observed for the monotherapy patients. Costs for IV administration and other visit-related costs were 38.3% of total cost per visit (detailed data not shown), compared with 41.0% for monotherapies.

Discussion

The objective of this study was to evaluate the costs associated with the administration of single-agent IV therapies in patients with MBC. To estimate the cost components, we examined more than 800 patients with MBC with more than 7,400 clinic visits from a large, national practice management system. Costs were analyzed on a per-visit and PPPM basis. The results showed average contracted payments of $2,477 per visit and $4,966 PPPM, with IV administration accounting for 10%-11% of the total and costs for other visit-related drugs, including antihypercalcemic agents, CSFs, and anticancer drugs being used off-label or for other conditions, accounting for 31%-32% of the total cost.

These costs above the drug acquisition cost for the principal chemotherapy drug represent a significant economic burden to payers. Even though this study focused on MBC, these IV administration and other visit-related costs have also been reported to comprise a significant portion of total costs for early stage breast cancer.[17] Results of the present study are comparable to those of a previous study based on administrative claims data for lung cancer, which reported non-lung cancer drug costs associated with

IV administration and related services to be 50% and 41% of total payments per visit, for small cell lung cancer and all types of lung cancer, respectively.[15]

In assessing the payment breakdown based on individual IV cancer drug, variability was observed for costs associated with administration and more so for the costs associated with other visit-related services and drugs. Part of the variation in these costs can be explained by the lower drug costs of the generic breast cancer therapies. For example, mean total costs per visit for generic fluorouracil treatment were $3,101, of which drug costs were only $32 (1.0%), costs for IV administration were $496 (16.0%), and costs for other visit-related services and drugs were $2,573 (83.0%). In contrast, the corresponding total cost ($4,347) breakdown for branded protein-bound paclitaxel was $3,044 (70.0%) for the study drug, $361 (8.3%) for IV administration, and $941 (21.6%) for other services. For example, to avoid the occurrence of severe hypersensitivity reactions, patients receiving non-protein-bound paclitaxel should be premedicated with corticosteroids (such as dexamethasone), diphenhydramine, and H2-blockers such as ranitidine or cimetidine; however, the cost for these agents is low—$4.51 per visit for corticosteroids, $0.47 per visit for antihistamines, and $0.39 per visit for H2-blockers.

It is also possible that the older agents may have been combined with newer, nonapproved, and nonrecommended anticancer agents. For example, bevacizumab was neither FDA-approved nor NCCN-recommended as a single agent for breast cancer for the study period, and may have been used more frequently in combination with older drugs (e.g., fluorouracil); this treatment pattern would result in high costs for the "other visit-related services and drugs" category.

Contracted allowed payments were also found to vary considerably by payer type. As expected, patients enrolled in government-funded programs (Medicaid and Medicare) had lower overall payments than did managed care and indemnity insured patients. This difference is probably attributable to differences in reimbursement rates for administration of IV therapies between government-funded and private insurance. Additionally, the analysis showed that Medicaid patients incurred less than 25% of total payments for additional costs above breast cancer study drug costs, whereas managed care and indemnity insured patients incurred more than 40% of total payments for these costs. However, the percentage of costs other than breast cancer study drug costs as a percentage of total costs was similar (40% per visit and 44% PPPM) in both Medicare and managed care. The patient age group analysis showed that, as in the payer type analysis, patients with MBC aged 65 years and older (i.e., Medicare eligible) had the lowest overall payments. Few differences in costs among the remaining age groups were observed.

Although this study does not compare the total costs of oral therapies with those of IV therapies for metastatic breast cancer, the increasing availability and use of effective oral therapies might help provide cost offsets in the treatment of MBC. The costs specifically associated with administration of the IV therapy are substantial and would clearly be avoided with the use of oral agents. Some of the other costs associated with the drugs and services provided at the time of IV administration (e.g., drugs used to dilute or reconstitute the IV product or to manage side effects associated with a particular IV therapy) may possibly be avoided with the use of oral agents. Even if an all-IV combination therapy is partially replaced with an oral therapy (i.e., IV plus IV replaced by IV plus oral), some of the costs associated with IV administration (depends upon length of time required to administer 2 or more IV therapies) might be avoided. However, the extent of cost avoidance for services other than IV administration is unknown and was not measured by this study. We also did not assess the possibility of any added costs associated with oral agents such as noncompliance or treatment of possible side effects with oral agents (e.g., gastrointestinal side effects).

