Survival and Toxicity After Cisplatin Plus Etoposide Versus Carboplatin Plus Etoposide for Extensive-Stage Small-Cell Lung Cancer in Elderly Patients

Laura A. Hatfield, PhD, Haiden A. Huskamp, PhD, and Elizabeth B. Lamont, MD, MS

Harvard Medical School, Boston, MA

Corresponding author: Laura A. Hatfield, PhD, Department of Health Care Policy, Harvard Medical School, 180A Longwood Ave, Boston, MA, 02115; e-mail: hatfield@hcp.med.harvard.edu.

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QUESTION ASKED: How do survival and health care utilization differ for older patients with advanced small-cell lung cancer after treatment with two distinct first-line chemotherapy regimens: cisplatin/etoposide versus carboplatin/etoposide?

SUMMARY ANSWER: Survival after each regimen was nearly identical, but patients who received carboplatin/etoposide used less subsequent hospital-based health care than similar patients who received cisplatin/etoposide.

WHAT WE DID: We identified patients with a first cancer diagnosis of extensive-stage small-cell lung cancer from the SEER cancer registries, which include detailed tumor information. Then using linked Medicare claims, we identified additional clinical details, cancer treatments, post-treatment health care utilization, and survival. We limited our study to patients who received first-line cisplatin/etoposide or carboplatin/etoposide in the outpatient setting. Each patient who received cisplatin/etoposide was matched to two patients who received carboplatin/etoposide using propensity scores that balanced demographic factors such as age, sex, and SEER region and clinical factors such as cancer characteristics, prior non-chemotherapy cancer treatments, prior health care utilization, and comorbidities. We compared post-treatment survival using non-inferiority tests and post-treatment health care utilization using conventional hypothesis tests.

WHAT WE FOUND: Survival after cisplatin/etoposide was 35.7 weeks and after carboplatin/etoposide was 35.9 weeks; statistical tests demonstrated that survival after carboplatin/etoposide was non-inferior to cisplatin/etoposide. After treatment, patients who received carboplatin/etoposide were less likely to be admitted to the hospital (80% v 86%), but not the ICU or ED. They also had fewer hospitalizations, ICU stays, and ED visits, but lengths of stay (for those who were hospitalized) were not different between the two treatment groups.

BIAS, CONFOUNDING FACTOR(S), REAL-LIFE IMPLICATIONS: Ideally, patients and physicians tailor treatments to individual clinical and personal characteristics. Treatment selection biases naïve comparisons between treatments when these characteristics also predict outcomes. For example, in our unmatched sample, patients who received cisplatin/etoposide were younger and healthier. Although our matching method nearly eliminated the observable differences between the two treatment groups, unobservable differences may remain. For example, patients who received cisplatin/etoposide may have preferred more aggressive treatment or had oncologists who preferred more aggressive treatment. Our sample restrictions, designed to make our comparisons more valid, limit the population to which we can generalize our conclusions. Our results apply only to Traditional Medicare enrollees with 2 years of continuous enrollment in Parts A and B diagnosed with extensive-stage small-cell lung cancer as a first cancer who receive first-line chemotherapy in the ambulatory setting. Despite clinical practice guidelines that continue to rank first cisplatin/etoposide as a preferred treatment, we find that for the age group studied, carboplatin/etoposide offers the same survival with less post-treatment utilization of hospital-based health care. **JOP**

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Harvard Medical School, Boston, MA

Abstract

Purpose

Elderly patients with cancer are under-represented in clinical trials and risk greater toxicity from chemotherapy. These patients and their physicians need better evidence to decide among guideline-recommended regimens. We test whether patients with extensive-stage small-cell lung cancer (ES SCLC) have noninferior survival and less hospital-based health care after carboplatin/etoposide compared with cisplatin/etoposide.

