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Variation in Modes of Chemotherapy Administration for Breast Carcinoma and Association with Hospitalization for Chemotherapy-Related Toxicity

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Abstract

BACKGROUND—To the authors' knowledge, few studies to date have addressed the patterns of how chemotherapy was administered (administration modes) over time. In the current study, the goal of the authors was to describe how chemotherapy for breast carcinoma was administered and to determine whether chemotherapy administration modes were associated with toxicity in a community-based large cohort.

METHODS—The authors studied 5256 women who were diagnosed with breast carcinoma at age 65 years or older between 1992-1999 and received chemotherapy. The patients were identified from the Surveillance, Epidemiology, and End Results (SEER)Program-Medicare linked databases. Chemotherapy drugs and modes of administration were determined through procedure codes in Medicare claims.

RESULTS—Of the 5256 patients who received chemotherapy, 33% received it through an intravenous infusion for less than 1 hour; 39% through an intravenous infusion lasting 1-8 hours; 15% through an intravenous infusion lasting longer than 8 hours and requiring a pump; 12% through an intravenous push technique; and 1% through a subcutaneous, intramuscular, or intralesional injection. These modes varied substantially across the 11 SEER areas. The risks of hospitalization for chemotherapy-related toxicities (neutropenia, fever, thrombocytopenia, and adverse effects of systemic therapy) were not found to be significantly associated with different modes of chemotherapy after adjusting for other factors. Compared with patients receiving 5-flurouracil using an intravenous infusion for longer than 8 hours, the risk of toxicity was determined to be 0.96 (95% confidence interval [95% CI], 0.63-1.47) for patients treated with an intravenous infusion lasting 1-8 hours; 0.94 (95% CI, 0.62-1.41) for patients treated with an intravenous infusion lasting less than 1 hour; and

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0.66 (95% CI, 0.38-1.08) for patients treated with subcutaneous, intramuscular, or intralesional injection or an intravenous push technique.

CONCLUSIONS—There were substantial geographic variations noted in the modes of administering chemotherapy; however, these variations did not appear to be associated with the risk of toxicities (neutropenia, fever, thrombocytopenia, and adverse effects of systemic therapy).

Keywords

breast carcinoma; chemotherapy; therapy mode; toxicity; cancer registry; Medicare

Chemotherapy involves the use of cytotoxic drugs for the purpose of eradicating nonoperable tumors or occult metastatic disease that otherwise would be fatal.[1-3] Chemotherapy has been well documented to be efficacious in prolonging survival for men and women with various malignancies.[4-6] In women diagnosed with breast carcinoma, chemotherapy is often used as an adjuvant therapy after surgery for early-stage disease, primary therapy for patients with locally advanced stage disease, and palliative therapy for women with metastatic breast carcinoma. Chemotherapy is administered in several ways, such as intramuscular injection, intravenous push technique, or intravenous infusion. These methods of administering chemotherapy are described in this study as “modes of chemotherapy administration.” There are consensus recommendations and clinical guidelines concerning the use of chemotherapy for patients with cancer, but to our knowledge, the modes of chemotherapy administration are less well specified and often left open to the providers. The new and improved changes in the drug approval process of the U.S. Food and Drug Administration have speeded the entry of many novel chemotherapy agents. As advances in drug therapy occur, the modes of chemotherapy administration continue to evolve. The choice of how chemotherapy is administered depends on many factors, including therapeutic intent, type of agents, and oncologist preference. However, to our knowledge, no large population-based studies have been conducted to date concerning how chemotherapy was administered in patients with cancer in the community, how it has changed over time from the 1990s to the present, and whether it is associated with chemotherapy-related toxicity.

We used the nationwide and population-based Medicare claims data, which were linked with the Surveillance, Epidemiology, and End Results (SEER) cancer registry data, to address the issue of current patterns of modes of chemotherapy administration and how they have changed over time from 1992 to 2001. Medicare claims are a unique data source with which to study cancer chemotherapy because it is among the few therapies that are covered by the Medicare program and therefore can be identified using Medicare claims. Because there are no specific guidelines or restrictions regarding what modes should be used, it is hypothesized that there could be substantial geographic variations in chemotherapy administration modes across the U.S. Because clinical trials and clinical observational studies[7-17] have indicated a possible link between different chemotherapy administration modes and toxicity rates, we also hypothesized that chemotherapy-related toxicity is associated with chemotherapy administration modes. If these hypotheses are confirmed, the findings can be expected to have significant clinical implications for the administration of chemotherapy by medical providers as well as for minimizing toxicities.

PATIENTS AND METHODS

Data Sources

The SEER program, which is supported by the National Cancer Institute (NCI), includes population-based tumor registries in 11 selected geographic areas[18-21]: the metropolitan areas

of San Francisco/Oakland, Detroit, Atlanta, and Seattle; Los Angeles county; the San Jose-Monterey area; and the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii.

The Medicare Program covers hospital, physician, and outpatient medical services for greater than 97% of persons age 65 years or older.[18,19] Cases reported by the SEER cancer registries until 1999 were matched against the Medicare master enrollment files; Medicare claims are available through 2001. Of those persons age 65 years or older appearing in the SEER records, Medicare eligibility could be identified for 94%. The method of linking these data has been described elsewhere.[18,19] The Committee for Protection of Human Subjects at the University of Texas Health Science Center in Houston approved this study.

