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Adjuvant Sunitinib for High-risk Renal Cell Carcinoma After Nephrectomy: Subgroup Analyses and Updated Overall Survival Results

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Abstract

Background: Adjuvant sunitinib significantly improved disease-free survival (DFS) versus placebo in patients with locoregional renal cell carcinoma (RCC) at high risk of recurrence after nephrectomy (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.59–0.98; $p = 0.03$).
Objective: To report the relationship between baseline factors and DFS, pattern of recurrence, and updated overall survival (OS).
Design, setting, and participants: Data for 615 patients randomized to sunitinib ($n = 309$) or placebo ($n = 306$) in the S-TRAC trial.
Outcome measurements and statistical analysis: Subgroup DFS analyses by baseline risk factors were conducted using a Cox proportional hazards model. Baseline risk factors included: modified University of California Los Angeles integrated staging system criteria, age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), weight, neutrophil-to-lymphocyte ratio (NLR), and Fuhrman grade.
Results and limitations: Of 615 patients, 97 and 122 in the sunitinib and placebo arms developed metastatic disease, with the most common sites of distant recurrence being lung (40 and 49), lymph node (21 and 26), and liver (11 and 14), respectively. A benefit of adjuvant sunitinib over placebo was observed across subgroups, including: higher risk (T3, no or undetermined nodal involvement, Fuhrman grade $\geq$2, ECOG PS $\geq$1, T4 and/or

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nodal involvement; hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.55–0.99; $p = 0.04$), NLR ≤3 (HR 0.72, 95% CI 0.54–0.95; $p = 0.02$), and Fuhrman grade 3/4 (HR 0.73, 95% CI 0.55–0.98; $p = 0.04$). All subgroup analyses were exploratory, and no adjustments for multiplicity were made. Median OS was not reached in either arm (HR 0.92, 95% CI 0.66–1.28; $p = 0.6$); 67 and 74 patients died in the sunitinib and placebo arms, respectively.
Conclusions: A benefit of adjuvant sunitinib over placebo was observed across subgroups. The results are consistent with the primary analysis, which showed a benefit for adjuvant sunitinib in patients at high risk of recurrent RCC after nephrectomy.
Patient summary: Most subgroups of patients at high risk of recurrent renal cell carcinoma after nephrectomy experienced a clinical benefit with adjuvant sunitinib.
Trial registration: ClinicalTrials.gov NCT00375674.

1. Introduction

The prognosis for renal cell carcinoma (RCC) depends on stage and on additional tumor and patient-specific risk factors obtained at diagnosis. Nearly 20% of all patients with RCC are diagnosed with locoregional disease [1], and up to 40% of these patients experience relapse after nephrectomy and develop metastasis [2,3]. Adjuvant therapies to decrease relapse after nephrectomy are needed. A decision to adopt a new adjuvant therapy in standard clinical practice depends on consideration of a patient's estimated risk of recurrence, the clinical benefit of the additional treatment, and the additive treatment related morbidity.

In the phase 3 S-TRAC study, sunitinib (50 mg once daily) was administered on a 4-wk on/2-wk off treatment schedule to patients with locoregional RCC at high risk of tumor recurrence after nephrectomy [4]. Adjuvant sunitinib significantly improved disease-free survival (DFS) versus placebo (median 6.8 vs 5.6 yr) according to blinded independent central review (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.59–0.98; $p = 0.03$) [4]. At 5 yr, the DFS rate gain was 8% in favor of sunitinib over placebo. Overall survival (OS) data were not mature at data cutoff [4]. The most common (>5% of patients) grade ≥3, all-causality adverse events (AEs) in the sunitinib group were palmar-plantar erythrodysesthesia (16%), neutropenia (8.5%), hypertension (7.8%), and thrombocytopenia (6.2%) [4].

In the present study, we examined treatment outcomes for subgroups of patients defined according to baseline characteristics, and report here the sites of tumor recurrence in the two treatment arms. Updated OS data, based on an additional 10 mo of follow-up, are also provided.

2. Patients and methods

2.1. Patients and treatment

As described previously [4], key inclusion criteria in the S-TRAC study included: nonmetastatic locoregional RCC defined as T3 or T4, no or undetermined nodal involvement, or any T stage with local nodal involvement; and for all patients, any Fuhrman grade and any Eastern Cooperative Oncology Group performance status (ECOG PS). In addition, patients had to have clear cell histology, no previous systemic therapy, ECOG PS ≤2 before nephrectomy, no evidence of macroscopic residual disease/metastasis (confirmed by blinded independent central review), and treatment initiation within 3–12 wk after nephrectomy. Patients were randomized to receive treatment with sunitinib or placebo for nine cycles (~1 yr) until recurrence, second cancer, significant toxicity, or consent withdrawal.

2.2. Analyses

Disease recurrence was determined via centrally confirmed imaging and/or histological findings. Prespecified subgroup analyses of DFS by baseline risk factors were conducted using a Cox proportional hazards model. The baseline risk factors were as follows: University of California Los Angeles integrated staging system (UISS) criteria [5]; age; gender; ECOG PS before first dose (as opposed to ECOG PS in risk groups before nephrectomy); weight; and neutrophil-to-lymphocyte ratio). Post hoc analyses of DFS by Fuhrman grade were also performed. Interaction terms (treatment × baseline factors) were analyzed to investigate possible interactions between treatment and the baseline factors in a univariate model. All subgroup analyses were exploratory, and no adjustments for multiplicity were made.

Patients were followed for survival status (regardless of treatment duration) every 12 wk until the time of the final analysis. OS was defined as the time from the date of randomization to the date of death due to any cause. In the absence of confirmation of death, survival time was censored at the last date on which the patient was known to be alive. OS was estimated using the Kaplan-Meier method, and data were compared using a two-sided log-rank test, stratified by UISS risk group.

3. Results

3.1. Patients and treatment

Overall, 615 patients ($n = 309$ sunitinib; $n = 306$ placebo) were enrolled from 97 sites, including 73 in Europe, 15 in Asia, and nine in the Americas. Of these patients, 306 were treated with sunitinib and 304 with placebo. Patient characteristics, summary of treatment, and treatment outcome are summarized in Table 1. Overall, 71% of patients received sunitinib for six or more cycles (8 mo) and 56% completed the full 1-yr treatment. It should be noted that the trial permitted a dose decrease to 37.5 mg/d, but not to 25 mg/d. The most common reasons for treatment discontinuation in the sunitinib group included AEs (28%), relapse (7.2%), and patient refusal to continue treatment for reason other than AEs (4.6%). In the placebo-treated patients, the most common reasons for treatment discontinuation included relapse (19%), AEs (5.9%), and patient refusal to continue treatment for a reason other than AEs (2.6%).

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