Original Study

Metformin Use and Kidney Cancer Outcomes in Patients With Diabetes: A Propensity Score Analysis

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Abstract

The present study of 158 diabetic patients evaluated whether the use of metformin, a medication with putative antineoplastic effects, was associated with survival outcomes in patients with kidney cancer. We found that metformin use was not significantly associated with disease-free, cancer-specific, or overall survival. Population-based studies may be needed to further evaluate the role of metformin in kidney cancer therapy.

Background: Exposure to metformin, a medication used to treat diabetes, has been associated with improved survival outcomes in various malignancies. However, studies evaluating the association between metformin use and kidney cancer survival outcomes have demonstrated conflicting results. **Patients and Methods:** We performed a retrospective review of diabetic patients undergoing nephrectomy for M0 renal cell carcinoma from 2000 to 2014 at a tertiary academic center. Medication use at the time of surgery was determined by medical record review. Inverse probability of treatment weights (IPTWs) were derived from a propensity score model that included various clinical, surgical, and pathologic characteristics. Cox proportional hazard models were used to evaluate the association between metformin use and disease-free, cancer-specific, and overall survival in the sample weighted by the IPTWs. **Results:** A total of 158 diabetic patients were identified, 82 (52%) of whom were taking metformin at the time of surgery. Before the application of the propensity score methods, the metformin users were significantly older and were more likely to undergo surgery between 2009 and 2014. After applying the IPTWs, the clinical, surgical, and pathologic characteristics were well balanced between the 2 groups. The median follow-up period was 43 months. Metformin use was not significantly associated with disease-free (hazard ratio [HR], 0.99; 95% confidence interval [CI], 0.36-2.74), cause-specific (HR, 0.38; 95% CI, 0.08-1.86), or overall (HR, 0.86; 95% CI, 0.40-1.85) survival. **Conclusion:** We found no significant association between metformin use and kidney cancer outcomes. Population-based studies are needed to further evaluate the role of metformin in kidney cancer therapy.

Clinical Genitourinary Cancer, Vol. 15, No. 2, 300-5
Keywords: Disease progression, Humans, Nephrectomy, Renal cell carcinoma, Survival

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Submitted: May 2, 2016; Revised: Jun 9, 2016; Accepted: Jun 11, 2016; Epub: Jun 23, 2016

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Introduction

Kidney cancer is the third most common urologic malignancy and the most lethal of all urologic malignancies with an estimated 61,650 new diagnoses and 14,080 kidney deaths in the United States in 2015.[1] Furthermore, the number of incident cases has been increasing worldwide[2] and is believed to be related to the increasing use of diagnostic imaging and the increase in obesity and hypertension, which are known risk factors for kidney cancer.[3] Despite earlier detection, the survival rates have only improved marginally.[4]

Surgical resection in the form of nephrectomy remains the mainstay of treatment of clinically localized disease. However, despite treatment for localized disease, 20% to 30% of patients experience

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2016.06.008

recurrence after nephrectomy, and most of those with progression will die of the disease.[5] However, no therapies have been approved to reduce the risk of recurrence, progression, or death from kidney cancer after primary treatment of localized disease.

Metformin, a biguanide, is used primarily to treat diabetes.[6] More recently, metformin has gained interest for its antineoplastic properties, because studies have shown that metformin use might be associated with improved survival outcomes among diabetic patients with cancer.[7,8] To date, a limited number of studies have evaluated the association between metformin use and kidney cancer survival outcomes, and these studies have demonstrated conflicting results.[9-14] Given the aggressive nature and increasing incidence of kidney cancer, further studies are required to properly explore the potential role of metformin in kidney cancer therapy. The objective of the present study was to evaluate the association between metformin use and survival outcomes in diabetic patients undergoing nephrectomy for M0 kidney cancer.

Patients and Methods

Patients and Data Sources

After obtaining institutional research ethics board approval (approval no. REB 14-8273-CE), diabetic patients who had undergone nephrectomy for kidney cancer from January 2000 to December 2014 were identified retrospectively using our institutional database (eKidney, University Health Network, Toronto, ON, Canada). The exclusion criteria were histologic features inconsistent with renal cell carcinoma, hereditary kidney cancer syndromes, bilateral disease, previous treatment of kidney cancer, and/or previous radiofrequency ablation on the same mass for which they underwent nephrectomy.