Study Population

The current study is based on the analytic SEER-Medicare files that excluded women who did not have full coverage of both Medicare Part A and Part B and those who were members of health maintenance organizations (HMO) because claims from these organizations may not be complete. The study population was comprised of 44,245 women age 65 years or older from the 11 SEER areas who were diagnosed with breast carcinoma during the period between 1992-1999.

Study Variables

Chemotherapy and types of drugs—The details regarding the methods of identification of chemotherapy use through Medicare claims have been previously described.[22-24] In brief, patients with breast carcinoma were defined as having received chemotherapy if any of the following Medicare procedure codes indicated so within 6 months of the diagnosis[25-28]: the 9th revision of the International Classification of Diseases-Clinical Modifications (ICD-9-CM) procedure code 9925 and the V codes of V58.1, V66.2, or V67.2[25]; Current Procedural Terminology (CPT) codes of 96400-96549, J9000-J9999, and Q0083-Q0085[26,27]; and revenue center codes of 0331, 0332, and 0335.[28]

In addition to identifying all patients who received chemotherapy, we identified those patients who specifically received three classes of chemotherapy: anthracyclines (CPT codes J9000, J9001, and J9010 for doxorubicin or J9293 for mitoxantrone). 5-fluorouracil (5-FU) (J9190). and taxanes (J9170 for docetaxel and J9265 for paclitaxel).

Chemotherapy administration modes—The five major types of chemotherapy administration modes were based on the first cycle of chemotherapy and were defined as follows using the CPT codes from the Medicate claims[26]: 1) subcutaneous or intramuscular administration with or without local anesthesia (CPT code 96400) or intralesional administration up to and including 7 lesions (code 96405) or greater than 7 lesions (code 96406), 2) intravenous-push technique (code 96408), 3) intravenous-infusion technique lasting less than 1 hour (code 96410), 4) intravenous-infusion technique lasting 1-8 hours (code 96412), and 5) intravenous-infusion technique, with initiation of prolonged infusion (lasting longer than 8 hours) requiring the use of a portable or implantable pump (codes 96414, 96425, 96520, or 96530). The uncommon chemotherapy administration modes included intraarterial (push technique) (codes 96420, 96422, or 96423); administration into the pleural cavity, peritoneal cavity, or intrathecal (codes 96440, 96445, or 96450); and subarachnoid or intraventricular administration via a subcutaneous reservoir (code 96542). Because there were only 12 patients who had submitted claims for these uncommon modes of administration, we excluded these patients for the analysis. Because some patients might have used two or more different chemotherapy administration modes, they were categorized into one group according to the following hierarchic order (low to high): 1) subcutaneous, intramuscular, or intralesional administration; 2) intravenous-push technique; 3) intravenous-infusion lasting up to 1 hour; 4)

intravenous-infusion lasting 1-8 hours; and 5) intravenous-infusion lasting longer than 8 hours (requiring the use of a portable or implantable pump).

Comorbidity index—Comorbidity was ascertained from Medicare claims through diagnoses or procedures made 1 year before and 1 month after the diagnosis of breast carcinoma. The Medicare inpatient, outpatient, and physician claims were used to create a comorbidity score. The rationale for including diagnoses from the outpatient and physician claims is that many more people visit the outpatient department and see a physician rather than being hospitalized, thereby increasing the possibility of identifying more complete comorbid conditions.[29] For physician and outpatient claims, a patient's comorbid diagnoses must appear on at least 2 different claims that are greater than 30 days apart. Conditions that do not appear on two different claims are considered to be "rule out" diagnoses, and are not considered as comorbid conditions. This is necessary to prevent the overestimation of comorbidity when using physician or outpatient claims. We used the SAS macro rule-out programs provided by the NCI on its website (SAS Institute Inc., Cary, NC; available from URL: http://healthservices.cancer.gov/seermedicare/program/comorbidity.html [accessed July 26, 2004]).[30] This SAS macro uses a dataset of claim records to calculate a comorbidity index for a patient with regard to cancer. This code reflects the Deyo adaptation of the Charlson comorbidity index,[31,32] with several procedural codes that reflect the Romano adaptation.[33] The SAS macro considers the ICD-9 diagnosis codes, ICD-9 procedural codes, and Healthcare Common Procedure Coding System (HCPCS) procedure codes on Medicare claims. Because cancer is the primary disease of interest under study, it is not included in the comorbid conditions described earlier. Women diagnosed with breast carcinoma at age 65 years have a shorter duration for identifying comorbid conditions on Medicare claims. However, these women were found to have comorbidity scores similar to those for women ages 66-69 years, and therefore were included in the analysis.

Toxicity related to chemotherapy use—Toxicity was initially defined as hospitalization for any of the following 9 diagnoses within 7 months after the diagnosis of breast carcinoma using the ICD-9-CM diagnosis codes for a hospital inpatient claim: any infection (001.0-139.8), neutropenia (288.0), fever (780.6), thrombocytopenia (287.4), dehydration (276.5), anemia (284.x-285.x), delirium (780.x), heart failure (428.x), or adverse effects of systemic therapy (E9331).[25] The reason for selecting events within 7 months of diagnosis is to have 1-month window after the administration of chemotherapy in which to capture immediate or early chemotherapy-related toxicity.

