Original Study

Correlation of Stomatitis and Cutaneous Toxicity With Clinical Outcome in Patients With Metastatic Renal-Cell Carcinoma Treated With Everolimus

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Abstract

In a retrospective study, we evaluated the impact of stomatitis–cutaneous toxicity events (SCTE) inducing an everolimus discontinuation or a dose reduction on the clinical outcome of patients with metastatic renal-cell cancer (mRCC). SCTE occurred in 20 (25%) of 79 patients. SCTE appeared a predictive marker of favorable outcome in mRCC patients treated with everolimus.

Background: In clinical practice, discontinuation or dose reduction of everolimus may be induced not only by grade 3 or 4 toxicities but also by prolonged grade 2 toxicities, such as stomatitis and/or cutaneous toxicity, which share some pathogenetic mechanisms. We assessed the correlation between either everolimus discontinuation or dose reduction induced by stomatitis–cutaneous toxicity events (SCTE) and clinical outcome of patients with metastatic renal-cell cancer (mRCC). **Patients and Methods:** We retrospectively reviewed the clinical data of patients with mRCC treated with everolimus in 2 Italian centers. Clinical evidence of SCTE was evaluated, and corresponding clinical data were reviewed for response and clinical outcome. **Results:** Seventy-nine mRCC patients treated with everolimus (57 male, 22 female; median age 66 years; range, 44-88 years) were evaluated. SCTE were observed in 20 (25%) of 79 patients at a median of 30.5 days of everolimus treatment (range, 10-270 days). Partial response or stable disease was achieved in 15 (79%) of 19 evaluable patients with SCTE compared to 28 (48%) of 58 with no SCTE ($P = .03$). At a median follow-up of 19 months, a significant difference was found in the median PFS equal to 7.8 months (95% confidence interval [CI], 2.8-24.4) in SCTE patients versus 4.3 months (95% CI, 2.7-7.5) in non-SCTE patients ($P = .029$), and in the median OS equal to 30.6 months (95% CI, 19.6–not reached) in SCTE patients versus 13.5 months (95% CI, 9.9-17.7) in non-SCTE patients ($P = .0007$). **Conclusion:** These data suggest that SCTE may be a predictive marker of favorable outcome in mRCC patients treated with everolimus.

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Introduction

Everolimus is a specific inhibitor of the mammalian target of rapamycin (mTOR), which represents a therapeutic option for vascular endothelial growth factor receptor–resistant metastatic renal-cell cancer (mRCC).[1] The results of a phase 3 study proved that treatment with everolimus prolongs progression-free survival (PFS) relative to placebo in patients with mRCC who experienced disease progression while receiving other targeted therapies.[2] However, in the pivotal trial, at least one treatment interruption occurred in 38% of everolimus-treated patients and 11% of placebo-treated patients.[2] Interruptions were due to adverse events (AEs) in 35% and 9%, and laboratory test alterations in 3% and 2% of everolimus- and placebo-treated patients, respectively.[2,3] The most frequent AEs were stomatitis, rash, fatigue or asthenia, and diarrhea. The proportion of grade 3 or 4 events was low for both groups. In clinical practice, discontinuation or dose reduction of everolimus may be induced not only by grade 3 or 4 toxicities but also by prolonged grade 2 toxicities, such as

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stomatitis and/or cutaneous toxicity, which share some pathogenetic mechanisms.

In patients with mRCC treated with mTOR inhibitor therapies, valid biomarkers to predict clinical activity and to properly guide management have been studied, although firm conclusions remain to be drawn.[4] Mechanism-based toxicities could serve as a surrogate biomarker of pharmacodynamic effect with some targeted therapies.[5,6] Examples of mechanism-based toxicities with targeted therapies include rash related to treatment with epidermal growth factor receptor inhibitors and hypertension or hypothyroidism with antiangiogenic drugs.[7-15] The onset of these AEs has been correlated with clinical outcome, although the pathogenetic mechanisms are still not fully understood. A retrospective review of 310 mRCC patients treated with temsirolimus and/or everolimus showed a significantly longer time on treatment (median, 4.1 vs. 2 months) and overall survival (OS) (median, 15.4 vs. 7.4 months) in patients who developed noninfectious pneumonitis compared to those without this AE.[16] This previous study concluded that an AEs may become a predictor of improved OS. In our work, we assessed the correlation between either everolimus discontinuation or dose reduction induced by stomatitis—cutaneous toxicity events (SCTE) and clinical outcome of patients with mRCC.

