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Transarterial Chemoembolization Treatment: Association between Multiple Treatments, Cumulative Expenditures, and Survival

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ABSTRACT

Objectives: To examine cumulative survival and Medicaid-paid expenses associated with multiple courses of transarterial chemoembolization (TACE) as primary treatment for hepatocellular carcinoma (HCC). **Methods:** Medicare enrollees diagnosed with primary HCC from 2000 to 2007, ever treated with TACE, but not transplant/resection, followed through 2009 by using the Surveillance, Epidemiology and End-Results Program and linked Medicare databases. Cumulative all-cause/HCC-related survival was estimated by using multivariate Cox proportional hazards models stratified by the total number of TACE treatments. Multivariate weighted Cox regressions estimated the average risk of mortality faced with nonproportional hazards. Lin's inverse probability-weighted least squares regression method estimated cumulative Medicare expenditures adjusted for censoring and covariates. **Results:** Of 1228 patients, 34% were stage 1, 16% stage 2, 19% stage 3, 6% stage 4, and 26% unstaged. About 44% were aged 65 to 75 years, 69% were men, and 72% were Caucasian. Over half (57%) of the patients received one course, 24% two, 11% three, and 8% four courses of TACE. One-course patients incurred an average $74,788 (95% confidence interval [CI] $71,890–$77,686), two-course patients $101,126 (95% CI $94,395–$107,856), three-course patients $111,776 (95% CI $101,931–$121,621), and four-plus-course patients $148,878 (95% CI $136,346–$161,409). One-course patients lived (all-cause) an average 1.86 (95% CI 1.82–1.90), two-course patients 2.09 (95% CI 2.05–2.13), three-course patients 2.81 (95% CI 2.66–2.97), and four-plus-course patients 3.06 (95% CI 2.95–3.18) years after diagnosis. Average risk of all-cause mortality was not significantly different between one/two courses or three/four-plus courses. **Conclusions:** Cumulative Medicare expenditures nearly doubled from one-course to four-plus-course patients. On average, four-plus-course patients lived over one more year than did one-course patients. Physician/patient decisions should be balanced with consideration of efficient use of limited resources, but payer's intervention in physician discretion may not be important in this setting.

Keywords: cost-effectiveness, hepatocellular carcinoma, SEER-Medicare, survival, transarterial chemoembolization.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and was the third most common cause of cancer-related death in 2008 [1]. While the prevalence of HCC is highest in developing countries, incidence in the United States has tripled between 1975 and 2005 from 1.6 to 4.9 incidences per 100,000 inhabitants [2]. HCC is an age-dependent cancer that peaks in incidence between 75 and 79 years of age [3]. The hepatitis B and C viruses are the main risk factor for HCC because they promote cirrhosis, which is found in 80% to 90% of HCC cases [4]. Incidence is expected to continue rising in the next few decades because of current trends related to the etiology of HCC as well as an aging population [4]. Recent advances in oncology have led to greater rates of early detection of HCC and more effective treatment [5], yet most HCC is still diagnosed at intermediate or advanced stages for which no curative therapy has been established [6,7].

In early stages of HCC, transplantation, surgical resection, and percutaneous ablation are considered to be potentially curative therapies [5]. Patients in early to intermediate stages, however, are often precluded from these procedures, for instance, because of tumor size, number of lesions, or complicating liver diseases [8,9]. In this case, transarterial chemoembolization (TACE) is often a first-line therapy that has been shown to positively impact survival, although overall survival benefit is largely dependent on the patients' baseline clinical characteristics [5]. For patients also eligible for ablation, concomitant TACE treatments have been shown recently to be more effective than ablative therapy alone, providing overall survival rates similar to that of surgical resection [10,11]. With TACE, chemotherapeutic agents—commonly doxorubicin or cisplatin [12]—are concentrated and isolated at the tumor site while blocking the primary artery feeding the tumor [7]. Because TACE can cause liver damage, patients with preserved liver function are carefully selected for the treatment [7,12]. Eligible patients often achieve

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maximum tumor response after repeated interventions, usually between three and four courses [12–15].

Changes in demographics and expanding therapeutic frontiers including TACE necessitate increased attentiveness of the long-term costs of cancer for payer organizations. Lang et al. [16] conservatively estimated that total health care cost per patient with HCC was an average $29,354 in 2006 US dollars ($34,947 in 2011 US dollars). The cost implications of HCC are particularly relevant for Medicare because many patients with HCC are eligible for Medicare because of age or other qualifying conditions.

