Pharmacological Research 113 (2016) 468–474

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Perspective

Medication use and survival in diabetic patients with kidney cancer: A population-based cohort study

Madhur Nayan[a], Erin M. Macdonald[b], David N. Juurlink[b,c], Peter C. Austin[b,d,e], Antonio Finelli[a], Girish S. Kulkarni[a], Robert J. Hamilton[a,*], for the Canadian Drug Safety and Effectiveness Research Network (CDSERN)

[a] Division of Urology, Departments of Surgery and Surgical Oncology, Princess Margaret Cancer Centre, University Health Network and the University of Toronto, Toronto, Canada
[b] Institute for Clinical Evaluative Sciences, Toronto, Canada
[c] Department of Internal Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada
[d] Institute of Health Management, Policy and Evaluation, University of Toronto, Toronto, Canada
[e] Schulich Heart Research Program, Sunnybrook Research Institute, Toronto, Canada

ARTICLE INFO

Article history:
Received 21 June 2016
Received in revised form
12 September 2016
Accepted 23 September 2016
Available online 24 September 2016

Keywords:
Kidney neoplasms
Diabetes mellitus
Hydroxymethylglutaryl-CoA reductase inhibitors
Anti-inflammatory agents
Non-steroidal
Metformin
Survival

ABSTRACT

Survival rates in kidney cancer have improved little over time, and diabetes may be an independent risk factor for poor survival in kidney cancer. We sought to determine whether medications with putative anti-neoplastic properties (statins, metformin and non-steroidal anti-inflammatory drugs (NSAIDs)) are associated with survival in diabetics with kidney cancer.

We conducted a population-based cohort study utilizing linked healthcare databases in Ontario, Canada. Patients were aged 66 or older with newly diagnosed diabetes and a subsequent diagnosis of incident kidney cancer. Receipt of metformin, statins or NSAIDs was defined using prescription claims. The primary outcome was all-cause mortality and the secondary outcome was cancer-specific mortality. We used multivariable Cox proportional hazard regression, with medication use modeled with time-varying and cumulative exposure analyses to account for intermittent use.

During the 14-year study period, we studied 613 patients. Current statin use was associated with a markedly reduced risk of death from any cause (adjusted hazard ratio 0.74; 95% CI 0.59–0.91) and death due to kidney cancer (adjusted hazard ratio 0.71; 95% CI 0.51–0.97). However, survival was not associated with current use of metformin or NSAIDs, or cumulative exposure to any of the medications studied.

Among diabetic patients with kidney cancer, survival outcomes are associated with active statin use, rather than total cumulative use. These findings support the use of randomized trials to confirm whether diabetics with kidney cancer should be started on a statin at the time of cancer diagnosis to improve survival outcomes.

1. Introduction

Kidney cancer is the most lethal and third most common urological malignancy, with an estimated 61,650 new cases and 14,080 deaths in the United States in 2015 [1]. Moreover, the incidence of kidney cancer has been rising in most countries [2], most likely because of greater use of diagnostic imaging and increasing rates of obesity and hypertension, established risk factors for the disease [3]. Despite an increase in incidence, survival rates have improved only marginally [4]. Furthermore, several studies demonstrate that patients with kidney cancer and pre-existing diabetes have poorer survival than those without diabetes [5,6]. In light of the increasing prevalence of diabetes [7] and studies suggesting that diabetes may be an independent risk factor for kidney cancer [8,9], research into improving outcomes in diabetics with kidney cancer is an increasingly important topic in oncology.

Several common medications have recently garnered interest for their putative anti-neoplastic effects, most notably statins [10], metformin [11,12] and non-steroidal anti-inflammatory drugs

* Corresponding author at: Division of Urology, Department of Surgery, Princess Margaret Cancer Centre, University Health Network, 610 University Ave 3-130, Toronto, Ontario, M5G 2M9, Canada.
E-mail address: rob.hamilton@uhn.ca (R.J. Hamilton).

http://dx.doi.org/10.1016/j.phrs.2016.09.027
1043-6618/

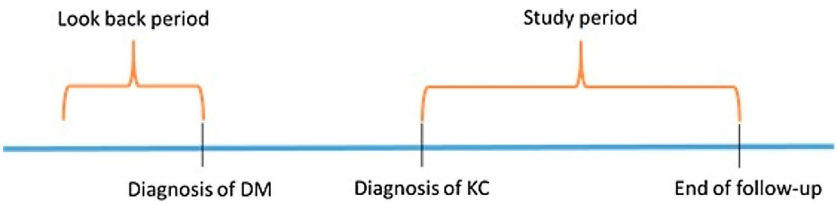

Fig. 1. Cohort of interest: patients with incident kidney cancer following diagnosis of incident diabetes.

