Original Study

Heterogeneity of Patients With Intermediate-Prognosis Metastatic Renal Cell Carcinoma Treated With Sunitinib

Avishay Sella,[1] M. Dror Michaelson,[2] Ewa Matczak,[3] Ronit Simantov,[3] Xun Lin,[4] Robert A. Figlin[5]

Abstract

Using data from 6 prospective clinical trials of sunitinib for metastatic renal cell carcinoma, we characterized the heterogeneity of patients identified as having an intermediate prognosis using the Memorial Sloan Kettering Cancer Center and International Metastatic Renal Cell Carcinoma Database Consortium risk models. In this group, the number of risk factors and Eastern Cooperative Oncology Group performance status might predict the outcome with sunitinib therapy.

Background: The Memorial Sloan Kettering Cancer Center (MSKCC) and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) models categorize patients with 1 or 2 risk factors as intermediate prognosis (INTMP). This category encompasses 15 and 19 permutations of the MSKCC and IMDC risk factors, respectively. The purpose of the present retrospective analysis of data from INTMP patients in 6 clinical trials was to determine whether this heterogeneity influences the response to sunitinib. **Patients and Methods:** Patients with INTMP metastatic renal cell carcinoma (mRCC) were identified using the MSKCC and IMDC classifications. The statistical data were analyzed using Cox regression analysis, Kaplan-Meier methods, and Pearson χ^2 tests. **Results:** The patient characteristics and risk factors were similar in the MSKCC (n = 548) and IMDC (n = 517) groups. Overall, 59% had 1 risk factor and 41% had 2 risk factors. The most common was low hemoglobin alone or with an interval of < 1 year since diagnosis. In both groups, patients with 1 risk factor had longer overall survival (OS) and progression-free survival (PFS) than did those with 2 risk factors ($P < .001$ for both outcomes). Patients in the IMDC group with 1 risk factor had a greater objective response rate (ORR; $P = .023$). In both groups, OS was longer for patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 0 than for those with ECOG PS 1 or 2 ($P < .001$). An ECOG PS of 0 was also associated with superior PFS and ORR in the MSKCC group ($P < .05$). **Conclusion:** INTMP comprises a heterogeneous group of mRCC patients in whom the number of risk factors and ECOG PS might predict the outcome with sunitinib.

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Introduction

Patients with metastatic renal cell carcinoma (mRCC) have diverse clinical characteristics and prognoses. The complexity of mRCC demands a patient-focused approach to treatment decisions, accounting for the individual patient's clinical and laboratory characteristics. This individualized approach is challenging to apply during the drug development process. Predictive models based on prognostic factors have been developed and used in clinical trials.[1-4] Among the most widely used is the Memorial Sloan Kettering Cancer Center (MSKCC) risk model, which was based on data from patients who participated in cytokine clinical trials. The MSKCC model stratifies patients with mRCC into 3 prognostic groups according to 5 risk factors: (1) low serum hemoglobin (Hgb); (2) elevated corrected serum calcium; (3) elevated serum lactate dehydrogenase; (4) poor performance status (PS); and (5) an interval of < 1 year between diagnosis and treatment.[3,4] Another widely used model is the International mRCC Database Consortium

[1]Sackler School of Medicine, Tel-Aviv University, Assaf Harofeh Medical Center, Zerifin, Israel
[2]Massachusetts General Hospital Cancer Center, Boston, MA
[3]Pfizer Oncology, New York, NY
[4]Pfizer Oncology, La Jolla, CA
[5]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA

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Address for correspondence: Avishay Sella, MD, Department of Oncology, Assaf Harofeh Medical Center, Zerifin 73100, Israel
E-mail contact: a_sella@asaf.health.gov.il

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(IMDC) classification, which was derived from patients receiving targeted treatments both on and off clinical trials. Four of the 5 variables included in the MSKCC model (Hgb, serum calcium, PS, and interval from diagnosis to treatment) and 2 additional factors (increased neutrophil count and platelet count) are incorporated into the IMDC model, which has been shown to independently predict survival.[1,2]

Both models segregate mRCC patients into 3 categories: favorable-, intermediate-, and poor-risk groups. The intermediate-prognosis (INTMP) risk group is characterized by the presence of 1 or 2 factors; hence, 15 possible permutations exist for the 5 risk factors in the MSKCC model and 19 permutations of the 6 risk factors in the IMDC model.[1-4] Therefore, patients within the INTMP category might differ, depending on the types of risk factors that determined their placement into this category. For example, a patient who has an intermediate risk based on 1 laboratory finding might differ from that of a patient with 2 clinical characteristics.

