Trends of Systemic Therapy Use for Renal Cell Carcinoma in the United States

Elizabeth K. Ferry, Brian J. Minnillo, Matthew J. Maurice, Robert Abouassaly, and Hui Zhu

OBJECTIVE To assess the utilization of immunotherapy after the advent of tyrosine-kinase inhibitors and mammalian target of rapamycin inhibitors for metastatic renal cell carcinoma (RCC) in the United States, as well as to better understand the variables associated with the implementation of these systemic therapies.

METHODS The National Cancer Data Base Participant User File for Renal Cancer was queried. Patients diagnosed with metastatic RCC were identified. From that group, patients who received either immunotherapy or chemotherapy (single or multiagent), given as a first-course therapy from 1998 to 2011 were selected. Multivariate analysis was used to assess patient, disease, and provider factors associated with immunotherapy or chemotherapy overall usage between 2003 and 2011.

RESULTS A total of 25,186 patients diagnosed with metastatic RCC were identified; 3107 received immunotherapy and 8640 received chemotherapy. The use of immunotherapy decreased from 30.3% in 1998 to 3.8% in 2011. The use of chemotherapy increased from 16.2% in 1998 to 54.0% in 2011. The most dramatic period of change was from 2004 to 2006. Independent negative predictors of receiving immunotherapy included progressive years of diagnosis ($P < .0001$), increasing age ($P < .0001$), female gender ($P = .001$), and African American race ($P = .04$).

CONCLUSION There has been a significant decrease in the use of immunotherapy for metastatic RCC in the United States since the introduction of targeted chemotherapeutic agents in the past decade. UROLOGY 85: 1399–1403, 2015. © 2015 Elsevier Inc.

The incidence of renal cell carcinoma (RCC) in the United States has been gradually increasing since the 1970s,[1,2] especially for higher grade disease and in younger patients.[3] Until the end of the 20th century, no effective systemic therapy was available for the treatment of RCC. In patients with metastatic disease, 5-year survival at that time was estimated at <10%[4] and median survival was less than a year.[5] In the early 1990s, immunotherapy with interferon alpha and interleukin 2 (IL-2) was popularized and regarded as the standard of care for metastatic RCC. The Food and Drug Administration approved high-dose IL-2 in 1992, and prolonged remission and even cures were reported, although only 15%-20% of patients respond and 7%-9% achieve complete regression.[6-8] Additionally, patients commonly experienced significant hypotension and fevers and required inpatient admission, occasionally to the intensive care units, during their treatment.[9] In the early 21st century, targeted chemotherapy was introduced in the form of tyrosine-kinase inhibitors and mammalian target of rapamycin inhibitors. These new treatments boasted applicability to a broader patient population, improved side effect profiles, and more convenient oral dosing strategies. Although curative responses were not attained, modest improvements in overall survival and significantly prolonged progression-free survival were documented.[10-13]

Despite the advantages of targeted chemotherapeutic agents, immunotherapy with high-dose IL-2 remains the only opportunity for cure among patients with advanced RCC. This study aims to assess the utilization of immunotherapy after the advent of tyrosine-kinase inhibitors and mammalian target of rapamycin inhibitors for metastatic RCC in the United States, as well as to better understand the variables associated with the implementation of these systemic therapies.

METHODS

The National Cancer Data Base (NCDB) Participant User File for Renal Cancer was obtained. The NCDB is cooperatively sponsored by the Commission on Cancer (CoC) of the

Financial Disclosure: *The authors declare that they have no relevant financial interests.*

From the Urology Institute, University Hospitals Case Medical Center, Cleveland, OH; the Case Western Reserve University School of Medicine, Cleveland, OH; the Louis Stokes Cleveland Veterans Affairs Medical Center, Cleveland, OH; the Department of Urology, Glickman Urological and Kidney Institute, Cleveland, OH; and the Cleveland Clinic, Cleveland, OH

Address correspondence to: Elizabeth K. Ferry, M.D., Urology Institute, University Hospitals Case Medical Center, 11100 Euclid Avenue, Cleveland, OH 44106. E-mail: Elizabeth.Ferry@UHhospitals.org