Research evidence about costs of treatment with IV-administered versus oral chemotherapeutic drugs is limited. A recent non-peer-reviewed study delivered in a poster presentation by Giuliani et al. evaluated the economic impact of treatment with (a) oral capecitabine plus IV cisplatin versus (b) IV fluorouracil plus IV cisplatin among patients with advanced gastric cancer in an Italian clinic.[18] The costs of the 2 regimens were estimated based on trial data on actual dose and the number of administrations. The adverse event profiles were used to estimate the costs of treating these events. Indirect costs for time and travel for study drug administration were estimated. The oral plus IV regimen received 5.2 cycles of therapy versus 4.6 cycles in the all IV regimen. The oral capecitabine-containing regimen had 17.6 fewer hospital outpatient clinic visits than did the IV fluorouracil-containing regimen; the difference yielded a net cost saving of approximately $2,686 per patient, but no statistical tests were reported. Additionally, due to the additional 17.6 visits for infusion of fluorouracil, patients incurred substantially greater indirect costs in terms of lost time and travel expenses. In a randomized multicenter study of patients with small cell lung cancer, Pashko et al. compared (a) IV etoposide plus IV cisplatin (n = 41) versus (b) oral etoposide plus IV cisplatin (n = 42) and reported a cost savings of 17% ($2,002 for the IV versus $1,653 for the oral regimen, a difference of $349) for the patients receiving the oral plus IV regimen but did not report the results of statistical tests.[19]

As demonstrated by Giuliani et al., in addition to the possible direct cost savings of an oral cancer therapy from a payer perspective, there may be additional benefits from a patient perspective in terms of time and indirect cost savings resulting from fewer clinic visits for IV administration.[18] Several studies have demonstrated patient preferences for oral over IV cancer therapies, provided that efficacy is not compromised by receiving an oral agent.[20-22] Fallowfield et al.[20] found greater preference for daily tablets of

endocrine therapy over monthly IM injections among women with breast cancer. The major reasons for preference of oral therapy included convenience and dislike for needles, although almost 49% of patients indicated that they sometimes forgot and about 13% opted not to take their medication at certain times. In a study by Liu et al., 103 patients with cancer were asked about their preference for oral or IV chemotherapy.[21] Patients were told initially that frequency of laboratory evaluations and clinic visits to see a doctor and risks of toxicities of oral or intravenous regimens were comparable. Almost 90% of patients expressed a preference for oral chemotherapy. The predominant reason for this result appeared to be problems with IV access (pain and difficulty starting an IV line) or convenience of administration outside a clinic setting. Gornas et al. reported in a poster presentation the results of a survey of 218 female patients with MBC who were eligible for oral capecitabine; patients were asked about factors that influenced their preference for oral therapy.[23] The most common reason for choosing oral capecitabine, cited by 71% of patients, was its more convenient form of drug delivery. Other reasons given included a preference to receive drugs in a "more friendly way" and to stay at home during therapy. However, unlike injectable drugs that are covered under the medical benefit, oral drugs typically would be covered under the pharmacy benefit—hence, any impact on patient out-of-pocket expenses would need to be weighed against these patient benefits.

Limitations

First, we excluded combination drug regimens from this analysis. However, this method excluded only 13% of patients with MBC and 27% of IV visits recorded in the database for the study period. A sensitivity analysis examining costs for the combination therapy visits showed results that were similar to those of the study analyses for monotherapy patients, including cost percentages across breast cancer IV therapy, IV administration, and other drugs and visit-related costs. Focusing on monotherapy regimens permitted us to capture a majority of the IV visits and report the cost components by therapy.

Second, we observed IV breast cancer treatment for only 11.7% of the patients with MBC. Some of these patients with MBC were referred to facilities that were not captured in the data. Third, the accuracy of diagnostic coding of breast cancer and metastasis, and other coding or administrative errors, may have affected the validity of the cost estimates. For example, some patients with MBC may have not received a secondary metastatic ICD-9-CM code and thus were not included in this study. Fourth, given the limited time frame of the study, it is possible that the patients' entire history of IV breast cancer therapy may not have been captured. However, this potential limitation has been addressed by using methods that are not reliant on complete patient therapy histories but based on estimating costs per IV administration visit or cost per month, which are less prone to loss-to-follow-up problems.