Methods

We analyzed SEER-Medicare data for beneficiaries with ES SCLC diagnosed at age 67 years and older between 1995 and 2009. Among patients treated with first-line chemotherapy in the ambulatory setting, 831 received cisplatin/etoposide and 2,846 received carboplatin/etoposide. Propensity score matching (2:1 ratio) yielded 778 cisplatin/etoposide and 1,502 carboplatin/etoposide patients.

Results

Survival was nearly identical in the two groups: 35.7 weeks for cisplatin/etoposide and 35.9 weeks for carboplatin/etoposide. The hazard ratio of 1 (95% CI, 0.91 to 1.09) excluded our prespecified threshold, indicating noninferiority. Mortality at 6 months was indistinguishable: 35% for cisplatin/etoposide and 34% for carboplatin/etoposide. After carboplatin/etoposide, patients were less likely to be admitted to a hospital (80% v 86%, $P < .001$) and had fewer hospitalizations (median 1 v 2, odds ratio 0.76, 95% CI, 0.65 to 0.9), ED visits (median 1 v 2, odds ratio 0.82, 95% CI, 0.7 to 0.96), and ICU stays (median 0 v 0, odds ratio 0.82, 95% CI, 0.69 to 0.99).

Conclusion

First-line carboplatin/etoposide is associated with similar survival and less subsequent hospital-based health care use than cisplatin/etoposide among elderly patients with ES SCLC treated in ambulatory settings.

ASSOCIATED CONTENT

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INTRODUCTION

Lung cancer kills more Americans than any other kind of cancer.¹ Although only 15% to 20% of diagnosed lung cancer tumors

have small-cell histology, most present as extensive-stage disease,² and most extensive-stage small-cell lung cancer (ES SCLC) is diagnosed at age 65 years and

older.² SCLC grows aggressively but responds well to chemotherapy.^{3,4} In one early randomized trial, 30% of ES SCLC patients randomly assigned to chemotherapy (oral cyclophosphamide) lived at least 6 months, compared with none of the patients randomly assigned to placebo.⁵ Subsequent studies demonstrated that combination chemotherapy extends survival more than single-agent chemotherapy.⁶⁻⁸ For nearly twenty years, guidelines⁹ have recommended two platinum-based combinations¹⁰: cisplatin/etoposide¹¹ and carboplatin/etoposide.¹² With these regimens, trial patients live a median of 9.5 months,¹³⁻¹⁵ and survival does not seem to differ between them. For patients with metastatic disease, the goal of treatment is palliative.^{16,17} One meta-analysis of 19 clinical trials identified higher tumor response rates (ie, rates of tumor shrinkage) after cisplatin/etoposide versus carboplatin/etoposide,⁷ leading some clinicians to prefer the former. However, tumor response is not a demonstrated predictor of subsequent survival in small-cell lung cancer, making it a dubious endpoint for comparing therapeutic efficacy.¹⁸ Moreover, the same meta-analysis showed that patients treated with cisplatin/etoposide experienced more clinically significant toxicity than those treated with carboplatin/etoposide. A more recent meta-analysis of four clinical trials found no differences in survival and small differences in toxicity between the two regimens.⁸ Despite trial evidence of equivalent survival and greater toxicity associated with cisplatin/etoposide, some oncologists still prefer it for fit patients of any age, and national treatment guidelines rank it above carboplatin/etoposide for patients with ES SCLC.¹⁹

Randomized controlled trial results strongly influence treatment guidelines, but trials typically enroll younger and healthier patients than the general patient population with the index cancer.²⁰ Older patients often have more comorbidities²¹ and experience more toxicity with standard chemotherapy regimens,²² but these patients and their physicians currently make treatment decisions on the basis of evidence from clinical trial populations. Our study addresses this gap by comparing the morbidity and mortality among elderly Medicare patients with ES SCLC after first-line treatment with cisplatin/etoposide versus carboplatin/etoposide in the ambulatory usual care setting. We hypothesize that survival after carboplatin/etoposide is not inferior and hospital-based health care use is lower compared with cisplatin/etoposide.

