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Cost-Effectiveness of Chemotherapy for Breast Cancer and Age Effect in Older Women

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ABSTRACT

Background: Previous economic evaluations compared specific chemotherapy agents using input parameters from clinical trials and resource utilization costs. Cost-effectiveness of treatment groups (drug classes) using community-level effectiveness and cost data, however, has not been assessed for elderly patients with breast cancer. **Objective:** To assess the cost-effectiveness of chemotherapy regimens by age and disease stage under "real-world" conditions for patients with breast cancer. **Methods:** The Surveillance Epidemiology and End Results-Medicare data were used to identify patients with breast cancer with American Joint Committee on Cancer stage I/II/IIIa, hormone receptor–negative (estrogen receptor–negative and progesterone receptor–negative) patients from 1992 to 2009. Patients were categorized into three adjuvant treatment groups: 1) no chemotherapy, 2) anthracycline, and 3) non–anthracycline-based chemotherapy. Median life-years and quality-adjusted life-years (QALYs) were measured using Kaplan-Meier analysis and were evaluated against average total health care costs (2013 US dollars). **Results:** A total of 4575 patients (propensity score–matched) were included for the primary analysis. The anthracycline group experienced 12.05 QALYs and mean total health care costs of $119,055, resulting in an incremental cost-effectiveness ratio of $7,688 per QALY gained as compared with the no chemotherapy group (QALYs 7.81; average health care cost $86,383). The non–anthracycline-based group was dominated by the anthracycline group with lower QALYs (9.56) and higher health care costs ($122,791). Base-case results were found to be consistent with the best-case and worst-case scenarios for utility assignments. Incremental cost-effectiveness ratios varied by age group (range $3,790–$90,405 per QALY gained). **Conclusions:** Anthracycline-based chemotherapy was found cost-effective for elderly patients with early stage (stage I, II, IIIa) breast cancer considering the US threshold of $100,000 per QALY. Further research may be needed to characterize differential effects across age groups.

Keywords: breast cancer, chemotherapy, cost-effectiveness, cost-utility.

Introduction

Analysts have called for economic evaluation of alternative treatment strategies for specific types of patients with breast cancer [1,2]. Previous research has examined the cost of treating breast cancer in the United States and the cost-effectiveness of alternative treatments, primarily associated with alternative drug regimens [3–5]. Economic evaluations of breast cancer treatment are often based on hypothetical cohorts and/or modeling of disease progression [4–9], in which health outcomes and costs are based on literature-derived parameters [4–9]. Age has rarely been examined as a factor in the assessment of cost-effectiveness of chemotherapy for patients with breast cancer [5]. Surveillance Epidemiology, End Results (SEER)-Medicare data have been used to estimate the cost of colorectal cancer treatment [10,11] but not to examine the cost-effectiveness of chemotherapy stratified by age group and stage of breast cancer. The present study advances the field by using a large, multiyear cohort to assess the cost-effectiveness of chemotherapy regimens by age and disease stage under "real-world" conditions for patients with breast cancer.

It is important to know whether the survival benefit associated with the administration of adjuvant chemotherapy in randomized clinical trials remains evident in community-based practices for elderly patients with breast cancer. Limited evidence exists (from clinical trials) for the benefit of chemotherapy in women 70 years or older with node-positive tumors or node-negative tumors of more than 1 cm [12–14]. The latest review [14] stated, "In subgroup analyses for trials of standard or near-standard cyclophosphamide, methotrexate, and fluorouracil

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versus no chemotherapy the proportional risk reduction appeared inversely related to age and nodal status, but again appeared independent of ER status." Their Web Appendix (Table P14) showed that the relative risk for mortality was 0.59 for women younger than 45 years, 0.66 for women aged 45 to 54 years, and 0.87 for women aged 55 to 69 years. In their study, the overall effect of chemotherapy in those 65 years or older combined was significant at 0.76 for mortality reduction. A significant age-chemotherapy interaction was clear.

Muss [15] and Muss et al. [16,17] reported on the efficacy of chemotherapy in older patients. In these studies, all patients were combined as 65 years or older versus younger than 65 years. Although the authors concluded that there was no association between age and disease-free survival, it was not clear that the efficacy of chemotherapy was the same in those aged 70 to 74 or 75 to 79 years as in those aged 65 to 69 years. A recent observational study found, however, that for women 80 years or older, adjuvant chemotherapy was not effective except in a few patients who received adriamycin-cyclophosphamide; the mortality risk was significantly reduced for those aged 80 to 84 years [18].

One explanation for no statistically significant chemotherapy-associated survival benefit for women with breast cancer aged 70 years or older is the small number of elderly patients enrolled in clinical trials. These results, however, are not consistent with findings for chemotherapy-associated survival benefits for older patients with ovarian, lung, and colon cancer where the number of elderly patients in clinical trials is also small [19–21]. The large number of cases in this study enables us to determine whether chemotherapy benefits patients in this population.

