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Economic burden of selected adverse events in patients aged ≥65 years with metastatic renal cell carcinoma

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Abstract

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Methods

Retro esults (SEER) Medi aged ≥65 years, w nd Decemb oxicities that have be sunitinib, sorafeni and

fatigue/asthenia, hand-foot syndrome, hypertension, lymphopenia, nausea/vomiting, neutropenia, proteinuria, and thrombocytopenia. Patients in SEER-Medicare with these events were identified based on ICD-9-CM diagnosis codes on Medicare claims. For each AE of interest, costs were tallied among evented patients over 30 days, beginning with the date of each patient's first mention of the AE, and were compared with those of non-evented patients over a similar 30-day period beginning with an identical 'shadow' index date. Total costs were compared on an unadjusted basis and with adjustment for differences in baseline characteristics using a generalized linear model.

Results:

A total of 881 patients with mRCC met study entry criteria; 60% of these patients had Medicare claims with mention of one or more AEs of interest. Events occurring with frequency >20% included abdominal pain, dyspnea, and fatigue/asthenia; 10–20% of study subjects had encounters for back pain, extremity pain, and nausea/vomiting. Mean (standard deviation) total cost of care over 30 days was substantially higher among patients with AEs ($13,944 [$14,529]) compared with those without mention of these events ($1878 [$5264]). Adjusting for differences in baseline characteristics, the mean (95% confidence interval) difference in costs between evented and non-evented patients was $12,410 ($9217–$16,522). Study limitations include problems in event ascertainment due to inaccuracies in ICD-9-CM coding on Medicare claims data, and restriction of the study population to patients with metastatic involvement at initial diagnosis of RCC.

Conclusions:

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Introd

In this article

Kidney cancer accounts for ~2% of all incident malignancies worldwide[1]. In 2012, there were an estimated 64,770 cases of newly diagnosed kidney cancer in the US, and 13,570 deaths due to the disease[2]. Renal cell carcinoma (RCC) accounts for ~85% of all kidney cancers; the remainder is comprised mainly of carcinoma of the renal pelvis (transitional cell carcinoma)[3]. Mean age at diagnosis of RCC is 64 years. Since RCC is often asymptomatic in its early stages, there is frequently metastatic involvement at initial diagnosis[4,5].

Metastatic RCC (mRCC) is a deadly disease with a very poor prognosis. Historically, 5-year survival has been no more than ~10%[6]. Nephrectomy, metastectomy, and cytotoxic chemotherapy have limited or no effectiveness[7]. Standard first-line therapy for mRCC traditionally has been cytokine therapy (interleukin-2 [IL-2] and/or interferon-α [IFN]); however, it is of limited benefit in selected patients only[7]. Advances in understanding of the biology and genetics of RCC have led to novel targeted approaches to treatment, including: tyrosine kinase inhibitors (e.g., sorafenib, sunitinib, pazopanib, axitinib); the monoclonal antibody (mAb), bevacizumab; and the mammalian target of rapamycin (mTOR) inhibitors, temsirolimus and everolimus[8].

While these targeted therapies are more effective than prior treatment and, therefore, have become the standard of care in patients with mRCC[3], they are not without their shortcomings. In particular, a number of adverse events (AEs) have been reported in clinical trials of these agents, including fatigue, diarrhea, hypertension, hand-foot syndrome, stomatitis, bleeding, and gastrointestinal perforation[9–12]. There is limited information on the economic costs associated of these events, especially among patients

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frequency ≥5% in randomized controlled trials of sunitinib, sorafenib, bevacizumab, and pazopanib (i.e., targeted therapies for mRCC). The economic burden of these AEs was estimated by comparing healthcare costs between patients with and without these events. All analyses were descriptive in nature, as there were no a priori study hypotheses.