The clinical, surgical, and pathologic characteristics were ascertained using electronic medical record review, including whether the patient was using metformin at the time of surgery. Recurrence and mortality data, including the cause of death, were obtained through electronic medical record review and the Princess Margaret Hospital Cancer Registry (which obtains data from the Ontario Cancer Registry, a population-based provincial validated registry that collects data from various sources for all Ontario residents diagnosed with cancer, including their death certificates).[15]

Outcome Measures

The outcome measures were disease-free survival (DFS), cancer-specific survival (CSS), and overall survival (OS). The survival times were measured from the date of nephrectomy. Disease relapse was defined as imaging or physical examination evidence of disease recurrence. Metachronous contralateral tumors were not considered recurrence. Patients not experiencing relapse or death were right censored at their last clinical visit.

Statistical Analysis

Patient characteristics were compared between groups using the χ^2 test, or Fisher's exact test when the cell counts were ≤ 5, for categorical variables, and continuous variables were compared using the Wilcoxon rank-sum test.

Propensity score methods were used to reduce the confounding due to differences in the distribution of measured covariates between those using metformin and those not using metformin. Propensity score methods allow for the comparison of outcomes in patients who are similar for all measured baseline characteristics, except for the exposure.[16] As such, they are well suited to minimize bias for observational studies in pharmacoepidemiology.[17]

The propensity score was estimated using a logistic regression model, in which metformin use was regressed on the measured baseline characteristics. Covariates for inclusion in the propensity score model were chosen according to their potential to be confounders or associated with the outcomes[17] and comprised patient characteristics (age, gender, Charlson comorbidity score, estimated glomerular filtration rate measured before surgery, and diabetes severity determined by evidence of end-organ damage [eg, documented neuropathy, ophthalmopathy, nephropathy]), surgical characteristics (year and type of surgery), and pathologic characteristics (pathologic stage, nodal stage, and histologic features). The effect of age on the log-odds of metformin use was modeled using restricted cubic splines with 3 knots.

Using the derived propensity score, inverse probability of treatment weights (IPTWs), defined as the reciprocal of the probability of receiving the treatment that was actually received,[18] were computed for all patients. To improve the precision of the estimated effects from the IPTW analyses, the weights were stabilized by multiplying the weights by the marginal probability of receiving the treatment that was actually received.[16,19] Stabilized weights aim to improve precision by reducing the variance of the weights.[19] To minimize the influence of outlying weights, weights greater than the 99th percentile were truncated.[20] The balance in the baseline covariates was evaluated by calculating the weighted standardized differences.[16,18]

IPTW-weighted adjusted survival curves were constructed for all outcomes.[21] The relative and absolute rate differences of the survival estimates were calculated at 5 years. IPTW-weighted Cox proportional hazard models with robust variance estimators were used to estimate the hazard of each outcome.[16,18] To do this, the hazard of the occurrence of the outcome was regressed on exposure status (metformin vs. control) in the sample weighted by the IPTW. The Cox proportional hazards assumption was evaluated through the cumulative score statistic[22] and was found to hold for all outcomes. A subgroup analysis was performed restricted to patients with clear cell renal cell carcinoma.

All tests were 2-sided, with $P < .05$ considered statistically significant. Statistical analyses were performed using Statistical Analysis Systems, version 9.4 (SAS Institute Inc, Cary, NC).

Results

Cohort Characteristics

A total of 158 diabetic patients underwent nephrectomy for unilateral, sporadic, M0, renal cell carcinoma from January 2000 to December 2014. Of these, 36 (23%) had diet-controlled diabetes, 17 (11%) required insulin (alone or as combination therapy), 82 (52%) were taking metformin, and 18 (11%) were taking oral hypoglycemic agents other than metformin at nephrectomy. The cohort characteristics are listed in Table 1. Before propensity score weighting, the metformin users were significantly older and were more likely to have undergone nephrectomy from 2009 to 2014. Trends were also seen for metformin users to be male and to have clear cell renal cell carcinoma. After applying IPTW propensity