METHODS

Data Source

The National Cancer Institute sponsors the SEER-Medicare program, which links data from the United States SEER cancer registries to Medicare billing claims.²³ Researchers use these data to study patterns of cancer risk, treatment use, and outcomes in a demographically representative population of patients with cancer.^{24,25} Our study uses SEER 18 cancer registry data linked with Medicare claims from 1993 through 2010. This study was approved by Harvard University's Committee on the Use of Human Subjects (ESTR #22744).

Cohort Selection

We identified patients age 67 years and older who were diagnosed with ES SCLC between 1995 and 2009. We required 2 years of prediagnosis claims to compute several baseline variables and one year of postdiagnosis claims to measure our outcomes of interest. We used the SEER histology and historical staging variables to select patients with distant disease (ie, we excluded patients with only local or regional disease).²⁶ We required continuous enrollment in Medicare Parts A (inpatient services) and B (outpatient services) from 2 years before diagnosis through death or last claim. We excluded people who were ever enrolled in a Medicare Advantage Health Maintenance Organization (HMO) during the observation period, because claims were not available for these plans. We also excluded patients who were diagnosed with cancer at autopsy, had prior cancer diagnoses, or received experimental therapy, defined in SEER as "any experimental or newly developed treatment, such as a clinical trial, that differs greatly from proven types of cancer therapy."²⁶ We also required sufficient claims to ensure linkage, specifically at least one Medicare claim between 45 days before diagnosis and 195 days after diagnosis. [Figure 1](#) shows the sample size at each step in this selection process.

We used published methods to identify patients receiving outpatient chemotherapy within 6 months after ES SCLC diagnosis.²⁷ Details of the sample selection and chemotherapy identification are found in the Appendix text (online only) and [Tables A1](#) through [A4](#) (online only). The selected cohort included 2,846 patients who received first-line carboplatin/etoposide and 831 who received first-line cisplatin/etoposide. The appendix also compares the characteristics of patients who received one of the two regimens of interest to those that received other chemotherapy regimens, which are also described.

FIG 1. Cohort selection. Numbers in the cohort at each step of inclusion, exclusion, and matching. Carbo, carboplatin/etoposide; Cis, cisplatin/etoposide; ES SCLC, extensive-stage small-cell lung cancer; PS, propensity score; sufficient claims, at least one Medicare claim between 45 days before diagnosis and 195 days after diagnosis.

To minimize confounding due to treatment selection, we fit a propensity score model for receipt of carboplatin/etoposide versus cisplatin/etoposide. Demographic predictors were SEER site, race/ethnicity, marital status, and sex. Clinical variables were indicators of radiation therapy before chemotherapy, brain metastases in the 90 days before chemotherapy, and measures of overall health in the 2 years before diagnosis: any ICU stay, number of hospitalizations, number of functional aids, and Charlson comorbidity score.²⁸ To account for temporal changes in treatment over the study period, we also included year of diagnosis in the model. Using the fitted propensity scores, we attempted to match each cisplatin/etoposide patient to two carboplatin/etoposide patients using a greedy matching algorithm with a caliper of 0.1.²⁹ The matching procedure yielded 778 cisplatin/etoposide patients and 1,502 carboplatin/etoposide patients.

Variable Definitions

Our primary outcomes were overall survival and hospital-based health care use after treatment, the latter being a proxy for posttreatment morbidity.³⁰ We computed survival time from the first chemotherapy administration claim to date of death from the Medicare enrollment file. Follow-up was very complete, with only 68 patients (3%) censored for survival at the end of the study period. The MEDPAR file (inpatient claims) provided information about hospitalizations, ICU stays, and ED visits, which we measured from the first ambulatory claim for chemotherapy until death or censoring.

