Prognostic Factors for Survival of Patients with Stage IV Renal Cell Carcinoma: Memorial Sloan-Kettering Cancer Center Experience

Robert J. Motzer, Jennifer Bacik, and Madhu Mazumdar
Genitourinary Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, and the Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, Boston, Massachusetts

ABSTRACT
Prospective identification of patients with stage IV renal cell carcinoma more likely to benefit from cytokine therapy could be used as a stratification factor in Phase III trials and in risk-directed therapy. The relationship between pretreatment clinical features and survival was evaluated in patients treated in Phase II and III clinical trials for metastatic renal cell carcinoma at the Memorial Sloan-Kettering Cancer Center. The first analysis was performed in 670 patients treated with cytokines or chemotherapy, and a multivariate model was created to predict survival. Studies that followed addressed four topics: (1) the survival of patients given interferon α as first-line therapy, (2) a comparison of survival for patients treated with chemotherapy versus cytokine therapy, (3) survival of patients with non-clear cell histologic features, and (4) survival of patients treated with a second-line therapy. Prognostic models based on pretreatment clinical and laboratory variables can help identify patients more likely to benefit from standard therapies, as well as assist in the interpretation of drug effectiveness in Phase II clinical trials. Investigations into new prognostic factors based on tumor biology are needed and of high priority.

INTRODUCTION
Metastatic renal cell carcinoma is highly resistant to chemotherapy. Interferon α and interleukin 2 have a low level of antitumor activity, and the identification of new agents with better antitumor activity against metastases is a high priority. The identification of prognostic factors is important in assessing treatment outcome of new therapies studied in Phase II and III trials and in adapting risk-directed therapy to patients with metastatic renal cell carcinoma who are treated with immunotherapy.

The relationship between pretreatment clinical features and survival was studied with patients treated in clinical trials for metastatic renal cell carcinoma at the Memorial Sloan-Kettering Cancer Center. The primary analysis was performed in 670 patients treated with mixed therapies, and a multivariate model was derived to predict survival. Studies that followed addressed the survival of patients given interferon α as first-line therapy, the role of risk-directed therapy, the prognosis for patients with non-clear cell histologic features, and prognostic factors for survival in patients treated previously to second-line therapy.

MEMORIAL SLOAN-KETTERING CANCER CENTER PRIMARY ANALYSIS
The study was performed with patients with advanced renal cell carcinoma treated in clinical trials of immunotherapy (regimen included interferon α, interleukin 2, or both as a component) or chemotherapy (1). The median survival time for the 670 patients was 10 months. The proportion of patients surviving at 1 year was 42%; the 2- and 3-year survival proportions were 20% and 11%, respectively. Pretreatment features associated with a shorter survival in the multivariate analysis were low Karnofsky performance status (<80%), high lactate dehydrogenase level (>1.5 times the upper limit of normal), low hemoglobin level (less than the lower limit of normal), high corrected serum calcium level (>10 mg/dL), and absence of nephrectomy. These five prognostic factors were used to categorize patients by prognosis into three different risk groups. The median time to death in patients with zero risk factors (favorable risk) was 20 months. The median survival time for patients with one or two of these prognostic features (intermediate risk) was 10 months. Patients with three or more risk factors (poor risk) had a median survival of 4 months.

The predictive performance of the model was internally validated through a two-step nonparametric bootstrapping process. The model was also applied to an external data set from the Eastern Cooperative Oncology Group, which was composed of 175 patients treated with interferon α therapy in a Phase III randomized trial. In this cohort, the median survival times of favorable-, intermediate-, and poor-risk patients were 29, 14, and 4 months, respectively.

RISK-DIRECTED THERAPY
Survival according to treatment with either cytokine therapy (interferon α or interleukin 2) or chemotherapy was compared (2). Patients treated with cytokine therapy had a longer survival compared with patients treated with chemotherapy. When compared according to risk group, the median survival times for favorable-risk, intermediate-risk, and poor-risk patients treated with cytokines were 27, 12, and 6 months, respectively. The median survival times for patients treated with chemotherapy were 15, 7, and 3 months for the three risk groups, respectively. The data suggest that patients with favorable prognostic features may derive benefit from cytokine ther-
apy, whereas patients with poor-risk features had a short survival regardless of type of treatment.