Patients and Methods

Study Patients

We retrospectively reviewed the clinical data of patients with mRCC treated with everolimus in 2 Italian oncology units. All patient had received at least one therapeutic regimen before everolimus treatment. In addition, selection criteria included Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2 as well as adequate cardiac, renal, hepatic, and bone marrow function.

Therapy consisted of everolimus 10 mg daily in 28-day cycles continued until evidence of progressive disease on scans, unacceptable AEs/patient's choice, or death. Patients were evaluated for safety and dosing compliance every 2 weeks for the first 3 treatment months, and then monthly thereafter until treatment discontinuation. Renal, liver, and bone marrow function were assessed monthly, while radiographic evaluation was left to the discretion of the treating physician. Patient follow-up consisted of regular physical examinations and laboratory assessments (hematologic and serum chemical measurements) every 4 to 6 weeks and imaging studies performed every 3 to 4 months, with the first imaging evaluation within the first 3 months.

The accuracy of all of the clinical, pathologic, and radiologic data retrieved from the respective institutions' databases were validated for each patient by an independent observer using the medical chart.

For each patient, toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4. Clinical evidence of stomatitis and/or cutaneous toxicity inducing a treatment discontinuation or a dose reduction were considered SCTE. SCTE were evaluated, and corresponding clinical data were reviewed for response and clinical outcome. Response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[17] The retrospective study was approved by the institutional review board of each center taking part in the study.

Statistical Analysis

Data were summarized by frequency for categorical variables and by median and range for continuous variables. Continuous variables were compared by the Wilcoxon test. Association between categorical variables was assessed by Fisher's exact test, when appropriate. Differences were considered statistically significant when $P < .05$. Progression-free survival (PFS) was calculated from the start of everolimus until disease progression or death for any cause, whichever occurred first. Patients who were lost to follow-up or whose disease did not progress were censored on the date of the last assessment of progression. OS was calculated from the start of everolimus until death. Patients lost to follow-up were censored at the time of last contact. The Kaplan-Meier method was used to estimate PFS and OS. Survival curves were compared by the log-rank test. All statistical analyses were carried out with SAS 9.3 software (SAS Institute, Cary, NC).

Results

Patients

A total of 79 enrolled patients (57 male, 22 female) with a median age of 69 years (range, 43-88 years) and diagnosis of mRCC were treated with everolimus in the study. Fifty-two patients (66%) received 1 previous vascular endothelial growth factor receptor tyrosine kinase inhibitor line before everolimus, and 27 (34%) received 2 previous lines. Over 90% of patients underwent nephrectomy, and tumor histology types were characterized by clear-cell and papillary disease in 96% and 4% of cases, respectively. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model, including 5 prognostic factors (anemia, thrombocytosis, neutrophilia, Karnofsky performance status < 80, and < 1 year from diagnosis to first-line targeted therapy) has been evaluated as a prognostic tool in this study.[18] Patients were divided into 3 categories using IMDC criteria: (1) favorable risk group, (2) intermediate risk group, and (3) poor risk group. Nine patients (11%) belonged to the first group, 60 (76%) to the second, and 10 (13%) to the third.

Toxicity

The most frequent AE was SCTE, which was reported in 20 (25%) of 79 enrolled patients at a median of 30.5 days of receipt of everolimus treatment (range, 10-270 days). Other common AEs included foot—hand syndrome (7.6%), asthenia (6.3%), and arterial hypertension (3.8%). In addition, less frequent AEs (< 1%) were anemia, thrombocytopenia, neutropenia, and hepatotoxicity.

Patient characteristics by onset of SCTE are summarized in Table 1; no statistically significant difference was found between the 2 groups. Up-front dose reduction or discontinuation in the SCTE group was done in frail patients according to the physician' clinical evaluations.

Response and Survival

Tumor response was evaluable in 77 of 79 patients (19 of 20 SCTE patients and 58 of 59 non-SCTE). Partial response or stable disease was noted in 15 (79%) of 19 patients with SCTE compared to 28 (48%) of 58 with no SCTE ($P = .03$). After a median follow-up of 19 months (range, 1-39 months), the median PFS was 5.5 months (95% confidence interval [CI], 3.4-7.7) and the median OS was 17.2 months (95% CI, 13.2-24.4). A significant difference was