Other characteristics—Patient and tumor characteristics such as age at diagnosis (categorized as 65-69 years, 70-74 years, 75-79 years, 80-84 years, and 85 years or older), race/ethnicity, tumor stage (AJCC Stage I to Stage IV and unstaged), year of diagnosis (1992-1999), and geographic areas (11 SEER areas) were available from the SEER data.

Statistical Analysis

Because SEER reported only the month and year of the diagnosis of breast carcinoma was made, we arbitrarily defined the day of diagnosis as the 15th of the month. The date of chemotherapy administration from inpatient claims was defined as the date of admission. For outpatient and physician claims, the date of chemotherapy administration was defined as the earliest date of service. The prevalence rate of chemotherapy use was the percentage of patients with breast carcinoma who received chemotherapy within 6 months of the date of diagnosis (Table 1). The percentage of Medicare claims for chemotherapy by different modes of administration was the number of claims for each different mode of administration divided by the total number of claims for chemotherapy each year from 1992-2001 among patients diagnosed with breast carcinoma between 1992-1999 (Table 2), whereas Table 3 presents the

percentage of patients who received their first cycle of chemotherapy by different modes of administration, stratified by other factors. The rate of hospitalization for toxicity was defined as the percentage of patients with chemotherapy who were admitted to the hospital because of chemotherapy-related toxicities (Tables 4, 5). Of the nine toxicity conditions studied, we presented the hospitalization rate for individual toxicity conditions as well as the hospitalization rate for all toxicity conditions combined. We also presented the hospitalization rates for four toxicity conditions combined (neutropenia, thrombocytopenia, fever, and adverse effects of systemic therapy) because these were adverse effects that appeared to be more specific to chemotherapy use. The chi-square statistic was used to test statistical significance for trend. Multivariable logistic regression analyses were used to assess the risk (odds ratio) of being hospitalized for toxicity in association with various modes of chemotherapy administration by simultaneously controlling for other factors. These analyses were adjusted for patient age, race, tumor stage, comorbidity scores, year of diagnosis, and geographic areas, which were potential confounding factors likely to affect the use of chemotherapy administration modes in women with breast carcinoma. All computer programming and analyses were completed using the SAS system (SAS Institute, Inc.).[34]

RESULTS

Of the total of 44,245 women diagnosed with breast carcinoma at age 65 years or older between 1992 and 1999 in the 11 SEER areas, 6680 patients (15.1%) had Medicare claims for chemotherapy within 6 months of diagnosis that were identified from all 3 sources of Medicare claims (inpatient, outpatient, and physician files). Of those patients who received chemotherapy, 5256 (79%) had Medicare claims that specified the type of modes for chemotherapy administration. Table 1 presents the percentage of patients receiving chemotherapy based on age, ethnicity, tumor stage, comorbidity, year of diagnosis, and geographic areas. As expected, the use of chemotherapy decreased by age and varied by ethnicity. Those patients with Stage III or Stage IV breast carcinoma had a higher percentage of receiving chemotherapy than those with Stage I or Stage II breast carcinoma. Patients with higher comorbidity scores had a lower percentage of receiving chemotherapy. The use of chemotherapy was found to increase in patients diagnosed in more recent years and varied in SEER areas. Table 1 also shows that patients with claims for chemotherapy administration modes had no apparent systematic difference in terms of other characteristics (age, ethnicity, stage of disease, comorbidity, year of diagnosis, and geographic areas) compared with all patients who received chemotherapy.

Table 2 presents the trend of overall Medicare claims between 1992-2001 for various chemotherapy administration modes among patients with breast carcinoma who were diagnosed between 1992-1999,. The use of subcutaneous, intramuscular, or intralesional administration of chemotherapy decreased over time. The commonly used intravenous push technique also decreased dramatically as a mode of administration from 39% in 1992 to 15% in 2001. In contrast, intravenous infusion administration lasting up to 1 hour as well as infusion lasting 1-8 hours increased significantly over this period, whereas the use of intravenous infusion lasting longer than 8 hours and requiring a pump was relatively stable over time.

Table 3 presents the patterns of chemotherapy administration modes in association with age, ethnicity, tumor stage, comorbidity, year of diagnosis, and geographic areas. Overall (bottom row in Table 3), the significant majority of patients (72%) received chemotherapy through intravenous infusion lasting up to 1 hour (33%) or intravenous infusion lasting 1-8 hours (39%). Approximately 15% of patients received chemotherapy through intravenous infusion lasting longer than 8 hours and requiring a pump. Approximately 12% of patients received this therapy through an intravenous push technique only, and 1% were treated using subcutaneous, intramuscular, or intralesional injection. Chemotherapy generally was administered in a similar

fashion across different age groups, although a slightly higher percentage of patients age 80 years or older received this therapy through subcutaneous, intramuscular, or intralesional injection. African-American patients received chemotherapy through intravenous infusion lasting longer than 8 hours and requiring a pump at a higher rate (25%) and through intravenous push technique at a lower rate (9%) compared with other ethnic groups. There appeared to be a trend toward using higher hierarchical modes of chemotherapy administration in patients diagnosed with advanced tumor stages, as well as in patients diagnosed toward the late 1990s. There were substantial geographic variations noted in the administration of chemotherapy across the 11 SEER areas. For example, patients diagnosed with breast carcinoma in Detroit were more likely to receive chemotherapy through intravenous infusion lasting longer than 8 hours and requiring a pump (27%), whereas those diagnosed in San Jose were more likely to be treated with intravenous push techniques (22%). Greater than 66% of patients diagnosed in Utah received chemotherapy through an intravenous infusion lasting less than 1 hour-a 3-fold difference compared with the San Jose area.