**INTERFERON FIRST-LINE THERAPY**

The primary analysis contained patients treated with varied systemic therapies, and ~20% had received prior therapy (1). Reducing heterogeneity prompted an analysis on prognostic factors for survival after interferon α therapy for patients untreated previously (3). The median overall survival time for the 463 patients was 13 months. The proportion of patients surviving at 1 and 3 years was 54% and 19%, respectively. Five variables were selected by univariate and multivariate analysis and used as risk factors for short survival: low Karnofsky performance status, high lactate dehydrogenase level, low serum hemoglobin level, high “corrected” serum calcium level, and time from initial renal cell carcinoma diagnosis to start of interferon α therapy of <1 year. The median time to death of patients deemed to be at favorable risk (zero risk factors) was 30 months. Median survival in the intermediate-risk group (one or two risk factors) was 14 months. In contrast, the poor-risk group (three or more risk factors) had a median survival of 5 months.

**NON-CLEAR CELL HISTOLOGIC FEATURES**

Progress in understanding the genetic features of renal cell carcinoma has facilitated classification into clear cell and non-clear cell subtypes such as papillary, chromophobe, and collecting duct carcinoma. The outcome data for 64 patients with carcinomas other than clear cell type were reviewed (4). The most prevalent carcinoma was collecting duct, present in 26 patients (41%). The number of patients with chromophobe and papillary histologic findings was 12 (19%) and 18 (28%), respectively. Eight (12%) of the patients had tumors that could not be classified for specific tumor type. Among the 43 patients treated with 86 systemic therapies, including 37 cytokine therapies, 2 patients (5%) were observed to have a partial response, 1 to interferon and 1 to gemcitabine chemotherapy. The median overall survival time was 9.4 months. The survival was longer for patients with chromophobe tumors compared with collecting duct or papillary tumors, and this group included patients with survival of >3 years.

**PROGNOSTIC FACTORS TO SECOND-LINE THERAPY**

Survival in patients treated previously with metastatic renal cell carcinoma was assessed in 251 patients treated in 29 clinical trials between 1975 and 2002 (5). The patients included in this retrospective series had been treated in clinical trials of new agents given as salvage therapy at Memorial Sloan-Kettering Cancer Center. Median survival for the 251 patients was 10.2 months and differed according to year of treatment, with patients treated after 1990 showing longer survival. In this group, the median overall survival time was 12.7 months. Because the purpose of this analysis was to establish prognostic factors for present-day clinical trial design, prognostic factor analysis was performed on these patients and then applied to patients treated in the early years. Pretreatment features associated with a shorter survival by multivariate analysis were low Karnofsky performance status, low hemoglobin level, and high “corrected” serum calcium level.

**CONCLUSIONS**

Prognostic models based on pretreatment clinical and laboratory variables can help define patients more likely to benefit from standard therapies, as well as assist in the interpretation of drug effectiveness in Phase II clinical trials. Investigations into new prognostic factors based on tumor biology are needed and of high priority.

**OPEN DISCUSSION**

**Dr. Michael Atkins:** Do you get any sense of a relationship between the symptoms or the laboratory abnormalities that you have described and tumor histology?

**Dr. Robert J. Motzer:** When we’ve looked at histology for the patients who have metastatic disease, about 95% have clear cell cancer. So the population that this primarily applies to is clear cell cancer patients. With regard to anemia and erythrocytosis, erythrocytosis is certainly reported in renal cell carcinoma and is probably higher than any other malignancies, but by far the more common clinical scenario is that patients with metastatic renal cancer have anemia.

**Dr. W. Marston Linehan:** I predict that the papillary tumors that are confined to the kidney are papillary type 1, which tend to spread much less, while those with metastases are papillary type 2 tumors that tend to spread quickly and progress rapidly.

**Dr. Motzer:** I agree with that. We are probably selecting out the type 2 patients.

**Dr. Michael Gordon:** It would be interesting to have a readily available test that measured erythropoietin (EPO) levels in patients and recreated the EPO hemoglobin graph. It would be interesting to see whether patients with mutated VHL fell on a particular line because of an inappropriately high production of EPO regardless of their hemoglobin. I don’t know if anyone has ever looked at that. It could be a poor man’s surrogate in some way for identifying the people who had the sporadic VHL mutations.

**Dr. Motzer:** We set up a study and measured levels, and the EPO levels varied widely.

**REFERENCES**

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