Analysis and Modeling

We compared the survival curves, hazards, and six-month mortality rates of the two regimens. Our null hypothesis was

that the hazard ratio (or risk ratio) for carboplatin/etoposide versus cisplatin/etoposide exceeded a prespecified non-inferiority threshold (ie, was inferior). We considered median survival differences of less than 4 weeks not clinically significant, which implies a hazard ratio noninferiority bound of 1.13. This is because the Kaplan-Meier estimate of median survival in the cisplatin/etoposide group is 35.7 weeks, and the survival times are approximately exponentially distributed. The exponential distribution median is $\ln(2) \times \text{scale}$, so the hazard ratio reduces to the ratio of the medians, $35.7/31.7 = 1.13$. We considered a 5 percentage point mortality increase at 6 months not clinically significant. Given 34% 6-month mortality in cisplatin/etoposide group, the risk ratio non-inferiority bound is 1.15. We compared the upper bounds of the hazard ratio and risk ratio confidence intervals to their respective noninferiority bounds. We also performed subgroup analyses of survival by age (< 75 and ≥ 75 years of age) as prior work has shown the importance of patient age for responses to treatment.³¹

We compared the proportions of patients in each treatment group who had any hospitalization, ED visit, and ICU stay using χ^2 tests. We fit proportional logistic regressions for the number of hospitalizations, ICU stays, and ED visits, coded as ordinal variables (0, 1, 2, and 3 or more). These models assume proportional odds across levels of the outcome, which we assessed via a score test and concluded it was not violated in any model. We fit Poisson regressions for the count of days spent in the hospital and ICU (for people with at least one hospitalization or ICU stay). These models included a scale parameter that allows the variance to exceed the mean and thus account for over-dispersion.

RESULTS

Appendix Table A1 summarizes the covariates in the two groups before matching. The cisplatin/etoposide group was younger, less likely to be widowed, and healthier (fewer hospitalizations before treatment, fewer functional aids, lower Charlson comorbidity scores, and more likely to receive radiation treatment). The distribution of patients among registry sites also differed widely, but differences over time were minimal. After matching, the groups were very similar on all the observed variables. Figure 2 shows the standardized mean differences between the treatment groups before and after matching. The matched treatment groups have no differences that exceed the 0.1 “rule of thumb”.³²

Overall Survival

Survival after carboplatin/etoposide was not worse than after cisplatin/etoposide. Median survival was 35.9 weeks in the carboplatin/etoposide group and 35.7 weeks in the cisplatin/etoposide group. Figure 3 shows the Kaplan-Meier survival

curves, which are indistinguishable. The Cox proportional hazards model estimate of the hazard ratio excluded the prespecified noninferiority threshold of 1.13, 1 (95% CI, 0.91 to 1.09) indicating carboplatin/etoposide is not worse than cisplatin/etoposide. Among patients younger than 75 ($n = 1,492$), the hazard ratio was 0.98 (95% CI, 0.88 to 1.1), indicating noninferior survival, but the smaller group of people 75 years and older ($n = 788$) had a hazard ratio of 1.03 (95% CI, 0.88 to 1.2). This estimate's upper bound crosses the a priori bound, indicating that we cannot reject the null hypothesis of inferiority.

The overall mortality rate ratio at 6 months was 0.97 (95% CI, 0.84 to 1.13), which excluded noninferiority bound of 1.15, as shown in Figure 4A. For patients younger than 75 years, the rate ratio of 0.91 (95% CI, 0.75 to 1.1) also excluded the noninferiority bound, but for older patients, the rate ratio of 1.02 (95% CI, 0.81 to 1.3), again included the noninferiority bound.

The two subgroups are smaller than the full sample and therefore yield wider confidence intervals; this partly explains

FIG 2. Pre- and post-matching differences between the treatment groups. Standardized mean differences between cisplatin/etoposide (cis) and carboplatin/etoposide (carbo) before (triangles) and after (circles) matching. Panel A displays demographic variables and Panel B displays clinical variables, where “prior” means in the 2 years before diagnosis. Arrow indicates the direction of change in the difference between the two groups from before matching to after matching. Brain mets, brain metastases; funct aids, functional aids; ICU, intensive care unit.

