Original Study

Prediction of Everolimus Toxicity and Prognostic Value of Skeletal Muscle Index in Patients With Metastatic Renal Cell Carcinoma

Edouard Auclin,[1] Camille Bourillon,[2] Eleonora De Maio,[3] Marie Agnes By,[4] Sofiane Seddik,[5] Laure Fournier,[2] Marie Auvray,[1] Antoine Dautruche,[1] Yann-Alexandre Vano,[1,6,7] Constance Thibault,[1] Florence Joly,[5] Laurent Brunereau,[4] Carlos Gomez-Roca,[3] Christine Chevreau,[5] Reza Elaidi,[1,8] Stéphane Oudard[1,8,9]

Abstract

Patients with metastatic renal cell carcinoma with a skeletal muscle index (SMI) in the highest tercile have better overall survival with everolimus therapy versus those with an SMI in the lowest tercile. Low SMI did not influence the toxicity of everolimus. Whether SMI provides additional prognostic value to the International Metastatic Database Consortium prognostic group criteria remains to be determined.

Background: The objective of the study was to assess the prognostic role of skeletal muscle index (SMI) in metastatic renal cell carcinoma (mRCC) patients treated with everolimus, and its effect of on everolimus-induced toxicity. **Patients and Methods:** Consecutive mRCC patients treated with everolimus between February 2007 and November 2014 underwent computed tomography scans at a single center performed by the same radiologist. SMI was assessed before everolimus treatment using the L3 cross-sectional area. Overall survival (OS) was analyzed according to SMI value. Results were adjusted using the International Metastatic Database Consortium (IMDC) prognostic group, body mass index (BMI), and/or number of previous tyrosine kinase inhibitor lines (NPL). **Results:** One hundred twenty-four mRCC patients (mean age, 60.21 years) were treated with everolimus as second- or third-line (82.3%) or > third-line (17.7%) therapy. Most patients (87.9%) had clear cell carcinoma. IMDC prognostic group was "favorable" (32.3%), "intermediate" (50%), or "poor" (17.7%). Median SMI was 40.75. OS was longer in patients from the highest versus lowest SMI tercile: 21.9 versus 10 months ($P = .002$). Continuous SMI at baseline was not significantly associated with OS after adjustment for IMDC prognostic group, BMI, or NPL but the highest versus lowest SMI tercile was an independent prognostic factor in multivariate analysis ($P = .025$). There was no difference in everolimus toxicity between SMI tercile groups. **Conclusion:** SMI was an independent prognostic factor for mRCC patients treated with everolimus. Whether this provides additional prognostic value to IMDC criteria needs to be confirmed in a larger cohort. SMI does not seem to be predictive of everolimus-induced toxicity.

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[1]Oncology Department
[2]Radiology Department, European Georges Pompidou Hospital, René Descartes University, Paris, France
[3]Oncology Department, Institut Universitaire du Cancer de Toulouse (IUCT)/Institut Claudius Regaud, Toulouse, France
[4]Oncology Department, Centre Hospitalier Bretonneau, Tours, France
[5]Oncology Department, Centre François Baclesse, Caen, France
[6]INSERM UMRS 1138, Cancer, Immune Control and Escape, Cordeliers Research Centre, Paris, France
[7]Université Paris-Descartes, Sorbonne, Paris, France
[8]Association pour la Recherche sur les Thérapeutiques Innovantes en Cancérologie, Paris, France
[9]U790 PARCC, European Georges Pompidou Hospital, René Descartes University, Paris, France

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Address for correspondence: Stéphane Oudard, MD, PhD, Oncology Department, European Georges Pompidou Hospital, René Descartes University, Paris 5, 20 rue Leblanc, 75015 Paris, France
E-mail contact: stephane.oudard@aphp.fr

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Introduction

Treatment of metastatic renal carcinoma has evolved enormously over the past 10 years because of the discovery and better understanding of tumor proliferation pathways. Blocking the vascular endothelial growth factor (VEGF) pathway with antiangiogenesis agents such as sunitinib, pazopanib, axitinib, sorafenib, and bevacizumab with interferon α has provided an overall survival (OS) benefit for patients with metastatic renal carcinoma.[1-4] The mammalian target of rapamycin (mTOR) pathway is another proliferation pathway in renal carcinoma; targeting this pathway can overcome resistance to first-line anti-VEGF therapy.[5]

Everolimus is an orally active mTOR pathway inhibitor approved for the second- and third-line treatment of metastatic renal cell carcinoma (mRCC) after sunitinib or sorafenib treatment.[6] In a double-blind, phase III study, progression-free survival in everolimus recipients was 4.6 months versus 1.8 months in the placebo group. Outcomes with everolimus are better if it is given in a second-line setting rather than as third-line therapy.[5]

