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Efficacy and Safety of Everolimus in Elderly Patients With Metastatic Renal Cell Carcinoma: An Exploratory Analysis of the Outcomes of Elderly Patients in the RECORD-1 Trial

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Abstract

Background: Elderly patients with metastatic renal cell carcinoma (mRCC) may require special treatment considerations, particularly when comorbidities are present. An understanding of the efficacy and safety of targeted agents in elderly patients with mRCC is essential to provide individualized therapy.
Objective: To evaluate the efficacy and safety of everolimus in elderly patients (those ≥65 and ≥70 yr of age) enrolled in RECORD-1.
Design, setting, and participants: The multicenter randomized RECORD-1 phase 3 trial (Clinicaltrials.gov identifier, NCT00410124; http://www.clinicaltrials.gov) enrolled patients with mRCC who progressed during or within 6 mo of stopping sunitinib and/or sorafenib treatment (n = 416).
Intervention: Everolimus 10 mg once daily (n = 277) or placebo (n = 139) plus best supportive care. Treatment was continued until disease progression or unacceptable toxicity.
Measurements: Median progression-free survival (PFS), median overall survival (OS), and time to deterioration in Karnofsky performance status (TTD-KPS) were assessed using the Kaplan-Meier method; the log-rank test was used to compare treatment arms. Other outcomes evaluated included reduction in tumor burden, overall response rate (ORR), and safety.
Results and limitations: In RECORD-1, 36.8% of patients were ≥65 yr and 17.5% were ≥70 yr of age. PFS, OS, TTD-KPS, reduction in tumor burden, and ORR were similar in the elderly and the overall RECORD-1 population. Everolimus was generally well tolerated in elderly patients, and most adverse events were grade 1 or 2 in severity. The toxicity profile of everolimus was generally similar in older patients and the overall population; however, peripheral edema, cough, rash, and diarrhea were reported more frequently in the elderly regardless of treatment. The retrospective nature of the analyses was the major limitation.
Conclusions: Everolimus is effective and tolerable in elderly patients with mRCC. When selecting targeted therapies in these patients, the specific toxicity profile of each agent and any patient comorbidities should be considered.

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1. Introduction

Over the last 5 yr, the treatment options available for the management of metastatic renal cell carcinoma (mRCC) have increased, with the approval of several agents targeting specific angiogenic or growth and proliferation pathways. Although these agents (ie, sunitinib, sorafenib, pazopanib, bevacizumab, temsirolimus, and everolimus) are now widely used in patients with mRCC, safety data continue to emerge from long-term follow-up and expanded-access programs. Improved understanding of the efficacy and safety profiles of targeted agents in specific populations may enhance the ability of clinicians to provide individualized therapy and improve outcomes in mRCC.

Elderly patients constitute a large component of the mRCC population because the incidence of mRCC increases with age, with a median age of 62 yr at diagnosis [1]. Comorbid conditions are generally more prevalent in elderly patients compared with their younger counterparts. In a population-based study, serious concomitant diseases were present in 9%, 25%, 49%, and 60% of patients with newly diagnosed cancer <45, 45–59, 60–74, and ≥75 yr of age, respectively [2]. Another study reported the most prevalent comorbidities observed in patients (n = 363) to be arthrosis-arthritis (31%), hypertension (29%), digestive diseases (23%), cardiac disease (21%), and vascular disease (19%) [3]. In addition, elderly patients with cancer are more likely to have a compromised performance status: In one study of 593 patients, a baseline Eastern Cooperative Oncology Group performance status ≥1 was observed in 30% of patients ≥70 yr of age versus 9% of patients <70 yr [4]. The presence of comorbidities and decreased performance status in an older patient may result in a decreased ability to tolerate cancer therapy and therefore to receive the intended dose intensity. An additional concern is that medications taken to manage comorbidities may interact with cancer treatments. Although clinical trials have not been performed directly comparing the safety and efficacy of targeted agents in the elderly population, retrospective analyses of outcomes in elderly subsets enrolled in large clinical trials may provide useful information about how age affects the efficacy and tolerability of individual targeted agents.

Everolimus is a mammalian target of rapamycin (mTOR) inhibitor approved in 65 countries for use in patients with mRCC who have failed prior vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFr-TKI) therapy. The phase 3 RECORD-1 trial demonstrated a significant improvement in progression-free survival (PFS) with everolimus. Median PFS by independent central review was 4.9 mo with everolimus versus 1.9 mo with placebo ($p < 0.001$) [5,6]. Stomatitis, infection, asthenia, and fatigue, the most commonly reported adverse events (AEs) with everolimus, were manageable and mainly grade 1 or 2 in severity.

In RECORD-1, age (<65 vs ≥65 yr) was not reported to have significant prognostic value for either PFS or overall survival (OS) [6]; however, a detailed subgroup analysis in elderly patients was not performed. Here we compare the outcomes and toxicities in patients ≥65 and ≥70 yr of age enrolled in RECORD-1 with those of the overall study population to further explore the tolerability and efficacy of everolimus in elderly patients.

2. Patients and methods

2.1. Eligibility and treatment

The study design of the randomized double-blind multicenter phase 3 RECORD-1 trial was previously reported [5,6]. Adult patients with metastatic clear cell RCC who experienced disease progression on or within 6 mo of stopping treatment with sunitinib, sorafenib, or both, were enrolled. Prior therapy with bevacizumab, interleukin-2, or interferon-α was allowed. Patients were assigned to receive everolimus 10 mg/d plus best supportive care (BSC) or placebo plus BSC. Randomization was stratified by Memorial Sloan-Kettering Cancer Center risk and number of prior VEGFr-TKI therapies (one vs two). Treatment continued until disease progression or unacceptable toxicity. Patients receiving placebo were allowed to cross over to the everolimus arm upon disease progression (during the blinded period of study) or at the end of the blinded study period.

2.2. Study design and outcome variables

Retrospective subgroup analyses compared efficacy and safety outcomes, including PFS, OS, reduction in tumor burden, time to deterioration of Karnofsky performance status (KPS), and the frequency and severity of AEs, in patients ≥65 and ≥70 yr of age versus the overall RECORD-1 population. Tumor measurements were performed by calculating the sum of the longest diameter of all target lesions as assessed by computed tomography or magnetic resonance imaging at baseline and every 8 wk thereafter until study discontinuation. Disease progression was assessed by a blinded independent central review committee. AEs were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, v.3.0.

2.3. Statistical analysis

Analyses were performed on the final RECORD-1 data set [6]. Subgroup analyses of efficacy were performed on the intent-to-treat population (n = 416). Subgroup analyses of safety were performed on the safety population (n = 411), which included patients who received one or more dose of the study drug with one or more valid postbaseline safety assessment. The Kaplan-Meier method was used to estimate PFS and median time to definitive worsening of KPS; the log-rank test was used to test the difference between the treatment arms. Descriptive statistics were used to compare safety outcomes. Definitive worsening was defined as a decrease in performance status by one or more Karnofsky category (ie, at least 10 points less) compared with baseline.

3. Results

3.1. Patients

Among the 416 patients enrolled in the RECORD-1 study, 36.8% were ≥65 yr and 17.5% were ≥70 yr of age. Of those ≥65 yr, 112 patients and 41 patients received everolimus or placebo, respectively. Of those ≥70 yr, 53 patients and 20 patients received everolimus or placebo, respectively. Table 1 summarizes the baseline characteristics.