This study compare life-years saved and quality-adjusted life-years (QALYs) saved for three alternative treatment regimens (no chemotherapy, anthracycline [doxorubicin or epirubicin]-based chemotherapy, and non–anthracycline-based chemotherapy). With quality-of-life adjustments assigned for cancer stage, recurrence, and debilitating adverse effects, the study considers both the positive and negative outcomes of chemotherapy and contrasts these outcomes with total health care cost. SEER-Medicare data are valuable for studying cancer outcomes because chemotherapy drugs are among the few drugs that are covered by the Medicare program over the past two decades, thus allowing chemotherapy-specific cost-effectiveness analyses. The results of economic evaluations have important clinical implications for physicians treating patients with cancer, for developing clinical practice guidelines, and for identifying critical target areas to be tested in future clinical trials. The potential impact of the present study is significant for treating patients with breast cancer 65 years or older in at least 16 of the regions in the United States captured in SEER and potentially generalizable to other areas.

Methods

Data Source, Population, and Chemotherapy Regimens

The SEER-Medicare–linked data provide information on patient and tumor characteristics and resource utilization information in 65 years or older patients with cancer. Accuracy and validity of these data have previously been established [22]. Women 65 to 94 years old diagnosed with breast cancer as the first primary tumor without other primary tumors from January 1992 to December 2009 were included. Women were excluded if the diagnosis was based on autopsy, death certificate, or if they died within 90 days of diagnosis. Enrollment in both Medicare parts A and B without any health maintenance organization enrollment from the time of diagnosis to death or the end of the study (December 31, 2010) was required. A total of 14,610 women diagnosed with American Joint Committee on Cancer stage I, II, or III A who had undergone either breast-conserving surgery or mastectomy for estrogen receptor and progesterone receptor–negative tumors from 16 SEER areas were included.

Propensity score matching was conducted to reduce selection bias, which is inherent to observation studies. A propensity score of receiving chemotherapy for each treatment group was calculated using multinomial logistic regression [23]. We also applied the inverse probability of treatment weighting (IPTW) method that uses the inverse of probabilities estimated from multinomial logistic regression as a weight to obtain the population estimate; however, a major limitation of this approach is high sensitivity to these weights and hence the probabilities need to be estimated very well [24–26]. The probabilities are as good as the covariates used to estimate them, and the covariates available using large administrative databases such as SEER-Medicare data are limited. Thus, the propensity score matching approach was selected as the primary analysis and IPTW as the secondary analysis. Although precision may be improved by selecting variables on the basis of their association with outcomes irrespective of the exposure [27], variable selection was based on regression covariates that have been found to be associated with chemotherapy selection [28–30], and were available in our data (i.e., age, race, marital status, tumor stage, tumor size, node positive/negative, tumor grade, type of surgery, radiation, comorbidity score, socioeconomic status, region, and year of diagnosis). A 1:1:1 propensity score matching was performed using the nearest-neighbor method [31]. The algorithm matches two treatment groups simultaneously with the referent group (no chemotherapy). All matched pairs of patients were within the prespecified caliper distance of 0.05. Chi-square test and standardized difference were used to assess the balance of covariates between the treatment groups [32–34]. An effect size of less than 0.1 indicated negligible difference between comparison groups [33]. A lifetime time horizon with maximum follow-up until December 2010 was applied.

Patients were placed into three treatment groups—no chemotherapy, anthracycline-based chemotherapy, and non–anthracycline-based chemotherapy—on the basis of Medicare claim codes identified within 12 months following diagnosis. Anthracycline-based chemotherapy was defined using Healthcare Common Procedure Coding System codes for doxorubicin (J9000, J9001, J9010) and epirubicin (J9178). Non–anthracycline-based chemotherapy was defined using chemotherapy-associated codes except for epirubicin and doxorubicin (Healthcare Common Procedure Coding System codes 96400-96549, J9002-J9009, J9011-J9177, J9179-J9999, and Q0083-Q0085; *International Classification of Diseases, Ninth Revision, Clinical Modification* codes V58.1, V66.2, and V67.2; *International Classification of Diseases, Ninth Revision, Clinical Modification* procedure code 9925) [35–37].

Effectiveness and Cancer Phases

Life-years and QALYs gained were the treatment outcomes. *Patient survival times* were defined as days from diagnosis to death or end of study and were categorized into three phases: initial, continuing, and terminal [38]. Health state utilities were obtained from the literature for assignment to the specific disease phase, for adjuvant chemotherapy receipt (with or without major adverse event), and for time since diagnosis and disease recurrence (Table 1) [39,40]. Health state utilities for the initial phase were based on the receipt of any chemotherapy and the severity of chemotherapy-related adverse events. Adverse events were evaluated as "moderate" or "severe" if they were reported in outpatient and inpatient claims, respectively [41]. Appendix Table 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.08.008 presents a detailed list of