Fifth, because health care services delivered at non-IV administration visits were excluded in this study, it is possible that other medical costs not measured in claims for the day of IV administration differ between patients on alternative therapies or insurance types. For example, if a patient returned to the facility at a later date for issues related to the IV therapy but an IV study drug was not administered during this visit, these costs would not be captured. Furthermore, due to the nature of administrative data (we did not have access to patient medical records), only minimal patient information was available. We were not able to examine the impact of clinical (e.g., disease severity and comorbidities) and nonclinical factors (e.g., formulary status of drugs) on costs across therapies. Also, although we were able to measure the total amount that the provider is eligible to receive from both payers and the patient from out-of-pocket payments, we were unable to determine what portion of this aggregated payment was paid by the patient.

Finally, although costs of IV administration are substantial and would clearly be avoided with the use of oral agents, we did not directly compare total costs for treatment using oral versus IV chemotherapeutic agents. We also did not assess the possibility of added costs associated with oral agents, such as noncompliance or treatment for gastrointestinal or other side effects.

Conclusions

Among patients with MBC treated with an IV-administered breast cancer drug, IV breast cancer drugs accounted for 56%-59% of total cost, IV administration costs accounted for 10%-11% of total costs, and 31%-32% of total costs were attributable to other drugs and services, primarily antihypercalcemic agents, CSFs, and anticancer drugs being used off-label or for other conditions. The use of safe and effective oral breast cancer therapies could potentially offset some of the costs of treating patients with MBC by reducing personnel time, clinic visits, and supplies and equipment associated with IV administration. Future research should include a direct comparison of oral versus IV drug costs in order to investigate these potential implications as well as to gain an understanding of both the costs and clinical implications of oral versus IV therapies when administered as sequential or combination therapy.

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DISCLOSURES

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All authors contributed to the concept and study design. Skonieczny collected the data, with assistance from Stavrakas. The data were interpreted primarily by Kruse and Amonkar. The manuscript was written primarily by Kruse, Amonkar, and Smith. Kruse, Amonkar, and Smith made the largest contribution to manuscript revision.

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APPENDIX Supplemental Information on Study Drug Selection[a]

Drug	FDA Approved for Breast Cancer	Listed as Preferred Single IV Chemotherapeutic Agent for MBC in NCCN Guidelines
Protein-bound paclitaxel	Yes	Yes
Doxorubicin	Yes	Yes
Fluorouracil	Yes	No[b]
Docetaxel	Yes	Yes
Non-protein-bound paclitaxel	Yes	Yes
Vinblastine	Yes	No[b]
Trastuzumab	Yes	No[c]
Gemcitabine	Yes	Yes
Fulvestrant (IM)	Yes	No
Cyclophosphamide	Yes	No
Vinorelbine	No	Yes
Epirubicin[d]	Yes	Yes
Thiotepa[d]	Yes	No
Bleomycin[d]	No	No
Mitoxantrone[d]	No	No

[a] *These 15 drugs were identified in the initial search of single-agent breast cancer drugs using a combination of sources, including the FDA Web site, NCCN guidelines, and cancer organization- and health-related Web sites to identify single-agent therapies for MBC. All other drugs not on the above list that may have been used for breast cancer during the study period without FDA approval for this indication or NCCN recommendation would fall into the "other drug" category and would represent "off-label" use (e.g., bevacizumab, irinotecan).*

[b] *Listed as "other active chemotherapeutic agent" for treatment of MBC.*

[c] *Considered as targeted therapy and hence may not be listed in the "preferred single chemotherapeutic agent" category by NCCN.*

[d] *No patients in the present study cohort were administered the last 4 drugs. Epirubicin and thiotepa are FDA approved, and 1 drug (epirubicin) is listed in NCCN guidelines. Bleomycin and mitoxantrone are neither FDA approved nor NCCN recommended for breast cancer.*

FDA = U.S. Food and Drug Administration; IM = intramuscular; MBC = metastatic breast cancer; NCCN = National Comprehensive Cancer Network.