Improvement in Overall Survival of Patients with Advanced Renal Cell Carcinoma: Prognostic Factor Trend Analysis from an International Data Set of Clinical Trials

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Purpose: We assessed temporal shifts in the frequency of risk factors for patients with metastatic renal cell carcinoma in a multicenter, international data set.

Materials and Methods: An international database of 3,748 patients treated with systemic therapy for metastatic renal cell carcinoma from 1975 to 2002 was constructed by pooling clinical trial data. Proportions of previously identified risk factors were examined during 6 specified time cohorts. Overall survival for each cohort was examined using the Kaplan-Meier method. Trends in overall survival from 1973 to 2008 were also examined in 25,271 patients from the SEER (Surveillance, Epidemiology and End Results) database.

Results: Median overall survival from start of treatment increased with each consecutive time cohort group. In the earliest cohort median overall survival was 0.5 years (95% CI 0.43–0.57), which increased to 1.63 years (95% CI 1.28–1.79) in 2001 to 2002. More patients had a history of nephrectomy in the most recent cohort ($p = 0.001$). The proportion of patients with low performance status, high lactate dehydrogenase and high adjusted calcium decreased by study entry year (each $p < 0.01$). Analysis of overall survival from the SEER database showed similar improvement in the more contemporary diagnosis cohorts ($p < 0.001$). Two-year overall survival in the earliest and latest diagnosis cohort was 14% (95% CI 13–14) and 22% (95% CI 21–24), respectively.

Conclusions: Higher representation of favorable risk factors in recent years may have partly contributed to the improvement in overall survival observed in more recent metastatic renal cell carcinoma clinical trials. These shifts could affect the outcome interpretation.

Key Words: kidney; carcinoma, renal cell; neoplasm metastasis; risk; SEER program

Abbreviations and Acronyms

ECOG = Eastern Cooperative Oncology Group

IFN = interferon-α

LDH = lactate dehydrogenase

mRCC = metastatic renal cell carcinoma

MSKCC = Memorial Sloan-Kettering Cancer Center

OS = overall survival

PS = performance status

TKI = tyrosine kinase inhibitor

ULN = upper limit of normal

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THE outlook for patients with mRCC has been historically poor with a 5-year survival rate of less than 10% for those presenting with stage IV disease.[1] Until recently, cytokines were widely used as first line mRCC therapy, which resulted in modestly improved response and survival rates. In pivotal phase III trials sunitinib, temsirolimus and bevacizumab (administered with IFN) showed superior efficacy compared with IFN alone and were incorporated into standard treatment, resulting in improved prognosis and a new treatment paradigm for patients with mRCC.[2–5]

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Prognostic factors are used in mRCC clinical trial design and interpretation, risk directed treatment and patient counseling.[6] The model developed at MSKCC classifies patients as at favorable, intermediate and poor risk according to the number of risk factors predictive of survival.[7–10] This model was validated externally and independently, and has been widely used in the research of cytokine, anti-angiogenic and targeted therapies. For example, sunitinib, bevacizumab plus IFN or pazopanib has been cited as preferred treatment for patients with mRCC with favorable or intermediate risk features, while temsirolimus has been recommended for those at poor risk with mRCC.[11] These risk groups were also part of a recent nomogram to guide mRCC treatment.[12]

In the current analysis we investigated whether changes in the distribution of known mRCC prognostic factors could contribute to the improvement in OS. A 2010 analysis showed a change in the MSKCC risk group distribution of patients in clinical trials done at this institution.[6] There has been an upward shift of prognostic features with time with the proportion of patients in the poor risk group decreasing and a larger proportion of patients qualifying for the favorable risk group. This migration may be attributable to earlier, more precise diagnosis, thereby increasing 5-year OS rates. Observed trends could also be due to more stringent clinical trial eligibility criteria.

Recently, Manola et al developed and validated a prognostic model in a multicenter, international cohort of patients with previously untreated mRCC.[13] We used this data set to study trends in the distribution of prognostic factors and OS. To understand the role of clinical trial eligibility on OS trends, we examined data from SEER, a population based cohort of incident cases in the United States, for trends in OS.

PATIENTS AND METHODS

Patients

The International Kidney Cancer Working Group established a comprehensive database of potential prognostic factors for survival in patients with previously untreated mRCC. The resulting data set included 3,748 patients with no prior systemic therapy. They were treated from 1975 to 2002 and were pooled from clinical trials led by groups from 11 centers or groups in the United States and Europe. Systemic therapy included cytokines, chemotherapy or various investigational agents. Details on the data set and the resulting prognostic factor analysis were previously reported.[13] Each clinical trial was approved by the institutional review board or independent ethics committee at each center.

Analysis

The primary aim of our study was to assess changes in the proportion of patients with mRCC with time according to each of 12 risk factors and disease characteristics, including ECOG PS (0 vs 1 vs 2 to 4), high LDH (greater than 1.5 × ULN), low serum hemoglobin (less than lower limit of normal), high corrected serum Ca (greater than 10 mg/dl), less than a 1-year interval from diagnosis to treatment, high alkaline phosphatase (greater than ULN), high neutrophils (greater than ULN), more than 1 metastatic site, no nephrectomy and the presence of lung, liver and/or bone metastases. The proportion of each risk factor was calculated by cohort, as defined by the year that treatment began. The frequency of the 5 risk factors used in the MSKCC model (less than 1-year interval, LDH, Ca, hemoglobin and PS)[7–10] was used to stratify patients into groups, including 0—favorable, 1 or 2—intermediate and 3 or greater—poor risk. To define the MSKCC groups PS was categorized as ECOG 0 vs 1 or greater.

Median OS for each of the 6 cohorts was calculated using Kaplan-Meier methods. OS was defined as the date of clinical trial entry to the date of last followup. Trends of each of the 12 risk factors across cohorts were tested by logistic regression with each cohort entered as a continuous variable and the binary risk factor as the dependent variable.

Missing Data

The overall percent of missing data was 0% to 42%. The highest magnitude of this gap was for LDH (37%), alkaline phosphatase (41%) and neutrophils (42%). All other variables had a missing rate of below 6%.

To make complete use of all data, multiple imputation with 5 imputations was used for all except Kaplan-Meier analyses.[14–16] We used a sequential regression methodology, as implemented by IVEware.[17] Using this methodology a sequence of regression models is fit and values are drawn from the corresponding predictive distributions.

Demographic data and all other variables reported in this study were included in the imputation. Research center was included to account for any center specific differences. Survival time was represented in the model by the cumulative hazard function, along with the censoring indicator.[18] Skewed variables were transformed toward normality and back transformed after the imputation procedure.

SEER Database

OS trends from 1973 to 2008 were examined in 25,271 patients with incident, distant kidney cancer from the SEER public use registry database (http://www.seer.cancer.gov). Patients were included in analysis if the primary tumor site was the kidney (94%) or renal pelvis (6%), the cancer recorded was a single primary tumor, or the first of 2 or more primary tumors and a diagnosis of distant disease was recorded. Distant disease was assessed using SEER summary and historical stage. According to the Summary Staging Manual 2000 (http://seer.cancer.gov/tools/ssm/), distant disease is defined as distant lymph node involvement, contiguous extension into the aorta, adrenal, kidney, ureter, liver, ribs, spleen or stomach, or other direct extensions or documented metastasis. SEER data do not include detailed information on therapy. Consequently, date of diagnosis was used to group patients into cohorts. The Kaplan-Meier method was used to estimate OS by