FIG 3. The Kaplan-Meier survival curves are plotted for each treatment group. This figure is truncated at 5 years, at which time only 17 patients remained at risk. Carbo, carboplatin-etoposide; Cis, cisplatin-etoposide.

the result that the subgroup intervals for older patients cross the noninferiority bound although the full sample interval does not.

Hospital-Based Utilization

Elderly Medicare patients treated with carboplatin/etoposide were less likely to be hospitalized than those treated with cisplatin/etoposide. Figure 4B shows the proportions of patients using hospital-based care. The vast majority of patients had at least one ED visit or hospitalization after chemotherapy. χ^2 tests indicated the proportion of patients with any hospitalization was significantly lower in the carboplatin/etoposide group (80% v 86%, $P < .001$), but not the proportion with any ICU stay (33% v 36%, $P = 0.08$) or ED visit (79% v 83%, $P = 0.06$).

The number of hospitalizations, ICU stays, and ED visits was lower in the carboplatin/etoposide group. Odds ratios less than 1 in Figure 4C indicate that the odds of additional visits (eg, the odds of 1 visit versus 0 or of 2 visits versus 1) are lower for patients in the carboplatin/etoposide versus cisplatin/etoposide group. The median number of hospitalizations is 1 in the carboplatin/etoposide group versus 2 in the cisplatin/etoposide group with an odds ratio of 0.76 (95% CI, 0.65 to 0.9). For ED visits, the medians are 1 in carboplatin/etoposide and 2 in cisplatin etoposide, yielding an odds ratio of 0.82

(95% CI, 0.7 to 0.96). The small median numbers of ICU visits are not apparently different (0 carboplatin/etoposide and 0 cisplatin/etoposide), but the odds ratio of 0.82 (95% CI, 0.69 to 0.99) is still significantly less than 1, indicating lower odds of additional ICU visits among patients in the carboplatin/etoposide group.

We did not find significant differences in the number of hospital days or ICU days. Figure 4D shows incident rate ratios from the Poisson regression. These quantify the incremental increase in the risk of an additional day of hospitalization for patients in the carboplatin/etoposide versus cisplatin/etoposide group. These regressions included only patients with any hospitalization or ICU visit, so the sample sizes were smaller, and the conclusions apply only to hospitalized patients. The incidence rate ratio for hospital days was 0.94 (95% CI, 0.86 to 1.02). The median was 11 hospital days for the carboplatin/etoposide group compared with 12 days in the cisplatin/etoposide group. The incidence rate ratio for ICU days of 1.09 (95% CI, 0.94 to 1.25) had a wider confidence interval that included 1, largely due to the small number of ICU stays.

DISCUSSION

In this study, we found that for Medicare patients with ES SCLC who received one of the two standard guideline-recommended first-line therapies, (1) treatment with carboplatin/etoposide was much more common than treatment with cisplatin/etoposide, (2) the median survival after treatment with either therapy was 36 weeks, and survival after carboplatin/etoposide was not inferior to cisplatin/etoposide, and (3) treatment with carboplatin/etoposide was associated with less posttreatment hospital-based health care use. Our findings complement those from a study of US Veterans with ES SCLC,³³ and add to the evidence in favor of treating elderly Medicare patients with ES SCLC with carboplatin/etoposide.

Despite guidelines recommending cisplatin/etoposide regimens as more effective, our data show that many clinicians are already treating their elderly ES SCLC patients with carboplatin/etoposide. The proportion of patients receiving carboplatin/etoposide increased from 68% in 1995 to a high of 82% in 2002, ending at 78% in 2009. This may reflect experience and clinical wisdom about the survival similarities and the excess toxicity of cisplatin/etoposide.

