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Original article

The association between metformin use and oncologic outcomes among surgically treated diabetic patients with localized renal cell carcinoma

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Abstract

Introduction: Metformin inhibits renal cell carcinoma (RCC) cell proliferation both in vitro and in vivo; however, clinical data regarding the effect of metformin in patients with RCC are lacking. We evaluated the association of metformin use with outcomes among patients with surgically treated localized RCC.

Materials and methods: We identified 283 consecutive diabetic patients treated surgically for localized RCC between January 1, 1994 and December 31, 2008. Clinicopathologic features were compared between patients exposed to metformin ($n = 83$, 29%) and those who were not ($n = 200$, 71%). Progression-free, cancer-specific, and overall survival rates were estimated with the Kaplan-Meier analysis, and Cox models were used to evaluate the association of metformin use with outcomes.

Results and conclusions: Patients receiving metformin had a better renal function (median estimated glomerular filtration rate = 65 vs. 55 ml/min/1.73 m^2, $P < 0.001$), performance status (Eastern Cooperative Oncology Group < 1: 89% vs. 71%, $P = 0.001$), and lower Charlson comorbidity index (median = 2 vs. 3, $P = 0.02$) compared with those who did not, but were otherwise similar across other clinicopathologic features ($P > 0.05$ for all). At a median postoperative follow-up of 8.1 years, patients exposed to metformin had similar 5-year progression-free (80% vs. 75%, $P = 0.6$) and cancer-specific survival rates (91% vs. 81%, $P = 0.16$), but significantly improved overall survival rate (79% vs. 62%, $P = 0.01$). However, metformin was not independently associated with the risks of progression, RCC-specific mortality, or all-cause mortality on multivariable analyses. In this surgical cohort of diabetic patients with M0 RCC, preoperative metformin exposure was associated with improved overall survival on unadjusted analysis. Although metformin was not independently associated with oncologic or survival outcomes, future studies appear warranted.

Keywords: Renal cell carcinoma; Diabetes; Metformin; Recurrence; Mortality

1. Introduction

Metformin (1,1-dimethylbiguanide hydrochloride) is an oral therapy ubiquitously used to treat type 2 diabetes and prediabetic syndromes. It received Food and Drug Administration approval in 1994 and is well tolerated, with a wide therapeutic window. Recent in vitro and in vivo studies have identified antineoplastic activity of metformin against renal cell carcinoma (RCC) through activation of the adenosine monophosphate–activated protein kinase. (AMPK) pathway. Liu et al. [1] investigated the effect of metformin on 2 RCC cell lines and tumor xenografts and reported that metformin inhibited the proliferation of RCC cell lines in both a dose- and time-dependent manner via AMPK activation. Furthermore, they observed inhibition of RCC cell colony formation and induction of cell cycle arrest in RCC cells treated with metformin, as well as inhibition of growth of RCC xenografts [1]. Additional work has

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identified the inhibitory effect of metformin on the mammalian target of rapamycin (mTOR) signaling pathway, likewise resulting in suppression of tumor growth [2].

Diabetes mellitus is associated not only with an increased risk of incident RCC, but also with both increased cancer-specific mortality (CSM) and all-cause mortality [3–7]. Emerging data from observational studies have suggested both a decreased incidence of malignancy among diabetic patients treated with metformin and a reduced risk of cancer progression and mortality among those with malignancy receiving metformin [8–10]. Given the biological and epidemiological plausibility for an interaction between metformin and RCC, our objective was to investigate the effect of preoperative exposure to metformin on the risks of disease progression, CSM, and all-cause mortality among patients with localized RCC undergoing nephrectomy.

2. Methods

2.1. Cohort selection

Following institutional review board approval, we identified 2,207 consecutive patients with localized (M0) sporadic RCC treated with either partial or radical nephrectomy at the Mayo Clinic between January 1, 1994 and December 31, 2008. In total, 283 patients (12.8%) were noted to be diabetic. Exposure to metformin before nephrectomy was determined by searching the Mayo Clinic electronic medical record in the 90 days before surgery for all medication formulations containing metformin (Appendix 1). Data regarding the duration and cumulative dose of metformin exposure was not available owing to the referral nature of the population and the fact that, in most cases, the patients' diabetes was managed by their local physicians.

The clinical features studied included age, sex, year of surgery, type of surgery, preoperative symptoms, smoking status, baseline serum creatinine, estimated glomerular filtration rate (eGFR) at diagnosis calculated using the Modification of Diet in Renal Disease formula, chronic kidney disease stage (defined as GFR $\geq$ 60, $\geq$45 to $<$60, $\geq$30 to $<$45, $\geq$15 to $<$30, and $<$15 ml/min/1.73 m^2), Eastern Cooperative Oncology Group performance status at surgery, baseline Charlson comorbidity index, and obesity (body mass index $\geq$30 kg/m^2). Patients with a palpable flank or abdominal mass, discomfort, gross hematuria, acute-onset varicocele, or constitutional symptoms including rash, sweats, weight loss, fatigue, early satiety, and anorexia were considered symptomatic at diagnosis.

The pathologic features studied included histologic subtype, tumor size, nuclear grade, coagulative tumor necrosis, and sarcomatoid differentiation. To obtain these pathologic features, one study pathologist reviewed the microscopic slides from all specimens without knowledge of patient outcome. Staging was assigned in accordance with the 2009 American Joint Committee on Cancer Staging System for RCC [11]. The Leibovich Progression Score (Mayo Clinic Prognosis score), which predicts disease progression following radical nephrectomy for clinically localized clear cell RCC [12], and the Mayo Clinic Stage, Size, Grade, and Necrosis score, a composite score associated with cancer-specific survival [13], were calculated for patients with clear cell histology.

Postoperatively, patients were surveyed for disease recurrence at 3- to 6-month intervals for the first 2 years and yearly thereafter with physical examinations and radiographic testing. For patients who were surveyed at their home institution, disease and vital status was updated via a yearly follow-up questionnaire, which was verified with the patient's physician. The primary outcomes of interest included progression-free survival, cancer-specific, and overall survival rates, which were calculated from the date of surgery.

2.2. Statistical analysis

Continuous features were summarized with medians and interquartile ranges (IQRs); categorical features were summarized with frequency counts and percentages. Comparisons of features between patients who did and did not receive metformin were evaluated using the Wilcoxon, chi-square, Fisher exact, and Cochran-Armitage trend tests. Progression-free, cancer-specific, and overall survival rates were estimated using the Kaplan-Meier method. Disease progression was defined as local ipsilateral or contralateral recurrence, distant metastases, or death due to RCC in the absence of local recurrence or distant metastases. The duration of follow-up was calculated from the surgical date to the date of progression, death due to RCC, death due to any cause, or to the date of last follow-up otherwise.

Univariable associations with time to disease progression, death due to any cause, and death due to RCC were evaluated using Cox proportional hazards regression models and summarized with hazard ratios (HRs) and 95% CIs. Multivariable models were developed using stepwise selection with the P value for a feature to enter or leave the model set to 0.05. Subanalyses were performed in patients with clear cell RCC histology. Statistical analyses were performed using the SAS software package (SAS Institute, Cary, NC). All tests were 2-sided, and $P < 0.05$ was considered statistically significant.

3. Results

Of the 283 diabetic patients with sporadic M0 RCC who comprised the analytic cohort, 83 (29%) received metformin. The proportion of diabetic patients with RCC on metformin undergoing surgery increased over the period of study (1994–1999: 13.4%, 2000–2004: 29.5%, 2005–2008: 41.7%; $P < 0.001$). A comparison of clinical and