We also analyzed chemotherapy use in association with hospitalization for chemotherapy-related toxicity. Initially, nine groups of diagnoses that might plausibly occur as a serious toxicity (i.e., resulting in hospitalization) of chemotherapy administration were assessed. These diagnoses were neutropenia, thrombocytopenia, fever, infection, dehydration, anemia, delirium, heart failure, and adverse effects of systemic therapy. Table 4 presents the hospitalization rates for chemotherapy-related toxicity among patients who received chemotherapy in association with chemotherapy administration modes, which were stratified by three classes of chemotherapy regimen. For example, among those who received anthracyclines (doxorubicin or mitoxantrone), the hospitalization rate for neutropenia was 10.5% in patients who received this therapy through an intravenous infusion lasting less than 1 hour, whereas the hospitalization rate was 11.7% for those receiving an intravenous infusion of chemotherapy lasting 1-8 hours. There was no significant trend in toxicity associated with the increased hours of infusion in patients who received anthracyclines or taxanes. However, among those patients who received 5-FU, there appeared to be a significant trend toward higher hierarchical chemotherapy administration modes for the increased hospitalization rates for neutropenia, fever, infection, anemia, and delirium.

Table 5 presents multivariable analyses of the risk (odds ratio) of being hospitalized for the above four and nine chemotherapy-related toxicities controlling for age, race/ethnicity, tumor stage, comorbidity, year of diagnosis, and geographic areas. This analysis was performed separately for those patients who received three different classes of chemotherapy regimens. Model 1 was an unadjusted odds ratio of being hospitalized for the four or nine chemotherapy-related toxicities. Model 2 adjusted for age, ethnicity, tumor stage, comorbidity, and year of diagnosis, whereas Model 3 added an additional risk factor for geographic areas. After adjusting for these factors, the modes of chemotherapy administration did not appear to be significantly associated with an increased risk of hospitalization for the four toxicities (neutropenia, fever, thrombocytopenia, and adverse effects of systemic therapy) in all three groups of patients with different classes of chemotherapy regimens. For example, in the analysis in which no adjustment was made for other factors (Model 1), patients receiving 5-FU through a subcutaneous, intramuscular, or intralesional injection or an intravenous push technique (the 2 categories were combined because of their small numbers) were significantly less likely to be hospitalized for any of the 4 chemotherapy-related conditions than those who were treated with an intravenous infusion lasting for longer than 8 hours. This finding remained statistically significant after controlling for age, ethnicity, tumor stage, comorbidity, and year of diagnosis. However, the risk of being hospitalized for this group of patients was no longer statistically significant compared with those patients treated with an intravenous infusion lasting longer than 8 hours, after controlling for geographic area. Those patients who received an intravenous infusion lasting less than 1 hour or those treated with a 1-8-hour infusion did

not demonstrate significant differences compared with patients treated with longer infusions before or after adjusting for other factors.

The risk of being hospitalized for any of the nine chemotherapy-related toxicity conditions remained marginally statistically significant for those patients receiving chemotherapy through subcutaneous, intramuscular, or intralesional injections or an intravenous push technique and for those patients treated with an intravenous infusion lasting less than 1 hour compared with those treated with an intravenous infusion lasting longer than 8 hours after controlling for geographic area. Again, those patients who were treated with an intravenous infusion lasting 1-8 hours did not demonstrate any statistically significant difference compared with those patients treated with a longer infusion after adjusting for other factors. Among those patients who received anthracyclines or taxanes, there was no significant difference noted with regard to the risk of hospitalization for toxicities associated with specific drug administration modes after adjusting for age, race/ethnicity, tumor stage, comorbidity, year of diagnosis, and geographic areas (Table 5).

DISCUSSION

The current study examined the patterns of chemotherapy administration (modes) in patients with breast carcinoma and their association with toxicity. The majority of patients (72%) received chemotherapy through an intravenous infusion lasting less than 1 hour or an intravenous infusion lasting 1-8 hours. Approximately 15% of patients received chemotherapy through an intravenous infusion lasting longer than 8 hours that required a pump; 12% through an intravenous push technique only; and 1% through subcutaneous, intramuscular, or intralesional injection. There were substantial geographic variations with regard to the modes of chemotherapy administration across the 11 SEER areas. Overall, the risk of hospitalization for the four chemotherapy-related toxicities (neutropenia, fever, thrombocytopenia, and adverse effects of systemic therapy) was not found to be significantly associated with different modes of chemotherapy administration after adjusting for other factors among the three groups of patients who received different classes of chemotherapy regimens. However, the risk of hospitalization for the nine toxicities was found to be reduced in those patients receiving 5-FU through a subcutaneous, intramuscular, or intralesional injection or an intravenous push technique and for those patients treated with an intravenous infusion that lasted less than 1 hour, compared with those treated with an intravenous infusion that lasted longer than 8 hours after controlling for geographic areas.

