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Prevalence and safety of off-label use of chemotherapeutic agents in older breast cancer patients: estimates from SEER-Medicare data

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Abstract

Background—The practice of prescribing oncology drugs outside of the label indication is legal and may reflect standard practice. However, some off-label use is against practice guidelines and may be inappropriate. We aimed to measure the prevalence and safety of off-label use in accordance with NCCN guidelines and off-label use inconsistent with guidelines in older breast cancer patients.

Patients and Methods—The SEER-Medicare dataset was used to identify women diagnosed with a first primary breast cancer between 2000-2007. Intravenous chemotherapy agents were identified using Medicare claims and classified as on-label, off-label/NCCN supported or off-label/unsupported using contemporary FDA approvals and NCCN guidelines. Off-label/unsupported regimens were matched to off-label/supported and on-label regimens using 1:1:1 matching on patient factors, and hospitalization/ER admission rates were compared across indication categories using conditional logistic regression.

Results—13,347 women were treated with 16,127 regimens (12% of women switched to a new regimen during followup). Sixty-four percent (10,391) of regimens were off-label/supported, 25% (3,987) were on-label and 11% (1,749) were off-label/unsupported. Drugs never supported for breast cancer accounted for 19% of off-label/unsupported use and 1% of total use. Hospitalization/ER admission occurred in 32% of off-label/unsupported regimens, compared to 27% of off-label/supported and 25% of on-label regimens ($p<.0001$).

Conclusions—Off-label use of chemotherapy without scientific support was not common in this cohort. Off-label/supported use accounted for 64% of use, reflecting the fact that widely-accepted indications are often not tested in registration trials. Off-label/supported use will likely increase as more drugs are expected to have activity across cancer sites, and understanding the safety implications of such use is critical.

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Introduction

When a new drug is developed, the manufacturer must apply for approval from the Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) before it can enter the market. The FDA grants approval for a specific setting (indication), including patient population, dosage, route of administration and other criteria, based on efficacy and safety data. Following approval, physicians may prescribe the drug for unapproved indications ('off-label use'), and doing so may in fact be standard medical practice, especially in the oncology setting. [1,2]

A 2006 report describing prescribing patterns of 160 commonly used drugs found an estimated 150 million off-label mentions (21% of overall use) and that 73% of off-label prescriptions had little or no scientific support.[1] Despite concerns about patient safety and costs to the health care system, little is known about the frequency of off-label use in oncology. A study conducted in 1991 by the United States General Accounting Office (GAO) based on a survey of 681 oncologists revealed that 33% of all anticancer drug administrations were off-label and 56% of patients received at least one off-label drug.[3] Twenty-eight percent of patients received a drug that did not have scientific support. Estimates from a more recent report on over 2 million administrations of ten intravenous chemotherapies were similar; 30% of use was off-label.[4]

The option to use drugs off-label preserves the oncologists' autonomy to consider their patients' individual medical status, allows accumulation of real world efficacy and safety data, and makes novel drugs available in a timely manner and for cancer types with limited viable treatment options. However, off-label use can have negative consequences if the risk-benefit profile of the drug is not well established in the off-label setting, possibly resulting in increased toxicities.[2] This problem may be exacerbated in older adults given the under-representation of this population in cancer registration trials, leading to lack of available data to guide treatment decisions.[5] Furthermore, financial incentives for doctors to prescribe new and costly medications encourage the use of treatments that extrapolate the label indication.[6,7] In the current economic environment where the need to control healthcare costs is universally recognized, utilization of off-label drugs without proven efficacy or comprehensive safety evaluation may be a target for cutting costs.

