Original Study

Long-Term Response to Sunitinib Treatment in Metastatic Renal Cell Carcinoma: A Pooled Analysis of Clinical Trials

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Abstract

A subset of patients with metastatic renal cell carcinoma treated with sunitinib achieved long-term response (ie, progression-free survival [PFS] > 18 months). Long-term responders had improved objective response rate, PFS, and overall survival versus others. Patient baseline characteristics predictive of long-term response to sunitinib were identified.

Background: We characterized clinical outcomes of patients with metastatic renal cell carcinoma (mRCC) treated with sunitinib who were long-term responders (LTRs), defined as patients having progression-free survival (PFS) $>$ 18 months. **Patients and Methods:** A retrospective analysis of data from 5714 patients with mRCC treated with sunitinib in 8 phase II/III clinical trials and the expanded access program. Duration on-study and objective response rate (ORR) were compared between LTRs and patients with PFS $\leq$ 18 months ("others"). PFS and overall survival (OS) were summarized using Kaplan–Meier methodology. **Results:** Overall, 898 (15.7%) patients achieved a long-term response and 4816 (84.3%) patients did not achieve long-term response. The median (range) duration on-study was 28.6 (16.8-70.7) months in LTRs and 5.5 (0-68.8) months in others. ORR was 51% in LTRs versus 14% in others ($P < .0001$). Median PFS in LTRs was 32.11 months and median OS was not reached. LTRs had higher percentage of early tumor shrinkage $\geq$ 10% at the first scan (67.1% vs. 51.2%; $P = .0018$) and greater median maximum on-study tumor shrinkage from baseline (−56.9 vs. −27.1; $P < .0001$) versus others. White race, Eastern Cooperative Oncology Group performance status 0, time from diagnosis to treatment $\geq$ 1 year, clear cell histology, no liver metastasis, lactate dehydrogenase $\leq$ 1.5 upper limit of normal (ULN), corrected calcium $\leq$ 10 mg/dL, hemoglobin greater than the lower limit of normal, platelets less than or equal to ULN, body mass index $\geq$ 25 kg/m^2, and low neutrophil-to-lymphocyte ratio were associated with LTR. **Conclusion:** A subset of patients with mRCC treated with sunitinib achieved long-term response. LTRs had improved ORR, PFS, and OS.

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Introduction

Sunitinib malate (Sutent), a multitargeted tyrosine kinase inhibitor, is approved globally for the treatment of metastatic renal cell carcinoma (mRCC).[1] Sunitinib has demonstrated efficacy in many clinical trials,[2-6] and is a standard-of-care first-line treatment for patients with mRCC.[7] In the pivotal trial, the median

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progression-free survival (PFS) was significantly longer in patients with mRCC treated with sunitinib versus interferon-alfa (11 vs. 5 months, respectively).[3] Efficacy of sunitinib was confirmed by almost all subsequent trials performed in the first-line setting.[2,8-12] Median PFS with sunitinib in the first-line setting ranged between 9 and 11 months.[2,8,10-12] Median PFS with other targeted therapies in the first-line setting ranged between 8 and 11 months,[4,13,14] and in the second-line setting ranged between 4 and 8 months.[15-18]

Molina et al[19] reported a subset of patients (n = 34) with mRCC treated in clinical trials at Memorial Sloan Kettering Cancer Center (MSKCC) who achieved a long-term response with sunitinib, defined as patients achieving durable complete response or remaining progression-free for > 18 months. Of this group, 3 patients achieved complete response and 24 achieved partial response at 18 months after treatment start; the median PFS at a landmark time point of 18 months after treatment initiation was 17.4 months (95% confidence interval [CI], 7.0-29.9 months).[19] Lack of bone or lung metastases and favorable MSKCC risk status were found to be associated with long-term response.[19]

The goal of this retrospective study was to identify and characterize sunitinib long-term responders (LTRs), defined as patients with mRCC having PFS > 18 months while on sunitinib therapy. We used a large, contemporary clinical trial database of patients with mRCC who were treated with sunitinib to describe the clinical characteristics, duration of treatment, and clinical outcome of patients identified as LTRs, and to identify risk factors that may predict long-term response.