As expected, there was substantial geographic variation with regard to how chemotherapy was administered. This geographic variation has important public health implications because if the modes of administration are associated with subsequent outcomes, it may be possible to take steps to prevent negative outcomes by controlling for the preferred mode or route of chemotherapy administration. Patients receiving 5-FU through subcutaneous, intramuscular, or intralesional injections or an intravenous push technique were found to be significantly less likely to be hospitalized for any of the 4 chemotherapy-related conditions (neutropenia, fever, thrombocytopenia, and adverse effects of systemic therapy) than those patients who were treated with an intravenous infusion lasting for longer than 8 hours, even after controlling for age, ethnicity, tumor stage, comorbidity, and year of diagnosis. However, the risk of being hospitalized for this group of patients was no longer statistically significant compared with those treated with an intravenous infusion lasting longer than 8 hours, after controlling for geographic areas. When the remaining 5 toxicity conditions that may be related to chemotherapy were added to the model, the risk of being hospitalized for toxicity remained marginally statistically significant for those patients receiving 5-FU through injection or an infusion lasting less than 1 hour compared with patients treated with an infusion lasting longer than 8 hours, even after controlling for geographic areas. These findings were largely due to

the effects of infection, dehydration, or delirium. Nevertheless, those patients treated with an intravenous infusion lasting 1-8 hours did not demonstrate any significant difference in the risk of being hospitalized for the 4 or 9 chemotherapy-related toxicity conditions compared with those patients treated with longer infusions. This finding is important because these modes of administration are the most frequently used routes of chemotherapy. Among patients who received anthracyclines or taxanes, modes of chemotherapy administration were not found to be significantly associated with an increased risk of toxicity.

The SEER-Medicare-linked dataset is unique in that it addresses the modes of chemotherapy administration. First, the SEER cancer registry provides what to our knowledge are the most authoritative data concerning cancer incidence and diagnosis in the U.S.[20] These data have been validated to be highly reliable and are extremely helpful for monitoring cancer control and prevention.[20] Second, Medicare is a national insurance program mainly for people age 65 years or older and provides lifelong coverage of medical services for these older individuals. Although the current study only included patients diagnosed with breast carcinoma in the 11 SEER areas, Medicare claims covered medical treatments or services that were received outside the SEER areas and therefore provided more complete information regarding cancer surveillance. Furthermore, chemotherapy agents are among the few drugs that are covered by the Medicare program whereas SEER datasets do not provide information regarding chemotherapy, making Medicare claims a unique data source for cancer chemotherapy. The validity of Medicare claims for chemotherapy has been documented both externally[22,35] and internally.[23,24,36-48] Medicare claims also have been used to address the correlation between chemotherapy use and toxicities.[49,50] Because the Medicare program reimburses the providers for both chemotherapy agents and the administration of chemotherapy, claims codes for the modes of chemotherapy administration are important to the providers in terms of accuracy and completeness. Although we cannot rule out any possibility of fraudulent Medicare claims, the criminal and civil penalties resulting from charging Medicare for nonexistent services would serve as a strong incentive for accuracy in Medicare billing.

The current study has several limitations. The study findings may be applied only to women diagnosed with breast carcinoma at the age of 65 years or older who were not members of HMOs and had both Medicare Part A and Part B coverage. The modes of chemotherapy administration and the chemotherapyrelated toxicity profile might be different for those breast carcinoma patients age younger than 65 years. Further studies are needed to address this issue. Second, because the Medicare codes for modes of chemotherapy administration do not indicate specific chemotherapy regimens, misclassification of chemotherapy administration modes could have occurred when multiple drugs were used. Third, because Medicare claims do not usually cover oral chemotherapy, the patterns and trends for oral chemotherapy are to our knowledge unknown. However, chemotherapy is rarely taken orally, although it is reported that more oral agents are being developed. Furthermore, the toxicity conditions addressed in the current study were not milder forms of toxicity but were mostly life-threatening complications that required hospitalization. Finally, to the best of our knowledge, information regarding chemotherapy dose cannot be obtained reliably from claims data, and the validity of Medicare claims for different chemotherapy modes of administration has not been evaluated externally.

In conclusion, the majority of patients in the current study (72%) received chemotherapy through an intravenous infusion lasting less than 1 hour or an intravenous infusion that lasted 1-8 hours. There were substantial geographic variations noted in the modes of chemotherapy administration across the 11 SEER areas. The modes of chemotherapy administration did not appear to be significantly associated with the risk of hospitalization for the four common toxicities (neutropenia, fever, thrombocytopenia, and adverse effects of systemic therapy). However, patients receiving 5-FU through an intravenous infusion lasting less than 1 hour

appeared to have a reduced risk for toxicities (that included the remaining 5 conditions) compared with those patients treated with an intravenous infusion of 5-FU that lasted for longer than 8 hours.