Our subgroup analyses indicated that patients under 75 years had noninferior survival, but the confidence interval for the smaller group of patients 75 and older did not support

FIG 4. Differences in hospital-based health care use. (A) Mortality rate ratios (and 95% CIs) of carboplatin plus etoposide (carbo) versus cisplatin plus etoposide (cis). (B) Proportions (and 95% CIs) of patients with any hospital-based health care use after chemotherapy. *P* values are from χ^2 tests. (C) Odds ratios (and 95% CIs) from ordinal logistic regression for number of hospital-based visits coded as 0, 1, 2, 3, or more. Summary statistics are median (25th, 75th percentiles) visits. (D) Incidence rate ratios (and 95% CIs) from over-dispersed Poisson regression for days of hospital-based care. Summary statistics are median (25th, 75th percentiles) days. ED, emergency department; ICU, intensive care unit.

noninferiority. These differences in significance may be due to sample size; the confidence intervals are wider when we divide the sample by age.

The significant differences in hospital-based health care use have important implications. Hospitalization exacts a substantial personal, psychosocial,³⁴ and financial toll on patients. In addition, clinicians and provider organizations need rigorous evaluations of both survival benefits and subsequent health care use by patients as they attempt to lower costs and improve quality in new contracting models that pass financial risk on to provider organizations, such as the Massachusetts Alternative Quality Contract.³⁵ Although the costs of the two chemotherapy regimens themselves are nearly identical, the differences in subsequent hospital-based care dwarf the direct costs of treatment. Drug costs for these two regimens (not including office visits, administration charges, etc.) are \$110 to \$130 per cycle (see Appendix), and treatment protocols typically recommend 4 to 6 cycles.⁹ By contrast, a single

hospital day averages \$2,157,³⁶ two and half times the cost of the drugs.

Our research has several limitations. SEER-Medicare data includes excellent cancer registry information, but represents only a portion of cancer diagnoses in the US and excludes several potentially important variables, such as Karnofsky performance score and specific chemotherapy regimens used in treatment. We use Medicare claims to identify the chemotherapy regimens, and coding limitations of inpatient claims (MEDPAR) prevent us from observing particular chemotherapy agents in the hospital, so our results apply only to patients who begin chemotherapy in the ambulatory setting. Moreover, we cannot reliably extract dosing from Medicare data because each opened vial of the drug is billed in full, regardless of amount the patient is given. Further, the registry does not collect patient-reported or other toxicity outcomes, so we also infer these from Medicare claims, which are not designed for collecting patient outcomes.

Our findings generalize to patients who resemble our matched cohort, which excluded many carboplatin/etoposide patients (who did not match), people in Medicare Advantage, and those without continuous enrollment in Parts A and B. Appendix Table A2 summarizes the differences between our selected cohort and the overall ES SCLC population as well as patients who received other ambulatory chemotherapy regimens. People who receive identifiable ambulatory chemotherapy regimens other than those studied here are very similar to those in our sample. Compared with the larger ES SCLC population, patients receiving ambulatory chemotherapy are slightly younger, more likely to have a previous ICU stay, had more hospitalizations and functional aids, and were more likely to have radiation therapy and brain metastases before chemotherapy.

In observational studies such as ours, the most significant challenge is selection bias due to unobserved differences between the patients receiving each treatment. We observed substantial differences before matching, with more patients who were older and sicker (ie, higher Charlson scores, more hospitalizations before diagnosis, more functional aids) in the carboplatin/etoposide group compared with the cisplatin/etoposide group. After matching, however, these observable differences were dramatically reduced.

Finally, choosing a noninferiority threshold depends on beliefs about treatment intent and toxicity burden, and research is ongoing to establish best practices for noninferiority studies.³⁷ We chose a five percentage point survival difference at 6 months as clinically insignificant given that the goal of chemotherapy in patients with ES SCLC is palliative. Our thresholds are relatively conservative compared with other noninferiority studies in cancer, which range from 4% to 25% for binary outcomes and 1.1 to 1.5 for hazard ratios.^{38,39} In a recent meta-analysis of trial data comparing these two therapies in ES SCLC, the hazard ratio for overall survival had a confidence interval of 0.92 to 1.27, from which the authors concluded “no difference” in efficacy.⁸

