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Original article

Evaluation of beta-blockers and survival among hypertensive patients with renal cell carcinoma

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Abstract

Objectives: Beta-blocker use is associated with improved survival for multiple nonurologic malignancies. Our objective was to evaluate the association between beta-blocker use and survival among surgically managed hypertensive patients with clear-cell renal cell carcinoma (ccRCC).

Methods: Hypertensive patients with ccRCC treated with either radical or partial nephrectomy between 2000 and 2010 were identified from our Nephrectomy Registry. Beta-blocker use within 90 days before surgery was identified. The associations between beta-blocker use and risk of disease progression, death from renal cell carcinoma (RCC), and all-cause mortality were assessed using Cox proportional hazards regression models.

Results: In total, 913 hypertensive patients were identified who underwent either partial or radical nephrectomy for ccRCC. Of these, 104 (11%) had documented beta-blocker use within 90 days before surgery. At last follow-up (median 8.2 y among survivors), 258 patients showed progression (median 1.6 y following surgery), and 369 patients had died (median 4.1 y following surgery), including 138 who died of RCC. After adjusting for PROG (progression-free survival) and SSIGN (cancer-specific survival) scores, beta-blocker use was not significantly associated with the risk of disease progression (hazard ratio [HR] = 0.94; 95% CI: 0.61–1.47; $P = 0.80$) or the risk of death from RCC (HR = 0.74; 95% CI: 0.38–1.41; $P = 0.35$). Similarly, on multivariable analysis adjusting for clinicopathologic features, there was not a significant association between beta-blocker use and the risk of all-cause mortality (HR = 0.83; 95% CI: 0.59–1.16; $P = 0.27$).

Conclusions: Beta-blocker use for hypertension within 90 days before surgery was not associated with the risk of progression, death from RCC, or death from any cause.

Keywords: Renal cell carcinoma; Beta-blocker; Hypertension; Survival

1. Introduction

It has been previously established that hypertension (HTN) is a risk factor for the development of renal cell carcinoma (RCC) [1,2]. Furthermore, a large population-based cohort study established a dose-dependent relationship between the degree of HTN—as measured by diastolic and systolic blood pressures—and the incidence of RCC [3]. This same study demonstrated that reductions in blood pressure among hypertensive patients reduced the risk of incident RCC, suggesting that HTN may represent a modifiable risk factor for RCC development.

Although the mechanism by which HTN may cause RCC is unknown, there is evidence that angiotensin can activate vascular endothelial growth factor (VEGF) signaling [4], the major driver of which is beta-adrenergic stimulation [5]. Thus, the use of beta-blocker therapy for HTN may affect oncologic outcomes in patients with RCC. Furthermore, there is recent evidence of improved

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cancer-specific survival (CSS) among patients using beta-blockers from a meta-analysis of beta-blocker use among patients with breast cancer, a meta-analysis of beta-blocker use among multiple nonurologic cancers, and a multi-institutional study of beta-blocker use in patients with ovarian cancer receiving chemotherapy [6–8].

Despite this clinical evidence in other nonurologic malignancies and the association of HTN with incident RCC, efforts at establishing a relationship between antihypertensive agents and oncologic outcomes in patients with RCC have provided limited evidence for pharmacologic modification of risk [9–12]. Unfortunately, given that HTN is a risk factor for RCC, most analyses failed to adequately control for HTN, and for those studies that did control for HTN, the analyses were limited by sample size and aggregate consideration of all classes of antihypertensive agents. Additionally, evaluations of HTN and the effect of antihypertensive therapy have focused on the incidence of RCC, as opposed to oncologic outcomes for patients with RCC. Based on this gap in the literature, we sought to evaluate the effect of beta-blocker use specifically on survival among hypertensive patients with RCC using a large institutional data set.

2. Materials and methods

Following institutional review board approval, we examined the Mayo Clinic Nephrectomy Registry to identify patients with HTN treated with either radical or partial nephrectomy for sporadic, unilateral, nonmetastatic clear-cell RCC between 2000 and 2010. Hypertensive patients were identified by documentation of HTN by CPT code (401.0, 401.1, and 401.9) before the date of surgery. Clinical features studied included age at surgery, sex, symptoms at diagnosis, smoking history, preoperative estimated glomerular filtration rate in ml/min/1.73 m^2 (calculated using the Chronic Kidney Disease Epidemiology Collaboration formula), Eastern Cooperative Oncology Group performance status at surgery, Charlson score at surgery, body mass index at surgery in kg/m^2, type of surgery, and beta-blocker use/type within 90 days before surgery. Beta-blocker use was identified by text search of medication lists in the patient medical record, with use defined as either present or absent. 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.

Pathologic features included histologic subtype; tumor size in cm; 2010 primary tumor, regional lymph node, and distant metastases classification; World Health Organization/International Society of Urological Pathology grade; and coagulative tumor necrosis. All specimens were evaluated by 1 urologic pathologist (J.C.C.) without the knowledge of patient outcome. The 2010 TNM classifications [13], tumor size, grade, and coagulative tumor necrosis were combined to calculate the Mayo Clinic SSIGN and PROG scores [14,15].

Disease status for patients in the Nephrectomy Registry is updated each year. For patients not seen at our institution within the previous year, a questionnaire is sent to the patient to ascertain disease status. For patients who document disease progression, the date, location, and treatment are verified in writing by the patient's local physician. Patient's vital status is similarly updated on a yearly basis. For patients who die within the previous year, a death certificate is ordered to determine the cause of death. If the patient was evaluated at our institution within 6 months of the date of death for metastatic RCC, then RCC is considered the cause of death. If the death certificate does not support this, the medical history is reviewed by an attending urologist to determine the cause of death, and if a death certificate cannot be obtained, the cause of death is verified by the patient's family or local physician.

Continuous features were summarized with medians, interquartile ranges (IQRs), and ranges; categorical features were summarized with frequency counts and percentages. Comparisons of features between patients who were and were not using beta-blockers were evaluated using Wilcoxon rank sum, chi-square, and Fisher exact tests. Progression-free survival (PFS), CSS, and overall survival (OS) were estimated using the Kaplan-Meier method. Progression was defined as local ipsilateral recurrence, local contralateral recurrence, distant metastases, or death from RCC. For PFS, the duration of follow-up was calculated from the date of surgery to the date of progression or last follow-up. For CSS and OS, the duration of follow-up was calculated from the date of surgery to the date of death or last follow-up. Associations of features with progression, death from RCC, and all-cause mortality were evaluated using Cox proportional hazards regression models and summarized with hazard ratios (HRs) and 95% CIs. Multivariable Cox proportional hazards regression models included the PROG score (in the PFS model), the SSIGN score (in the CSS model), and clinical characteristics of age, sex, symptoms at presentation, smoking history, renal function, Eastern Cooperative Oncology Group status, Charlson score, type of surgery, pathologic T and N classification, grade, and coagulative necrosis (in the OS model). Associations with the cumulative incidence of progression after accounting for the competing risk of death without progression and the cumulative incidence of death from RCC after accounting for the competing risk of death from non-RCC causes were evaluated using the proportional subdistribution hazards model [16,17]. Statistical analyses were performed using version 9.3 of the SAS software package (SAS Institute Inc., Cary, NC). All tests were two-sided, and $P < 0.05$ was considered statistically significant.

3. Results

We identified 913 hypertensive patients with clear-cell RCC (ccRCC) for analysis, of whom 104 (11%) had documented beta-blocker use within 90 days before surgery.