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TABLE 1

Percentage of Women with Breast Carcinoma Who Had Chemotherapy Claims, Based on Patient and Tumor Characteristics, Year of Diagnosis, and Geographic Areas

			Distribution of other factors (column %)	
	No. of cases	**Percentage of patients receiving chemotherapy (row %)**	**All patients who received chemotherapy (*n* = 6,680)**	**Patients who received chemotherapy and had claims for modes of chemotherapy (*n* = 5,256)**
Age (yrs)				
65-69	11,991	27.8	50.0	2663 (50.7)
70-74	10,566	17.5	27.7	1480 (28.2)
75-79	9268	11.3	15.7	799 (15.2)
80-84	6638	5.2	5.2	252 (4.8)
85	5782	1.7	1.5	62 (1.2)
Race/ethnicity				
White	3925	14.6	86.0	4618 (87.9)
African	3039	20.7	9.4	449 (8.5)
Americans				
Other ethnicities	1688	17.4	4.4	176 (3.4)
Unknown	193	7.3	0.2	13 (0.3)
Tumor stage				
Stage I	21,624	4.3	13.7	677 (12.9)
Stage II	13,941	25.5	53.3	2888 (55.0)
Stage III	2672	42.1	16.8	878 (16.7)
Stage IV	2203	35.6	11.7	594 (11.3)
Un-staged	3805	7.7	4.4	219 (4.2)
Comorbidity score				
0	27,012	16.7	67.6	3532 (67.2)
1	10,653	13.3	21.3	1132 (21.5)
2	4006	12.4	7.4	401 (7.6)
≥ 3	2574	9.7	3.7	191 (3.6)
Year of diagnosis				
1992	5603	12.6	10.6	570 (10.8)
1993	5325	11.7	9.3	505 (9.6)
1994	5405	12.8	10.4	534 (10.2)
1995	5556	13.4	11.1	570 (10.8)
1996	5385	13.6	11.0	579 (11.0)
1997	5687	17.0	14.5	764 (14.5)
1998	5542	19.1	15.9	826 (15.7)
1999	5742	20.2	17.4	908 (17.3)
Geographic areas				
San Francisco	3395	11.9	6.0	311 (5.9)
Connecticut	6676	15.0	14.9	826 (15.7)
Detroit	7074	17.8	18.9	998 (19.0)
Hawaii	1115	17.0	2.8	80 (1.5)
Iowa	6322	13.0	12.3	619 (11.8)
New Mexico	1821	13.4	3.7	161 (3.1)
Seattle	4714	14.7	10.4	410 (7.8)
Utah	2087	16.0	5.0	302 (5.8)
Atlanta	2653	17.8	7.1	438 (8.3)
San Jose	2080	15.6	4.9	278 (5.3)
Los Angeles	6308	14.9	14.1	833 (15.9)
Total	44,245	6680 (15.1)	6680 (100.0)	5256 (100.0)

TABLE 2

Percentage of Medicare Claims for Chemotherapy among Women Diagnosed with Breast Carcinoma between 1992 and 1999 with Their Medicare Claims through the Year 2001

Modes of chemotherapy administration	Column percentage of total claims for chemotherapy by mode of administration									
	1992	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**
Subcutaneous, intramuscular, or intralesional injection	5.7	8.4	7.2	7.8	8.9	2.1	2.2	2.1	1.3	0.9
Intravenous injection-push technique	39.1	42.1	40.8	35.4	33.0	34.8	32.6	25.1	19.8	15.2
Intravenous-infusion technique lasting; up to 1 h	35.3	31.6	32.8	31.8	33.4	37.1	39.1	44.5	48.2	53.0
Intravenous-infusion technique lasting; 1-8 hrs	12.1	9.3	11.0	12.5	12.5	14.2	15.9	20.2	22.6	20.9
Intravenous-infusion technique lasting longer, than 8 hrs and requiring a pump	6.0	6.4	6.6	9.2	7.4	7.1	6.3	5.4	5.1	4.8
Other modes[a]	0.3	0.8	0.1	0.0	0.1	0.1	0.3	0.1	0	0.1
Unspecified	1.5	1.3	1.4	3.3	4.7	4.6	3.6	2.6	3.0	5.1
Total claims for chemotherapy	8984 (100.0)	11.317 (100.0)	12.842 (100.0)	14.885 (100.0)	17.014 (100.0)	18.278 (100.0)	21.444 (100.0)	24.086 (100.0)	16.795 (100.0)	11.016 (100.0)

[a]Other modes included intraarterial (push technique); administration into pleural cavity, peritoneal cavity or intrathecal; and subarachnoid or intraventricular via subcutaneous reservoir, as defined in Patients and Methods.