The choice of anticancer treatment is on the basis of an individual patient's predicted survival. To assess this, prognostic scores such as the International Metastatic Database Consortium (IMDC) or the Memorial Sloan Kettering Cancer Center risk score (MSKCC) are used.[7,8] The IMDC score is on the basis of 6 independent variables predictive of poor survival: <1 year from diagnosis to treatment, low Karnofsky performance status (<80%), hypercalcemia (corrected calcium concentration higher than the upper limit of normal), anemia (hemoglobin concentration below the lower limit of normal), thrombocytosis (platelet count greater than the upper limit of normal), and neutrophilia (neutrophil count above the upper limit of normal). The score divides patients into 3 prognostic groups: favorable (no factors), intermediate (1 or 2 factors), and poor (≥ 3 factors).

The IMDC or MSKCC scores do not have a morphologic component such as low muscle index, which reflects low muscle mass. An indicator of low muscle mass is the skeletal muscle index (SMI), calculated using the third lumbar vertebra (L3) cross-sectional muscle area from a computed tomography (CT) scan. Sex-related cutoff values for SMI on the basis of mortality risk have been determined.[9] Low muscle index is defined as an SMI <55.4 in men, and <38.9 in women. The SMI has already been showed to be a prognostic factor in patients treated for lung and gastrointestinal cancers when associated with loss of weight, with a significant survival difference between patients with and without sarcopenia.[10] However, in that study, the prognostic value of SMI was not verified for patients with a low body mass index (BMI). Moreover, data suggest that SMI might predict treatment-induced toxicity with sunitinib in low BMI patients with mRCC,[11] and in hepatocellular carcinoma patients treated with sorafenib.[12] Although data exist with other treatments and in other cancers, no studies have been conducted to evaluate the effect of sarcopenia in mRCC patients treated with everolimus. Biological data support the fact that sarcopenia might have an effect in patients treated with everolimus because of its role in the promotion of lipid synthesis, insulin resistance, and in the oxidative metabolism of skeletal muscle.[13] In mice, specific muscle mTOR complex 1 knockout induces muscle dystrophy with reduced muscle mass and oxidative function.[14]

The aim of this study was to determine whether SMI is a prognostic factor for mRCC patients treated with second- or third-line everolimus therapy, and to assess the effect of sarcopenia on everolimus toxicity.

Patients and Methods

Patients

This multicenter, retrospective study was conducted in 4 oncology departments in France. Data for consecutive mRCC patients treated with everolimus between February 2007 and November 2014 were collected. To be included in the study, patients had to fulfill the following criteria: received everolimus as second- or third-line treatment after antiangiogenic agents, and had an available CT scan at everolimus initiation. Clinical data on survival were collected from computerized patient files.

Skeletal Muscle Index Assessment

Skeletal muscle index was assessed on baseline CT. Two slices at halfway on L3, preferably 2.5-mm in thickness slices (or if not available, 1.25-mm [7 patients] or 5-mm [2 patients] slices), were transferred in DICOM format onto Slice-O-Matic version 5.0 (Tomovision; Yves Martel, Magog, Canada) image postprocessing software. Skeletal muscle cross-sectional area (in cm^2) was calculated by a radiologist with 10 years of experience with a threshold of density of between 25 and 130 Hounsfield units. Final skeletal muscle area was determined by averaging the results obtained on each slice. The SMI was later calculated using the following formula: SMI = lumbar muscle area/body surface (cm^2/m^2). Low muscle index was defined as an SMI <55.4 in men, and <38.9 in women. These cutoff values for sarcopenia were determined in cancer patients and were used as done in other studies.[11,15]

Statistical Analysis

Overall survival was defined as the duration from the start of everolimus therapy until a patient's death/last contact. The secondary end point was everolimus-induced toxicity.

The effect of SMI as a prognostic factor for OS was analyzed in univariate and multivariate analysis with Cox proportional hazard models. In the multivariate analysis, results were adjusted for IMDC prognostic group, BMI, and number of previous treatments with a tyrosine kinase inhibitor (TKI). SMI was analyzed as a continuous variable as well as using terciles. A comparison of OS between terciles 1 and 3 was made using the log rank test, Kaplan−Meier estimates, and score test for the Cox model. The hypothesis of proportional hazard was checked by examination of Schoenfeld residuals. Survival analysis was performed using the XLstat 2016.7 software (Addinsoft) and descriptions of population and toxicities were made with R software (*https://www.r-project.org*).

Results

One hundred twenty-four mRCC patients treated with everolimus were included in the study. Baseline patient characteristics are described in Table 1. Most patients were male, the most common histological type was clear cell carcinoma, and two-thirds of patients had intermediate or poor prognosis on the basis of the IMDC score. Almost half of all patients received everolimus as

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