The National Comprehensive Cancer Network (NCCN) is an alliance of twenty-six cancer centers in the United States whose mission is "to advance the quality, effectiveness, and efficiency of oncology care so that patients can live better lives."[8] The organization publishes clinical practice guidelines that serve as established measures for appropriate disease management in the oncology community. The guidelines also influence the Centers for Medicare and Medicaid Services (CMS) reimbursement of chemotherapy treatments; since 1993 Medicare has been required to cover off-label uses mentioned in accepted drug compendia (among which NCCN guidelines are central) or with scientific support in certain peer-reviewed journals.[9] Even in the absence of FDA labeling, treatment in accordance with NCCN guidelines is widely regarded as 'appropriate', thus it is important to differentiate between NCCN supported and unsupported off-label use. In their 2013 report, Conti et al, found that about half of the off-label use identified was NCCN-supported.[4]

In this study, we set out to estimate the prevalence of off-label use of chemotherapies and to determine whether off-label use is associated with increased rates of hospitalization and emergency room (ER) admission, in a cohort of elderly Medicare beneficiaries diagnosed with breast cancer. To focus on use that could be considered 'inappropriate,' we differentiate between off-label utilization in agreement with NCCN guidelines, versus off-label use without scientific support.

Methods

Data Source and Cohort Definition

The SEER-Medicare linked database (including cancer diagnoses through 2007 and Medicare claims through 2008) was utilized.[10] Female Medicare beneficiaries 65 and older residing in geographic areas contained in the SEER registries and diagnosed with a first primary invasive breast cancer between 2000-2007 were identified. Patients were excluded for any of the following: diagnosis made at time of death, missing month of diagnosis, prior cancer diagnosis, enrollment in an HMO, lack of continuous Part B Medicare enrollment in the first 6 months following diagnosis. To restrict our analysis to patients whose treatment followed standard guidelines, we excluded patients with stage I-III disease who did not undergo surgical resection within 4 months of diagnosis (or within 4 months of completion of neoadjuvant therapy), as well as patients diagnosed with stage IV disease who underwent surgery.

FDA Approval and NCCN Guideline Recommendation

Drugs approved for breast cancer were identified and available labels were compiled.[11,12] Approval dates and breast cancer indications (adjuvant and/or metastatic; if metastatic, first line and/or after failure of another agent) were recorded for each label version. The same information was compiled from all versions of the NCCN Guidelines for Breast Cancer for the years 2000-2008.[13] Drugs approved and/or NCCN supported in the adjuvant setting were also considered to be approved (supported) in the neoadjuvant setting, as separate approvals (support) specifically for the neoadjuvant setting were not standard in this era. FDA approval and NCCN guideline information is displayed in Figure 1.

Characterization of Chemotherapy Use

Medicare claims associated with intravenous chemotherapy administration following breast cancer diagnosis and prior to diagnosis with a second cancer were identified. The specific agent was identified using the HCPCS J-code (Appendix 1). Patients were considered to have received chemotherapy if at least one chemotherapy claim was identified within 4 months of surgery (stage I-III) or diagnosis (stage IV).

The Medicare claims data contains information on each agent administered (including the date of administration) but does not indicate whether the agent is part of a combination regimen or whether it is being used in the neoadjuvant, adjuvant, first line or later line setting, thus we developed an algorithm to separate claims into regimen-lines, which we defined as a period of time during which a patient was being treated with a specific single-agent or combination regimen. Each patient's first regimen line started on the first day

chemotherapy was administered. Any additional agents given in the next 15 days were considered to be part of a combination regimen. After 15 days, if a new agent was given, this was considered to indicate the start of the subsequent regimen line, except in the case of established sequential regimens (Appendix 2); in these cases a new agent was counted as part of the same regimen line since the regimen is designed to contain multiple phases.[14] (For example, if a patient received doxorubicin/cyclophosphamide followed by docetaxel, this would count as a single regimen line). The same algorithm was used to define each subsequent regimen line of intravenous chemotherapy. Examples demonstrating the algorithm are shown in Figure 2. In the metastatic setting, each change in regimen represents a higher line of treatment; in the adjuvant setting, the first treatment given after surgery is referred to as initial adjuvant and treatment following a deviation from initial adjuvant regimen is referred to as altered adjuvant. All agents administered preoperatively were considered to be part of a single neoadjuvant regimen line. For stages I-III, in order to limit our analysis to treatment for the primary tumor and to avoid capturing treatment after disease recurrence, the end of adjuvant therapy was identified when Medicare claims did not indicate chemotherapy administration for at least 120 days. We assumed that treatment breaks of up to 120 days could be due to toxicity or other delays, but that a longer break would indicate the completion of initial chemotherapy, and that additional treatment after such a break may be for metastatic or recurrent disease.