To our knowledge, ours is the first comparison of health care use and survival for Medicare patients with ES SCLC after receiving first-line cisplatin/etoposide or carboplatin/etoposide in the usual care setting. While we cannot observe nuanced or codified clinical practice, our results show that for elderly Medicare patients with ES SCLC, most oncologists use carboplatin/etoposide, and patients who receive cisplatin/etoposide are healthier at baseline. For those who

begin guideline-recommended first-line combination treatment as outpatients, after accounting for observable differences in baseline health, carboplatin/etoposide is as effective as cisplatin/etoposide and is associated with less subsequent health care use. **JOP**

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Authors' Disclosures of Potential Conflicts of Interest

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Author Contributions

Conception and design: All authors

Collection and assembly of data: All authors

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

Corresponding author: Laura A. Hatfield, PhD, Department of Health Care Policy, Harvard Medical School, 180A Longwood Ave, Boston, MA, 02115; e-mail: hatfield@hcp.med.harvard.edu.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Survival and Toxicity After Cisplatin Plus Etoposide Versus Carboplatin Plus Etoposide for Extensive-Stage Small-Cell Lung Cancer in Elderly Patients

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Laura A. Hatfield

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Haiden A. Huskamp

Travel, Accommodations, Expenses: IMS Health

Elizabeth B. Lamont

Employment: Salient Care

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Appendix

Classifying Chemotherapy Regimens

We scanned the Medicare claims in the outpatient, carrier, and durable medical equipment files for the first chemotherapy treatment that occurred after diagnosis, using administration codes (eg, 964xx). If Healthcare Common Procedure Coding System (HCPCS) codes for cisplatin (J9060, J9062) and etoposide (J8560, J9181, J9182) occurred on the first day of chemotherapy, we classified the patient as having received cisplatin plus etoposide. If HCPCS codes for carboplatin (J9045) and etoposide occurred on the first day, we classified the patient as having received carboplatin plus etoposide.

Table A1. Baseline Characteristics of Cohorts

Variable	% of Patients			
	ES SCLC (n = 14,958)	Cis (n = 831)	Carbo (n = 2,846)	Other Ambulatory Chemotherapy (n = 1,565)
Marital status				
Single	7	5	6	6
Married	49	59	55	55
Separated	1	< 1	1	1
Divorced	9	9	7	8
Widowed	31	23	29	28
Unknown	3	3	3	2
Male	49	53	49	53
Race				
White	89	92	90	90
Black	7	5	6	5
Other	2	1	1	2
Asian	2	1	2	2
Hispanic	1	1	1	1
SEER region				
Connecticut	8	8	9	8
Detroit	11	10	10	9
Hawaii	1	1	1	1
Iowa	9	15	9	8
New Mexico	2	4	2	2
Seattle	7	3	8	9
Utah	1	1	2	1
Atlanta	3	2	2	3
Kentucky	10	11	10	12
Louisiana	6	5	5	4
New Jersey	11	9	10	10
Georgia	7	6	9	6
California	25	25	24	26
Brain metastases in 90 days before first chemotherapy	9	15	14	14
ICU/CCU stay 2 years before chemotherapy	19	25	26	26
Radiation therapy before first chemotherapy	12	27	21	22
Mean (95% CI) No. of functional aids in 2 years before first chemotherapy	0.26 (0.25 to 0.27)	0.34 (0.30 to 0.38)	0.47 (0.44 to 0.50)	0.43 (0.40 to 0.47)
Mean (95% CI) age at diagnosis, years	75.5 (75.4 to 75.6)	73 (72.8 to 73.4)	74.8 (74.6 to 74.9)	74.5 (74.1 to 74.7)
Mean (95% CI) Charlson score 2 years before first chemotherapy	2.7 (2.7 to 2.8)	2.3 (2.2 to 2.5)	2.8 (2.7 to 2.8)	2.6 (2.5 to 2.7)
Mean (95% CI) No. of hospitalizations in the 2 years before first chemotherapy	0.83 (0.81 to 0.85)	0.98 (.88 to 1.1)	1.1 (1.1 to 1.2)	1.16 (1.09 to 1.23)

NOTE. The only variables with any missing values were marital status (n = 28, cisplatin plus etoposide; n = 76, carboplatin plus etoposide) and ethnicity (n = 0, cisplatin plus etoposide; n = 4, carboplatin plus etoposide). We coded these into separate missing categories for the propensity score model.