Submitted: November 19, 2014, accepted (with revisions): March 9, 2015

Table 1. Patient characteristics overall, as well as in those who received either immunotherapy or chemotherapy for metastatic RCC

Patient Characteristics	Total (%)	Immunotherapy (%)	Chemotherapy (%)
Total	25,206	3107	8640
Age (y)			
<50	3303 (13)	659 (21)	1224 (14)
50-59	6738 (27)	1059 (34)	2568 (30)
60-69	7605 (30)	883 (28)	2764 (32)
70-79	5455 (22)	446 (14)	1640 (19)
≥80	2105 (8)	60 (2)	444 (5)
Gender			
Male	16,778 (67)	2221 (71)	5885 (68)
Female	8428 (33)	886 (29)	2755 (32)
Race			
White	21,962 (87)	2790 (90)	7558 (87)
Black	2233 (9)	200 (6)	744 (9)
Other	1011 (4)	117 (4)	338 (4)
Insurance status			
Medicare/medicaid	10,584 (42)	866 (30)	3273 (41)
Private/managed	12,551 (50)	2014 (70)	4730 (59)
Charlson score			
0	13,067 (52)	998 (78)	5594 (74)
1	3497 (14)	214 (17)	1483 (20)
2	1367 (5)	61 (5)	484 (6)
Hospital type			
Community	2770 (11)	266 (9)	925 (11)
Comprehensive	12,958 (51)	1403 (45)	4560 (53)
Academic/research	8916 (35)	1371 (44)	3031 (35)
Other	562 (2)	67 (2)	124 (1)
Tumor size (cm)			
<4	1883 (7)	196 (6)	616 (7)
4-7	5119 (20)	572 (18)	1658 (19)
8-10	6131 (24)	783 (25)	2281 (26)
11-14	4770 (19)	665 (21)	1885 (22)
>14	7202 (29)	889 (29)	2165 (25)

RCC, renal cell carcinoma.

American College of Surgeons and the American Cancer Society and captures 70% of all newly diagnosed cancer cases in the United States and Puerto Rico. The NCDB collects deidentified individual patient information from CoC-accredited cancer programs using nationally standardized coding definitions.[14] The strict quality control used within the NCDB and its applicability to research in trends of cancer care has been detailed elsewhere.[15]

Patients diagnosed with histologically confirmed synchronous metastatic clear-cell RCC or RCC not otherwise specified, without additional malignancies, were included from the NCDB Participant User File. From that group, patients who received either first-course immunotherapy or chemotherapy (single or multiagent) were identified. Systemic therapies and surgical procedures may both be provided as parts of the first course of treatment within NCDB coding. CoC-accredited reporting institutions are also required to report the use of systemic therapies from any institution for an individual patient.[16]

Utilization of immunotherapy and chemotherapy were separately analyzed by year of diagnosis to assess overall trends between 1998 and 2011. The trends were assessed by graphing the percentage of patients who underwent immunotherapy or chemotherapy of the total number of patients diagnosed with metastatic RCC in each year.

Multivariate analysis was performed to identify factors that independently predicted the type of systemic therapy implemented from 2003 to 2011. Variables analyzed included patient (age, gender, race, Charlson score, and insurance status), provider (hospital type), disease (tumor size), and treatment (use of cytoreductive nephrectomy) factors, as well as year of diagnosis. Cytoreductive nephrectomy was defined using the surgery-to-primary-site codes. These included subtotal, simple, complete, radical nephrectomy, and nephrectomy not otherwise specified with or without the removal of other involved organs.

Statistical Analysis

Statistical analyses were performed using SAS v9.3 (SAS Institute Inc., Cary, NC). Continuous variables were analyzed using a 2-tailed Student *t* test. Categorical variables were analyzed using a chi-square test. Multivariate logistic regression was used to assess the impact of patient, provider, and disease variables on the probability of immunotherapy and chemotherapy use. Odds ratios and 95% confidence intervals were obtained for each variable. Logistic model calibration and discrimination were assessed with the Hosmer-Lemeshow goodness-of-fit test. *P* values <.05 were considered statistically significant.

RESULTS

A total of 25,186 patients with histologically confirmed metastatic RCC diagnosed between 1998 and 2011 were identified (Table 1). Of these, 3107 patients received