Prognostic Factors in Patients Receiving Third Line Targeted Therapy for Metastatic Renal Cell Carcinoma

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Purpose: Several prognostic models have been proposed for metastatic renal cell carcinoma but none has been validated in patients who receive third line targeted agents. We evaluated prognostic factors in patients with metastatic renal cell carcinoma who received a third line targeted agent.

Materials and Methods: We retrospectively reviewed data on 2,065 patients with clear cell metastatic renal cell carcinoma who were treated with targeted therapy at a total of 23 centers in Italy. Included in final analysis were 281 patients treated with 3 targeted agents. Overall survival was the main outcome. Cox proportional hazards regression followed by bootstrap validation was used to identify independent prognostic factors.

Results: Three clinical characteristics (ECOG performance status greater than 1, metastasis at diagnosis and liver metastasis) and 2 biochemical factors (hemoglobin less than the lower limit of normal and neutrophil count greater than the upper limit of normal, respectively) were prognostic. Patients were classified into 3 risk categories, including low—zero or 1, intermediate—2 and high risk—more than 2 risk factors. Median overall survival was 19.7, 10.1 and 5.5 months, and 1-year overall survival was 71%, 43% and 15%, respectively. The major limitation was the retrospective nature of this study and absent external validation.

Conclusions: This nomogram included clinical and biochemical prognostic factors. In clinical trials it may be useful to select patients and define the prognosis.

Abbreviations and Acronyms

CCF = Cleveland Clinic Foundation

C-index = concordance index

ECOG = Eastern Cooperative Oncology Group

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium

IRTL = Italian Renal Cell Carcinoma Third-Line

LLN = lower limit of normal

MIRS = median improvement in risk scores

mRCC = metastatic renal cell carcinoma

MSKCC = Memorial Sloan Kettering Cancer Center

NRI = net reclassification index

OS = overall survival

PS = performance status

ULN = upper limit of normal

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Study received internal review board approval.

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TREATMENT of mRCC has dramatically changed since targeted agents were introduced in the clinical armamentarium. Despite the low curative rate median OS has increased with time from 10 months in the cytokine era to about 30 months in the targeted therapy era.[1–3]

Increased survival and the growing number of available targeted agents have resulted in the treatment of a greater number of patients with 2 or more lines of therapy. Considering this wealth of new agents identifying prognostic factors remains a cornerstone of clinical management of advanced disease. Prognostic factors allow patient stratification based on the cancer related risk of death and provide important information on disease evolution. Moreover, this allows homogeneous stratification of patients for clinical trials to avoid selection related bias and consequently identify the group in which a target agent has the greatest activity.

To date the most frequently used prognostic criteria have been those described by Motzer et al in patients treated with interferon immunotherapy and chemotherapy at MSKCC.[4] These criteria were validated in a retrospective analysis of 353 patients treated at CCF.[5]

Heng et al subsequently reported a large analysis in patients treated with tyrosine kinase inhibitors as first or second line therapy and included in the IMDC.[6] The role of low hemoglobin and high serum corrected calcium, such as Karnofsky PS and time from diagnosis to therapy initiation, were confirmed as independent predictors of short survival. Neutrophil and platelet counts greater than the ULN were also prognostic. Similar to previous analysis[7] there was no prognostic difference when patients received targeted agents as first line therapy or after cytokines.[6] Moreover, the role of histology was not investigated.

Despite validation in therapy naïve patients the MSKCC model has also been used in patients enrolled in second line trials. More recently the IMDC model confirmed its discriminatory capacity in this setting.[8]

We evaluated prognostic factors in patients with mRCC who received a third line targeted agent and we compared these factors to current nomograms.

PATIENTS AND METHODS

Patients

We retrospectively reviewed data on 2,065 patients with mRCC treated with targeted therapy at a total of 23 centers in Italy. Only patients who received 3 lines of targeted agents were included in final analysis. Patient inclusion criteria were diagnosis of clear cell mRCC and treatment with 3 targeted therapies. Patients treated with a combination of therapies or previously with cytokines were excluded from study.

Baseline demographic, clinical and laboratory data, and characteristics previously found to have prognostic value were collected retrospectively using uniform database templates to ensure consistent data collection. OS outcome data were obtained from patient files and by telephone contact. The study received internal review board approval.

Statistical Analysis

The primary outcome was OS, defined as time from third line therapy initiation to death from any cause or censoring at the date of last followup. Median OS with the 95% CI was estimated by the Kaplan-Meier method. Associations between OS and potential prognostic factors were assessed by the log rank test on univariable analysis with p values adjusted for multiplicity using the Bonferroni correction. The Cox proportional hazards model was then fitted on multivariate analysis. Model selection was performed using a forward stepwise procedure. The proportionality of hazards assumption was assessed graphically by using plots of log (log[survival]) vs log of survival time.

After prognostic factors were identified and the final model was fit a risk group variable was created by counting the number of unfavorable features per patient. The predictive performance of the newly constructed score(s) was assessed by the C-index, which corresponds to the ROC AUC and represents the ability of a score to correctly predict events. A C-index of 1 indicates perfect ability to distinguish patients, greater than 0.5 indicates good predictive ability and 0.5 indicates no predictive ability.

We also assessed the predictive performance of the final model by internal validation using 2-step bootstrap resampling procedures. As the first step 1,000 bootstrap samples were generated randomly with replacement from the original study population. The stepwise Cox regression procedure was used for each sample with the same selection criteria as the original modeling, as described. We then calculated the frequency of including each variable in the resulting models in the 1,000 bootstrap samples. Risk factors present in more than 50% of the models were considered significant.

As the second validation step we validated parameter estimates of the final model. We generated 1,000 bootstrap samples randomly from the original study population for the final model. For each sample we refit the Cox regression model using the variables selected in the final model and calculated regression parameters and HRs. The mean, SD and CI were calculated from the 1,000 samples and compared to those of the model using the original study population.

Improvement compared to other scores was assessed by continuous NRI and MIRS, which were calculated as