Data source

Data for this study were obtained from the linked SEER-Medicare database. SEER is an epidemiologic surveillance system of the National Cancer Institute (NCI) that is comprised of population-based tumor registries; the system is designed to track cancer incidence and survival in the US. The SEER tumor registries routinely collect information from multiple reporting sources, including hospitals, outpatient clinics, laboratories, private medical practitioners, nursing, convalescent homes, hospices, autopsy reports, and death certificates on all persons in geographically defined areas who have newly received diagnoses of cancer. About 28% of the US population is represented in SEER[13]. By combining information from both SEER and Medicare files, the linked dataset provides information on cancer diagnosis and treatment, as well as downstream medical care. This combined data source offers the opportunity to link service utilization over time to stage at diagnosis as well as time from diagnosis to death. The source population for this study consisted of all persons in the January 2011 release of the SEER-Medicare database who met the selection criteria described below.

Study subjects

We selec nosed mRCC be ER; the study po at initial clinical p study subjects SEER (‘index date’) ate of initial diagn e excluded all perso eriod precedin

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We limited our attention to Grade 3 or 4 toxicities (i.e., moderate or severe in severity) that have been reported with frequency ≥5% in randomized controlled trials of sunitinib, sorafenib, bevacizumab, and pazopanib (i.e., targeted therapies for mRCC), as noted in package labeling information for these agents[9–12], and that could be identified using ICD-9-CM diagnosis codes in healthcare claims data. AEs that met these criteria for one or more targeted therapies for mRCC are listed in Table 1. Patients were deemed to have been 'evented' if they had any evidence of any of these events during follow-up, based on a scan of all inpatient and outpatient medical claims.

Table 1. Grade 3 or 4 adverse events included in the study*.

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Patient characteristics

Patients were characterized in terms of gender, age as of index date, race, US census region, Charlson comorbidity index at index date, total cost during pre-index period, and duration of follow-up.

Outcome measures and analysis

We estimated the number of patients with evidence of each of the AEs of interest following diagnosis of mRCC, based on a scan of all Medicare claims, on an overall basis and by time since index date. Patients were counted once only for each event, and time to first e

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In this article

diagnosis of mRCC to the post-event periods therefore was similar between evented and non-evented patients. A 30-day follow-up was used to tally costs, since most of the AEs of interest are transient and would be expected to resolve within a short time frame.

Non-evented patients who disenrolled prior to the 'shadow' index date were excluded from the analyses. Patients who disenrolled during the post-event period were not censored. While it would be possible for both evented and non-evented patients to experience other AEs within the post-event period for any given AE, we assumed that there was no obvious reason for a patient with abdominal pain, for example, to experience other AEs more (or less) frequently than a patient who did not have abdominal pain.

To control for differences in baseline characteristics between patients with and without evidence of AEs, healthcare costs during the 30-day post-event period were analyzed using multivariate generalized linear (GLM) models with a log-link function and gamma response probability distribution. A separate model was estimated for each AE. Independent variables in each model included a binary variable indicating presence/absence of the event in question and the following covariates: gender, age as of index date, race, US census region, Charlson comorbidity index at index date, and total cost during pre-index period. Using the estimated parameter (β) for the binary (i.e., 0/1 dummy) variable for the event in question and mean total costs among patients who did not experience the AE of interest (X), the increase in total costs of medical-care services among patients who experienced the event was estimated as X* [exp(β) -

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exclusion (not mutually exclusive) included lack of continuous eligibility for Medicare Part A and B during the 12-month period preceding the index date (18%), and age <65 years at diagnosis (15%). A total of 881 patients met all study entry criteria.

Figure 1. Patient selection—Patients with metastatic renal cell carcinoma (RCC) in the SEER-Medicare Database.1 For Medicare Part A and B during a 12-month period prior to diagnosis date.2 Subsequent diagnosis records dated prior to 2007.