TABLE 3

Variations in Modes of Chemotherapy Administration for Breast Carcinoma based on Age, Race, Tumor Stage, Year of Diagnosis, and Geographic Area

	% of patients, by hierarchical order of modes of chemotherapy administration (low to high)					
	Subcutaneous, intramuscular, or intralesional	Intravenous-push technique	Intravenous-infusion lasting < 1 hr	Intravenous-infusion lasting 1-8 hr	Intravenous-infusion lasting longer than 8 hr and requiring a pump	Total no. of cases (%)
Age						
65-69	0.5	11.0	33.4	38.8	16.2	2663 (100.0)
70-74	0.5	12.6	33.9	38.3	14.7	1480 (100.0)
75-79	0.5	13.6	32.5	41.1	12.3	799 (100.0)
80-84	1.2	11.1	32.5	39.3	12.7	252 (100.0)
85	3.2	12.9	27.4	40.3	16.1	62 (100.0)
Race/ethnicity						
White	0.6	12.0	33.8	39.3	14.4	4618 (100.0)
African	0.9	8.9	29.2	36.5	24.5	449 (100.0)
Americans						
Other ethnicities	0	17.6	35.2	39.8	7.4	176 (100.0)
Unknown	0	0	38.5	53.9	7.7	13 (100.0)
Tumor stage						
Stage I	1.2	16.8	39.2	33.4	9.3	677 (100.0)
Stage II	0.4	12.8	35.2	37.8	13.8	2888 (100.0)
Stage III	0.7	8.2	27.9	43.1	20.2	878 (100.0)
Stage IV	0.5	8.3	26.8	44.8	19.7	594 (100.0)
Un-staged	0.9	9.6	32.9	42.5	14.2	219 (100.0)
Comorbidity score						
0	0.6	11.8	33.8	40.2	13.6	3532 (100.0)
1	0.5	11.7	33.4	37.2	17.2	1132 (100.0)
2	0.3	12.7	28.9	38.9	19.2	401 (100.0)
3	1.6	13.1	36.7	30.4	18.3	191 (100.0)
Year of diagnosis						
1992	0.4	20.7	35.6	26.4	16.8	570 (100.0)
1993	0.6	20.6	36.0	25.4	17.4	505 (100.0)
1994	1.1	13.3	31.8	36.3	17.4	534 (100.0)
1995	0.9	11.4	31.9	38.6	17.2	570 (100.0)
1996	1.6	8.8	33.8	40.6	15.2	579 (100.0)
1997	0.4	10.1	32.9	40.7	16.0	764 (100.0)
1998	0.1	10.1	34.3	44.6	11.0	826 (100.0)
1999	0.1	6.2	32.2	49.3	12.2	908 (100.0)
Geographic areas						
San Francisco	0.3	10.6	32.2	48.2	8.7	311 (100.0)
Connecticut	0.7	15.3	29.3	49.5	5.2	826 (100.0)
Detroit	0.2	13.1	25.6	34.1	27.0	998 (100.0)
Hawaii	0	10.0	37.5	48.8	3.8	80 (100.0)
Iowa	0.2	6.8	49.0	32.6	11.5	619 (100.0)
New Mexico	0	5.0	42.9	41.0	11.2	161 (100.0)
Seattle	0.7	21.5	24.4	31.2	22.2	410 (100.0)
Utah	0	10.6	66.6	19.2	3.6	302 (100.0)
Atlanta	0	2.3	34.0	45.0	18.7	438 (100.0)
San Jose	0.7	22.3	22.3	46.8	7.9	278 (100.0)
Los Angeles	1.8	10.2	29.7	40.3	18.0	833 (100.0)
Total	0.6	11.9	33.5	39.1	15.0	5256 (100.0)

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TABLE 4

Modes of Chemotherapy Administration in Association with Hospitalizations for Chemotherapy Related Toxicity in Women with Breast Carcinoma who Received Chemotherapy

Discharge diagnosis for cases hospitalized (ICD-9-CM code) (no. of cases)	Hospitalization rate (%) for toxicity condition, by hierarchical order of modes of chemotherapy administration (low to high)					
	Subcutaneous, intramuscular, or intralesional	Intravenous-push technique	Intravenous-infusion lasting <1 hr	Intravenous-infusion lasting, 1-8 hrs	Intravenous-infusion lasting longer than 8 hr and requiring a pump	*P* value for trend
Anthracyclines (doxorubicin or mitoxantrone; [*n* = 2365])						
No. of cases	*n* = 3	*n* = 98	*n* = 863	*n* = 1110	*n* = 291	
Neutropenia	0	6.1	10.5	11.7	9.6	0.436
Thrombocytopenia	0	0	0.6	0.8	1.0	0.243
Fever	0	2.0	3.4	2.7	5.2	0.276
Unspecified adverse effects	0	2.2	2.4	2.5	3.8	0.272
Any of above 4 conditions	0	7.1	12.5	13.2	13.1	0.238
Infection	0	5.1	8.1	8.3	10.3	0.142
Dehydration	0	8.2	3.8	5.7	7.6	0.078
Anemia	0	8.2	9.4	11.2	10.3	0.244
Delirium	33.3	7.1	6.1	4.7	8.9	0.845
Heart failure	0	0	0.5	0.5	1.0	
Any of above 9 conditions	33.3	23.5	22.0	23.6	27.5	0.124
5-FU (*n* = 3581)						
No. of cases	*n* = 1	*n* = 717	*n* = 1513	*n* = 1055	*n* = 295	
Neutropenia	0	4.7	7.5	8.3	8.5	0.008
Thrombocytopenia	0	0.8	0.5	1.0	0.7	0.607
Fever	0	1.1	2.5	2.8	5.4	0.002
Unspecified adverse effect	0	1.4	2.9	2.1	1.7	0.892
Any of above 4 conditions	0	6.1	10.1	10.1	11.9	0.003
Infection	100.0	4.0	7.3	7.7	13.2	<0.001
Dehydration	0	3.8	4.6	4.7	9.5	<0.002
Anemia	0	8.5	9.9	10.7	12.9	0.029
Delirium	0	2.8	5.1	5.0	9.2	0.003
Heart failure	0	0.4	1.1	0.5	0.7	0.870
Any of above 9 conditions	100.0	15.6	21.0	21.9	30.9	0.001
Taxanes (paclitaxel or docetaxel; *n* = 493)						
No. of cases	*n* = 1	*n* = 4	*n* = 52	*n* = 391	*n* = 45	
Neutropenia	0	0	13.4	11.5	17.8	0.376
Thrombocytopenia	0	0	1.9	1.0	2.2	0.856
Fever	0	0	0	1.8	4.4	0.115
Unspecified adverse effect	0	0	3.9	2.3	4.4	0.788
Any of above 4 conditions	0	0	13.5	13.0	24.4	0.088
Infection	0	25.0	11.5	6.4	13.3	0.835
Dehydration	0	0	13.5	6.4	11.1	0.823
Anemia	0	0	11.5	12.5	15.6	0.372
Delirium	0	0	5.8	4.4	6.7	0.718
Heart failure	0	0	0	0.3	0	0.941
Any of above 9 conditions	0	25.0	26.9	24.3	31.1	0.597