Abbreviations: Carbo, carboplatin-etoposide; CCU, critical care unit; Cis, cisplatin-etoposide; ES SCLC, extensive-stage small-cell lung cancer; ICU, intensive care unit; SD, standard deviation; SEER, Surveillance, Epidemiology, and End Results.

Table A2. Cost of Carboplatin Chemotherapy Regimen

Day	Agent	Dose (mg)	Vial Size (mg)	No. of Vials	Cost/Vial (\$)	Cost (\$)
1	Carboplatin	1,280.6 (men)	525	3	26.67	80.01
1	Carboplatin	1,111.0 (women)	525	3	26.67	80.01
1	Etoposide	170	100	2	5.12	10.24
2	Etoposide	170	100	2	5.12	10.24
3	Etoposide	170	100	2	5.12	10.24
						110.73*

NOTE. Carboplatin AUC6 on day 1, etoposide 100 mg/m² on days 1 to 3 (Quoix E, et al: Ann Oncol 12:957-962, 2001; Schmittl A, et al: Ann Oncol 17:663-667, 2006).¹⁴

*Cost of one cycle (for men or women).

Table A3. Cost of Cisplatin Chemotherapy Regimen

Day	Agent	Dose (mg)	Vial Size (mg)	No. of Vials	Cost/Vial (\$)	Cost (\$)
1	Cisplatin	56.1	100	2	24.07	49.40
1	Etoposide	170	100	2	5.12	10.24
2	Cisplatin	56.1	100	2	24.07	49.40
2	Etoposide	170	100	2	5.12	10.24
3	Cisplatin	56.1	100	2	24.07	49.40
3	Etoposide	170	100	2	5.12	10.24
						129.52*

NOTE. Cisplatin 33mg/m² on days 1 to 3, etoposide 100 mg/m² on days 1 to 3 (Ihde DC, et al: J Clin Oncol 12:2022-2034, 1994; Noda K, et al: N Engl J Med 346:85-91, 2002; Eckardt JR, et al: J Clin Oncol 24:2044-2051, 2006; Lara PN, et al: J Clin Oncol 27:2530-2535, 2009; Zatloukal P, et al: Ann Oncol 21:1810-1816, 2010).¹³

*Cost of one cycle.

Table A4. Other Identifiable Ambulatory Chemotherapy Regimens

Chemotherapy Regimen Component					No. of Patients Receiving Regimen
Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	
Etoposide					454
Cisplatin	Irinotecan				198
Carboplatin	Paclitaxel				186
Carboplatin					121
Carboplatin	Irinotecan				96
Cisplatin					52
Cyclophosphamide	Doxorubicin	Vincristine sulfate			47
Carboplatin	Docetaxel				44
Topotecan					28
Irinotecan					25
Paclitaxel					25
Not otherwise classified					20
Carboplatin	Gemcitabine				17
Carboplatin	Etoposide	Not otherwise classified			15
Etoposide	Not otherwise classified				14
Carboplatin	Etoposide	Vincristine sulfate			11
Gemcitabine HCl					11

NOTE. This table shows the drugs administered on the first day of ambulatory chemotherapy after diagnosis, limited to regimens with at least 10 people. The majority (n = 335) of patients who received etoposide only received another drug, usually carboplatin or cisplatin, in the 1 or 2 days after this initiation of chemotherapy. We excluded these patients from our cohort because they did not receive one of the two regimens of interest (those regimens specified in guidelines and studied in clinical trials).