The efficacy and safety of the multitargeted receptor tyrosine kinase inhibitor (TKI), sunitinib malate (Sutent; Pfizer Inc, New York, NY), for first- and second-line treatment of mRCC has been established in prospective clinical trials.[5-10] The objective of the present analysis was to characterize the heterogeneity of patients identified as having an intermediate prognosis using the MSKCC and IMDC risk models and to determine the responses to sunitinib in patients with INTMP mRCC, including defined subpopulations of this risk group.

Patients and Methods

Study Designs and Treatment

The present retrospective analysis used pooled results from a database of 1059 patients with mRCC who were enrolled in 6 sunitinib clinical trials from January 2003 to June 2008 for the first-line (n = 783; 74%) and second-line (n = 276; 26%) treatment settings.[5-10] Five of these studies were phase II (ClinicalTrial.gov identifiers, NCT00054886, NCT00077974, NCT00137423, NCT00338884, and NCT00267748), and 1 was phase III (ClinicalTrial.gov identifier, NCT00083889). Sunitinib was administered according to one of the following schedules: 50 mg once daily for 4 consecutive weeks followed by 2 weeks without treatment in repeated 6-week cycles (n = 689; 65%) or 37.5 mg on a continuous once-daily dosing schedule (n = 370; 35%). The present analysis focused on the results in the sunitinib arms of each study, not the control arms.

The institutional review boards or ethics committees approved the studies. The principles of the Declaration of Helsinki were followed. Each participant provided written informed consent.

The efficacy endpoints used in the 6 clinical trials included the objective response rate (ORR) and progression-free survival (PFS), both assessed by investigators using the Response Evaluation Criteria for Solid Tumors, version 1.0,[11] and overall survival (OS). The PFS events included progression or death from any cause during study treatment or the 28-day follow-up period. OS events included death from any cause at the time of the database lock for OS analysis. Patients who were alive when the database was closed were censored on the date they were last known to be alive.

Population

The key eligibility criteria common to all 6 studies included age $\geq$ 18 years, histologically confirmed mRCC, the presence of measurable disease, no known brain metastases, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 (or Karnofsky PS of $\geq$ 70% in 1 trial[7]), and adequate organ function.

Analytical Method and Statistical Analysis

Pooled analyses were performed on the total INTMP population and patient subgroups, defined by the presence of 1 versus 2 risk factors and ECOG PS 0 versus 1 or 2. The median PFS and OS were estimated using the Kaplan-Meier method for each subgroup, with 95% confidence intervals (CIs) calculated using the Brookmeyer and Crowley method. Between-group comparisons were performed using a log-rank test. Hazard ratios (HRs) for these comparisons were calculated using a Cox proportional hazards model. A Pearson χ^2 test was used to assess the differences in the ORR between the defined subgroups.

Results

A total of 548 patients (52%) from the pooled study population were identified as having INTMP mRCC according to the MSKCC criteria and 517 patients (49%) according to the IMDC criteria.

Table 1 Baseline Patient Characteristics of Sunitinib-Treated Patients With INTMP mRCC

Characteristic	MSKCC Model	IMDC Model
Patients (n)	548	517
Age (years)		
Median	60	60
Range	24-87	24-87
Male gender	379 (69)	361 (70)
ECOG PS		
0	332 (61)	319 (62)
1	208 (38)	193 (37)
2	8 (1)	5 (1)
Histologic type[a]		
Clear cell	509 (93)	476 (92)
Non-clear cell	37 (7)	39 (8)
Risk factors (n)		
1	325 (59)	303 (59)
2	223 (41)	214 (41)
Sites of metastases		
Lung	427 (78)	400 (77)
Bones	171 (31)	171 (33)
Liver	129 (24)	118 (23)
Previous therapy		
Cytokine	101 (18)	126 (24)
Radiation	85 (16)	88 (17)
Nephrectomy	426 (78)	413 (80)

Data presented as n (%).
Abbreviations: ECOG = Eastern Oncology Cooperative Group; IMDC = International mRCC Database Consortium; INTMP = intermediate-prognosis; mRCC = metastatic renal cell cancer; MSKCC = Memorial Sloan Kettering Cancer Center; PS = performance status.
[a]Histologic data missing for 2 patients (< 1%).