ICD-9-CM: International Classification of Diseases-Clinical Modifications, 9th revision: 5-FU: 5-fluorouracil.

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TABLE 5

Risk of Hospitalization for Chemotherapy Related Toxicity in Association with Different Modes of Chemotherapy Administration Controlling for Comorbidity and Geographic Areas

Hierarchical order of modes of chemotherapy administration (low to high)	OR (95% CI) of being hospitalized[a]					
	For any of the 4 conditions[a]			For any of the 9 conditions[a]		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
For patients receiving anthracyclines (doxorubicin or mitoxantrone; [*n* = 2365])						
Subcutaneous, intramuscular, or intralesional injection, or intravenous-push technique	0.50 (0.21-1.15)	0.40 (0.20-1.09)	0.51 (0.21-1.20)	0.82 (0.49-1.39)	0.74 (0.43-1.28)	0.79 (0.45-1.36)
Intravenous-infusion lasting less than 1 hr	0.95 (0.64-1.42)	1.02 (0.68-1.53)	1.01 (0.67-1.53)	0.75 (0.55-1.01)	0.80 (0.58-1.09)	0.80 (0.58-1.11)
Intravenous-infusion lasting 1-8 hrs	1.01 (0.69-1.48)	1.08 (0.73-1.59)	1.10 (0.74-1.65)	0.82 (0.61-1.09)	0.87 (0.64-1.17)	0.88 (0.65-1.20)
Intravenous-infusion lasting longer than 8 hrs and requiring a pump	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
For all cases receiving 5-FU (*n* = 3581)						
Subcutaneous, intramuscular, or intralesional injection, or intravenous-push technique	0.49 (0.30-0.77)	0.62 (0.38-0.99)	0.66 (0.41-1.08)	0.42 (0.31-0.58)	0.54 (0.38-0.75)	0.60 (0.42-0.84)
Intravenous-infusion lasting less than 1 h	0.83 (0.56-1.23)	0.99 (0.67-1.49)	0.94 (0.62-1.41)	0.60 (0.45-0.79)	0.71 (0.53-0.95)	0.71 (0.53-0.96)
Intravenous-infusion lasting 1-8 hrs	0.83 (0.55-1.24)	0.95 (0.62-1.43)	0.96 (0.63-1.47)	0.63 (0.47-0.84)	0.72 (0.53-0.97)	0.76 (0.56-1.03)
Intravenous-infusion lasting longer than 8 hrs and requiring a pump	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
For all cases receiving taxanes (paclitaxel or docetaxel, [*n* = 493])						
Subcutaneous, intramuscular, or intralesional injection, or intravenous-push technique	0	0	0	0.55 (0.06-5.41)	0.55 (0.05-6.14)	0.71 (0.06-7.94)
Intravenous-infusion lasting up to 1 hr	0.48 (0.17-1.37)	0.49 (0.16-1.51)	0.56 (0.16-1.82)	0.82 (0.34-1.39)	0.88 (0.33-2.31)	0.93 (0.34-2.55)
Intravenous-infusion lasting 1-8 hrs	0.46 (0.22-0.97)	0.44 (0.20-1.01)	0.47 (0.20-1.10)	0.71 (0.36-1.39)	0.67 (0.32-1.40)	0.65 (0.30-1.41)
Intravenous-infusion lasting longer than 8 hrs and requiring a pump	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)

OR: odds ratio: 95%: CI: 95%: confidence interval; Model 1: without adjusting for other factors: Model 2: adjusted for patient age, ethnicity, tumor stage, comorbidity, and year of diagnosis: Model 3: adjusted for 11 geographic areas, in addition to the factors in Model 2; 5-FU: 5-fluorouracil.

[a] Odds ratio of being hospitalized for toxicities was generated based on logistic regression (see the Materials and Methods section for the 4 and 9 conditions).