Much of the evidence on the effectiveness of TACE comes from randomized clinical trials that often represent nontypical demographics and risk factors. Randomized clinical trials have yet to produce evidence for the effectiveness of repeated courses of TACE in treating HCC, possibly because it is difficult to establish intent to treat when additional courses of TACE are continued according to tumor response. No observational study has evaluated the survival benefit associated with repeated TACE treatments for HCC. Moreover, health care organizations have an interest in knowing the costs of TACE because there are no such evaluations in the populations for which it is most treated. The objective of this study was to examine cumulative survival across Medicare patients who received multiple courses of TACE to treat HCC and examine its association with long-term direct medical costs to Medicare. Real-world evidence will not only inform further analysis of emerging therapies such as TACE but also help guide coverage and budget decisions by payers and providers for patients with HCC at different stages.

Methods

Data Source

The National Cancer Institute's Surveillance, Epidemiology and End Results (SEER)-Medicare-linked database collects clinical information on incident-based cancer diagnoses from cancer registries covering nearly 26% of the U.S. population. Data collected include demographic characteristics, date of diagnosis, details about the cancer (e.g., histology, stage, and grade), and cause of death, if applicable. Medicare enrollment and claims files from Parts A (inpatient), B (provider), and D (drugs) are linked to SEER such that information can be collected regarding utilization, particularly types and timing of treatments undertaken, as well as underlying comorbidity. The database has been found representative of the national population and is described in detail elsewhere [17] (http://seer.cancer.gov).

We selected patients with primary HCC initially diagnosed between January 1, 2000, and December 31, 2007. Patients were excluded if they were enrolled in a health maintenance organization (HMO) within 12 months prior to the diagnosis of HCC. This was to eliminate possible censoring of information due to switching between an HMO and Part A/B enrollment. Patients were also excluded if they had an unknown diagnosis month or year, had a history of other cancers within 5 years prior to diagnosis, or for whom cancer was diagnosed upon death. Eligible patients were followed until the week of death or until censored because of the loss of Part A/B coverage, HMO enrollment, or December 31, 2009.

Survival

Survival was calculated as the number of weeks from diagnosis to death. Mortality was defined as all-cause or as HCC-related if the cause of death was indicated as "liver."

TACE Treatments

The sample consists of all patients with HCC who met the inclusion and exclusion criteria above and had undergone at least one course of TACE in the follow-up period. Patients who received transplant or resection in the follow-up period were excluded (n = 228) because these therapies dominate alternative therapies in the Barcelona Clinic Liver Cancer staging system, the most widely used system for staging and treatment [5,7]. TACE is often used to reduce the dropout rate for patients on the waiting list for liver transplantation (bridge-therapy) or to downstage patients not initially meeting the criteria for transplantation or resection eligibility [18,19]. Patients were not precluded from the receipt of percutaneous ablation, systemic chemotherapy, or radiation therapy before or after their TACE treatment(s). A large fraction of TACE patients had undertaken multiple courses of TACE throughout the follow-up period. We delineate patients who received two, three, or four or more TACE treatments from those who received only one.

Patient Characteristics

Age, sex, and race/ethnicity were recorded for all patients at diagnosis. Patients were categorized into four age brackets: younger than 65 years, 65 to 74 years, 75 to 84 years, and older than 84 years. Race/ethnicity was categorized as Caucasian, African American, Hispanic, or other race. Patients resided in either urban or rural counties.

Patients with HCC were classified as stage 1, 2, 3, 4, or unstaged upon diagnosis. For patients diagnosed after 2003, cancer stage was determined by using the American Joint Committee on Cancer 6th edition staging system. The TNM staging system was used prior to 2003. Patient comorbidities were assessed by using Medicare Part A or B claims for 1 year prior to HCC diagnosis. Indicators for hepatitis B and C, alcohol-related liver disease (ALD), and moderate-severe liver disease (MSLD) were created. A modified Charlson comorbidity index (CCI) was constructed by excluding liver-related risk factors, and patients were categorized into three categories: CCI = 0, 1, or greater than 1.

Costs

Economic costs were assessed from Medicare's perspective over the follow-up period (i.e., patient costs, including indirect cost, were not considered). All patients were covered under Medicare Part A, which covers inpatient care in short- and long-stay hospitals, skilled nursing facilities, home health, and hospice care. All patients were covered under Part B, which covers physician services, outpatient care, durable medical equipment, and home health in some cases. Medicare-paid expenditures for each patient were ascertained from Parts A and B claims data. Total direct medical costs to Medicare per patient per month were calculated from diagnosis until end of follow-up. Total Medicare expenditures may be somewhat underestimated. While several oral anticancer and antiemetic drugs are/were covered under Medicare Part B, data for oral prescription drugs covered under Part D were not available prior to 2007 and therefore not incorporated into the analysis. All expenditures were inflated to represent 2011 U.S. dollars by using the Bureau of Labor Statistics' annual average Consumer Price Index for medical care.

Statistical Analysis

The frequencies and proportions of patients who underwent one, two, three, or four or more courses of TACE were calculated. Chi-square tests were conducted to compare patient characteristics between the latter four cohorts because all variables were