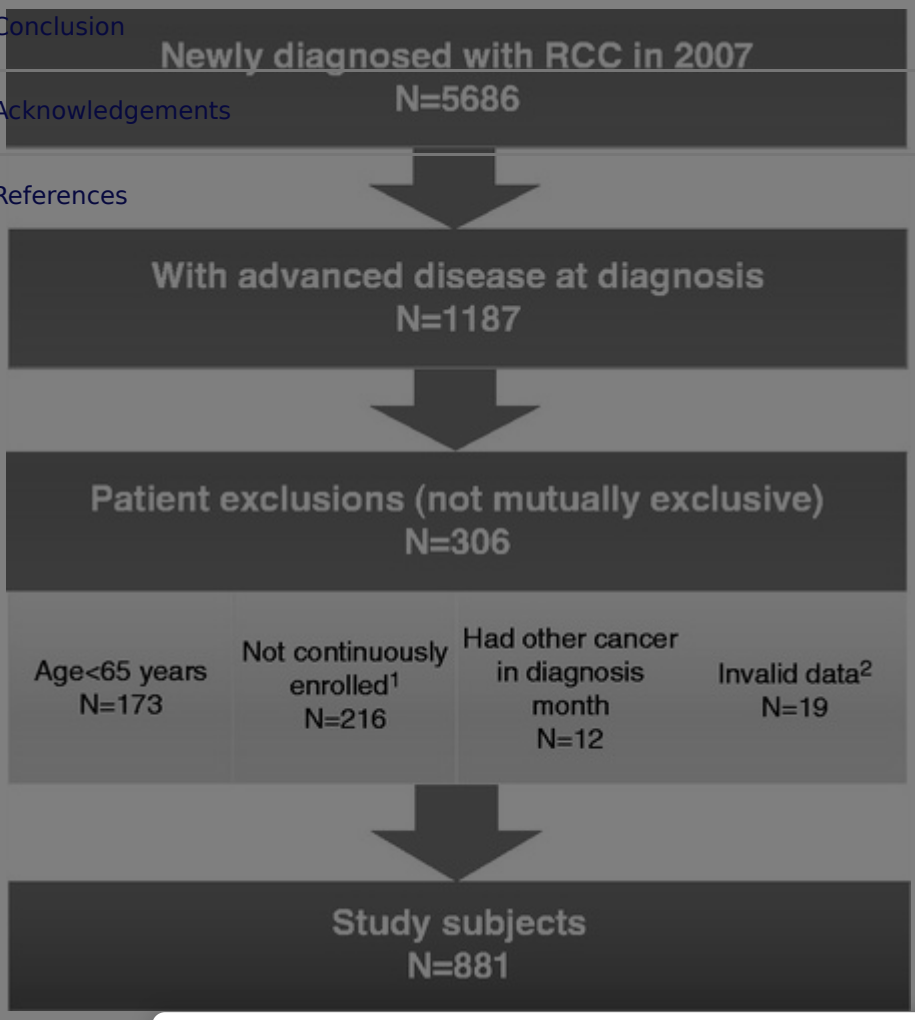

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Table 2. Characteristics of patients with metastatic renal cell carcinoma, by evidence of treatment-related adverse events (n = 881).

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The numbers of patients who experienced the AEs of interest are reported in Table 3, by time since index date. During the first 3 months following diagnosis of mRCC, >20% of patients had one or more Medicare claims for abdominal pain and fatigue/asthenia, and 14% had claims for dyspnea; other frequently observed events included back pain (11%), extremity pain (8%), nausea/vomiting (8%), and diarrhea (3%). During months 4–12 following diagnosis, the same AEs were observed, but at somewhat lower rates.

Table 3. Incidence of selected treatment-related adverse events among patients with metastatic renal cell carcinoma, by time since index date (n = 881)*.

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Total medical-care costs during the 30-day post-event period, excluding the cost of targeted therapies, are reported in Tables 4 and 5. Mean time to event among patients with AEs ranged from 88 days for abdominal pain to 211 days for proteinuria; across all events c with evidence nts without any evid mean total cost was e event.

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Table 5. Estimated increase in mean total cost of medical-care services (excluding cost of targeted therapies) associated with evidence of treatment-related adverse events during 30-day post-event period* in patients with metastatic renal cell carcinoma (estimates adjusted for differences in baseline characteristics) (n = 881).