Methods

Patients and Study Design

A retrospective analysis of data in patients (n = 5714) with mRCC treated with sunitinib in 8 phase II or III clinical trials (n = 1173) and patients (n = 4543) treated in the expanded access program (EAP; Supplemental Table 1 in the online version). In 6 trials (n = 5199), sunitinib was started at 50 mg daily for 4 weeks followed by a 2-week break ("4/2 schedule")[3,5,6,10,11,20-22]; in 2 trials (n = 226), the starting dose was 37.5 mg administered on a continuous once-daily dosing (CDD) regimen[8,23]; and, in 1 trial (n = 289), the starting dose was 50 mg 4/2 schedule or 37.5 mg CDD.[9]

Phase II or III trials included patients with histologically confirmed clear cell RCC with measurable disease, metastases (except for 1 study by Motzer et al,[9] wherein patients could have locally recurrent or mRCC), adequate organ function, and Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1 or Karnofsky performance score > 70.[3,5,6,8,9,20,22,23] In the EAP trial, patients had histologically confirmed mRCC (of all histological subtypes) with adequate organ function.[10,11] In all trials, tumor response was assessed according to Response Evaluation Criteria in Solid Tumors criteria. A central independent review of response was conducted in 3 trials.[3,6,22] All trials were registered on ClinicalTrials.gov and were previously reported (Supplemental Table 1 in the online version).

Statistical Analysis

Dose reduction/interruptions, treatment discontinuation, and treatment-related adverse events (AEs) were summarized between LTRs and patients who had PFS ≤ 18 months ("others").

Multiple univariable logistic regression analyses were conducted to identify potential baseline characteristics associated with LTRs. Baseline characteristics assessed included age, race, sex, ECOG PS, time from diagnosis, histology, metastasis, serum lactate dehydrogenase (LDH), corrected serum calcium, hemoglobin, platelets, prior nephrectomy, prior therapy, body mass index (BMI), and neutrophil-to-lymphocyte ratio (NLR). A multivariable logistic regression analysis was further conducted for the baseline characteristics that were statistically significant ($P < .05$) in the univariable analyses to identify the independent baseline factors associated with LTRs.

A Cox proportional analysis was conducted to identify baseline and post-baseline characteristics associated with overall survival (OS).

Tumor burden was determined based on the sum of the longest diameters of the target lesions by the investigators. Median tumor burden at baseline was compared between LTRs and others. Early tumor shrinkage, defined as ≥ 10% reduction in sum of the longest diameters of target lesions at the first scan after initiation of sunitinib treatment, was calculated and compared between LTRs and others. The 10% threshold was selected based on a study showing that early tumor shrinkage ≥ 10% at first post-baseline assessment could serve as a putative early end point in patients with mRCC.[24] Patients from the EAP were excluded from the analysis of tumor burden and tumor shrinkage because tumor response assessments were not mandated and were performed at the discretion of the investigators. Because early decline in NLR is associated with favorable outcome and early increase in NLR with worse outcome,[25] these trends were compared separately.

Results

Patients

A total of 898 (15.7%) patients met the definition of LTRs. The remaining 4816 (84.3%) had PFS < 18 months that included stable disease, progressive disease, or death (ie, others). Patient demographics were similar between the LTRs and others (Supplemental Table 2 in the online version). Patient disease characteristics were mostly similar between the 2 groups, except for ECOG PS 0, time from diagnosis to treatment ≥ 1 year, and low MSKCC risk group that were more common in the LTR versus others. LTRs also had favorable laboratory findings versus others (Supplemental Table 2 in the online version).

Sunitinib Treatment and AEs

Overall, 14.9% of LTRs and 14.0% of others received sunitinib as first-line therapy, whereas 85.1% of LTRs and 86.0% of others received sunitinib as second-line therapy. Most patients (865 [96.3%] of LTRs and 4406 [91.5%] of others) received sunitinib on a 4/2 schedule; 33 (3.7%) of LTRs and 410 (8.5%) of others received sunitinib on CDD. The median (range) duration on-study was 28.6 (16.8-70.7) months in LTRs and 5.5 (0-68.8) months in others.

A similar number of patients discontinued treatment due to insufficient clinical response in the 2 groups (34.9% in LTRs and 36.1% in others). Dose reduction/interruption occurred in 58.5% of LTRs and 31.5% of others and discontinuation of treatment due to AEs occurred in 11.1% of LTRs and 16.5% of others (see