Each regimen line was classified into one of the following indication categories based on the stage and line of chemotherapy:

- **On-label:** All chemotherapies included in the regimen line were consistent with the FDA label indication.
- **Off-label/NCCN supported:** All chemotherapies included in the regimen line were supported by NCCN guidelines, and at least one chemotherapy included in the regimen line was not consistent with the FDA label indication.
- **Off-label/Unsupported:** At least one chemotherapy included in the regimen line was not consistent with the FDA label indication and was not supported by NCCN guidelines

Indication category determinations were made based on the versions of FDA labels and NCCN guidelines in use 90 days following the date of administration, allowing for uses of a drug shortly prior to approval/support to be counted as approved/supported. For off-label/unsupported drug administrations, the reason the drug was not supported was classified as either: 1) drug was never NCCN-supported for breast cancer, 2) use was more than 90 days prior to NCCN support, or 3) drug was used in a stage or line outside of NCCN recommendations. To be conservative, J-Code J9999 (“Not otherwise classified antineoplastic drugs”) was considered on-label.

Comparison of hospitalization and ER admission rates

Each off-label/unsupported regimen line was matched with one off-label/supported regimen line and one on-label regimen line. Matching factors were age, line of chemotherapy,

number of prior comorbidities, stage at diagnosis, and history of prior hospitalizations/ER admissions, categorized as in Supplemental Table 1.[15]

A hospitalization or ER admission was assigned to a regimen line if it occurred on or after day 16 of a regimen line (when all agents comprising a combination regimen would have been started) and before the start of a new regimen line (before date of surgery for neoadjuvant lines), or within 30 days of the last chemotherapy administration if no subsequent lines were initiated. Using the matched regimen lines, rates of hospitalization and/or ER admission and corresponding Wald 95% confidence intervals (CI) were compared between indication categories, overall and by stage. Wald type III p-values were obtained using conditional logistic regression. Analyses investigating the distribution of indication category by stage and line of chemotherapy were descriptive and tests were not conducted. All statistical analysis was performed in SAS 9.4 (SAS Institute, Cary, NC).

Results

Figures 1A and 1B list drugs FDA approved and/or NCCN supported for the treatment of breast cancer between 2000-2008, and their stage-specific and line-specific indications. It can be noted that more drugs are approved for advanced stage than early stage, and in the advanced stage setting, some drugs are only approved in line 2 or later.

Study Cohort

The initial cohort consisted of 78,824 women. Seventeen percent (n=13,347) received chemotherapy (5%, 33%, 50% and 21% for stages I-IV, respectively) and are included in the analyses. The breakdown by demographic and clinical factors is presented in Supplemental Table 1.

Prevalence of off-label use

Use by indication category is presented in Table 1. Overall, only 25% of all regimen lines consisted exclusively of on-label drugs. Most regimen lines (64%) were off-label/NCCN supported. Eleven percent of all regimens were off-label/unsupported, with higher rates of such use in patients with stage III (16%) or IV (12%) disease.

Initial adjuvant regimens were rarely off-label/unsupported (7%). However, following a change in adjuvant regimen, prevalence of inappropriate use increases dramatically to 34%. The use of off-label/unsupported regimens in the neoadjuvant setting was 15%. Regimens used in advanced disease were more likely to be off-label/unsupported if used in the first line of chemotherapy (rate of off-label/unsupported use: 17% vs 6% in second line or higher), likely the reflection of the fact that a large number of agents are approved and/or NCCN supported for use as second line therapy, but not as first line (Figure 1B). Rates of off-label/unsupported and off-label/supported use by age and comorbidity index are shown in Table 1.

For those chemotherapy drugs that were part of at least 24 regimen lines, Figure 3 presents the proportion of off-label/unsupported use, as a function of the total use. Six of the most commonly used agents (cyclophosphamide, doxorubicin, 5-FU, methotrexate, paclitaxel, epirubicin), accounting for 81% of the total drug use, were FDA approved and/or NCCN

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