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In the GLM models, costs associated with each AE during the 30-day post-event period were estimated based on the parameter estimate for the binary event flag and mean total cost among patients without evidence of the AE (Table 5). The estimated increase (95% CI) in costs during the 30-day post-event period among patients with evidence of any AEs (vs none) was $12,410 (95% CI = $9217–$16,522). For all types of AEs reported, the estimated difference was positive, and the 95% CI did not include zero.

Discussion

Using the linked SEER-Medicare database, we estimated the costs of AEs associated with treatment of mRCC in patients aged 65 years and older, limiting our attention to moderate-to-severe (i.e., Grade 3 or 4) AEs that have been reported with a frequency ≥5% in randomized controlled trials of sunitinib, sorafenib, bevacizumab or pazopanib (as repo

More tha ore AEs associat ency ≥20% (abdomi less frequen ow-up was prob or proteinu ension, lymphop the duration nce of AEs and thos d not impart

a bias to our estimates, since mean time to AEs (65 days) was well within the mean duration of follow-up among non-evented patients.

Mean (SD) total costs of medical-care services (excluding costs of targeted therapies) during the 30-day post-event period were considerably higher among patients with AEs —$13,944 ($14,529) vs $1878 ($5264) for those without evidence of these events. When adjusted for differences in patient baseline characteristics, the estimated increase in cost (95% CI) was $12,410 ($9217–$16,522). We note that we limited our attention to the direct cost of AEs alone. A comprehensive assessment of the impact of AEs in elderly patients with mRCC also would need to consider effects on health-related quality-of-life.

There are three retrospective studies of AEs in patients with metastatic RCC receiving angiogenesis inhibitors[14–16]. Choueiri et al.[14] reviewed the medical charts of 144 patients with mRCC at two US oncology centers to assess the costs of AEs experienced by those receiving sunitinib, sorafenib, or bevacizumab. The cost of treatment of AEs was $729 for sunitinib, $636 for sorafenib, and $291 for bevacizumab. Our study did not assess AEs by individual therapy nor the cost of treatment of AEs for each drug. Feinberg et al.[15] examined the medical records of 250 patients with mRCC who received sunitinib or sorafenib and reported that the mean duration of therapy with these agents was ~5–6 months. The overall incidence of AEs (all grades) was 86–87%, and the incidence of Grade 3/4 events was 28–30%. In our study, 60% of study subjects had evidence of Medicare claims for at least one type of adverse event.

Although it is not a retrospective study, Miskisch et al.[16] estimated the costs of managi b in combina ng a linear decision r patient that ran

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subjects with AEs of interest. The impact of such errors in coding on our findings is unknown.

Moreover, since unique ICD-9-CM diagnosis codes do not exist for some of the AEs of interest, we do not know the sensitivity and specificity of the methods we employed to identify patients who were evented. Fewer than 1% of patients had Medicare claims for hypertension, while rates reported in package inserts (Grade 3/4 severity) were 13% for sunitinib, 6% for bevacizumab, and for 3% sorafenib. This difference probably reflects errors deriving from the use of ICD-9-CM coding.

Our analyses of costs associated with AEs were limited to the 30-day period following first mention of each event. While we believe this period was sufficiently long to capture most of the important economic consequences associated with these events, we do not know this for certain. To the extent that costs remain elevated beyond 30 days, we may have under-estimated the costs of AEs. We also did not distinguish between the costs of diagnosis and those of treatment, since it is infeasible from a practical standpoint to do so using health insurance claims data.

Finally, we note that our study sample was limited to patients aged 65 years and older. The generalizability of our findings to patients who are younger is unknown.

Conclusion

In our study in a Medicare population, we found that more than one-half of patients with mR rgeted therapie are substant entially reduce t also needed to subst

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Declaration of financial/other relationships

MH and GO are employees of Policy Analysis Inc. and have received funding for the research from GlaxoSmithKline. MDH is an employee of GlaxoSmithKline and owns stock options in GlaxoSmithKline.

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