(NSAIDs) [13]. To date, however, limited data exist on the influence of these medications in kidney cancer [14–25]. We sought to evaluate the association between use of statins, metformin, and NSAIDs and survival in patients with incident kidney cancer in the setting of type 2 diabetes.

2. Methods

2.1. Setting

We conducted a population-based retrospective cohort study of Ontarians aged 66 or older with kidney cancer in the setting of diabetes. This study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Ontario.

2.2. Data sources

We used the Ontario Diabetes Database to identify patients with diabetes [26], and the Ontario Cancer Registry [27] to identify patients with kidney cancer (ICD-9: 189.0; ICD-10: C64). We identified medication use through prescription claims of the Ontario Drug Benefit Database [28], which contains comprehensive records of prescription drugs dispensed to all Ontario residents aged 65 or older. We excluded subjects during their first year of eligibility for prescription drug coverage (age 65) to avoid incomplete assessment of medication use. We obtained hospitalization data from the Canadian Institute for Health Information Discharge Abstract Database [29], which contains detailed clinical information regarding all hospital admissions in Ontario. We used the Ontario Health Insurance Plan database to identify claims for physician services, and obtained basic demographic data and date of death from the Registered Persons Database, a registry of all Ontario residents eligible for health insurance. These databases were linked in an anonymous fashion using encrypted health card numbers. Details regarding all databases used and their validity are provided in Supplemental Methods 1.

2.3. Study participants

We identified patients with incident diabetes aged 66 or older. Among these patients, we studied those with kidney cancer first diagnosed after the diagnosis of diabetes (Fig. 1). All subjects had universal access to physician services, hospital care and prescription drug coverage. We accrued patients from April 1st, 1998, following them until December 31st, 2012 (for kidney cancer-specific mortality) and December 31st, 2014 (for all-cause mortality). These dates were based on the most recent update of the database used for each outcome.

We deemed study subjects to have localized kidney cancer at presentation if they underwent surgery (OHIP billing codes S411, S412, S413, S415, S416), radiofrequency ablation (OHIP billing code J069) or cryotherapy (OHIP billing code S400) as the first treatment following diagnosis of kidney cancer. Other subjects were deemed to have advanced disease if they received immunotherapy (OHIP billing codes G381, G281, G345, G359, G075, G390, G388) or no intervention as their first treatment following diagnosis of kidney cancer. This classification is consistent with other studies conducted in Ontario [30,31].

We excluded patients who died within 30 days of intervention (surgery, radiofrequency ablation, or cryotherapy), since this is unlikely to reflect the effects of medication exposure. We also excluded patients with any diagnosis of malignancy (excluding non-melanoma skin cancers) prior to their kidney cancer diagnosis in order to exclude patients whose overall survival may be influenced by a pre-existing malignancy. Finally, we excluded patients whose histology indicated a primary malignancy other than kidney cancer.

2.4. Exposure assessment

We quantified medication exposure from the diagnosis of kidney cancer to the end of follow-up using prescription dates and the number of days supplied in each, as done previously [32,33]. This allowed for calculation of the duration of cumulative exposure for each day of follow-up, as well as accounting for periods of intermittent use.

2.5. Outcome assessment

The primary outcome was all-cause mortality and the secondary outcome was kidney cancer-specific mortality. For each outcome, patients were followed until their date of last contact with health services, death or the end of the study period, whichever occurred first.

2.6. Statistical methods

We conducted time-to-event analyses using multivariable Cox proportional hazard regression to estimate the effect of drug exposure on the risk of the primary and secondary outcomes. For the secondary outcome, we focused on the cause-specific hazard of death from kidney cancer, accounting for the competing risk of death from other causes. Covariates in the model were selected a priori and include age at kidney cancer diagnosis, sex, duration of diabetes, comorbidity (defined by the Johns Hopkins Adjusted Clinical Groups score [34]), year of kidney cancer diagnosis (to account for temporal changes in exposure and outcomes), disease stage, rurality, socioeconomic status and exposure to each medication after kidney cancer diagnosis.

We evaluated the association between medication exposure and outcomes in two ways. First, we studied medication use as a time-varying covariate denoting whether or not the subject was actively receiving the medication of interest, determined using prescription claims. Second, we examined cumulative medication use as a time-varying covariate (Supplemental Methods 2). Both of these models account for intermittent use; however, they evaluate different hypotheses. In the time-varying analyses, a patient can contribute survival time to both the exposed and unexposed group, based on the date and duration of their prescription, offsetting the selection bias associated with a simple comparison of