Original Study

Impact of Second-Line Targeted Therapy Dose Intensity on Patients With Metastatic Renal Cell Carcinoma

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Abstract

The relative dose intensity (RDI) at 4 weeks after second-line targeted therapy induction may be a possible predictor of prognosis in patients with metastatic renal cell carcinoma treated with second-line targeted therapy, particularly in the International Metastatic Renal Cell Carcinoma Database Consortium poor-risk group and everolimus-treated subjects. Overall survival of patients with second-line RDI < 0.7 is significantly shorter than those with RDI ≥ 0.7.

Background: Relative dose intensity (RDI) is a simple index for evaluation of the amount of drug administered per unit time. We retrospectively investigated the prognostic impact of RDI for patients with metastatic renal cell carcinoma (mRCC) treated with second-line targeted therapy. **Methods:** We enrolled 168 patients with mRCC. We assessed RDI at 4 weeks after second-line targeted therapy induction. **Results:** The median follow-up after second-line targeted therapy was 18.1 months. The median time-to-treatment-failure (TTF) and overall survival (OS) were 4.9 and 25.4 months, respectively. In the Kaplan-Meier analysis, the median OS of patients with second-line RDI < 0.7 was significantly shorter than those with RDI ≥ 0.7 (12.1 vs. 31.3 months; $P = .030$). In the subgroup analysis, second-line RDI was definitely prognostic in the poor-risk group of the International Metastatic Renal Cell Carcinoma Database Consortium criteria, showing second-line RDI was an independent predictor for both TTF (hazard ratio [HR], 3.6; 95% confidence interval [CI], 1.6-8.0; $P = .002$) and OS (HR, 3.1; 95% CI, 1.1-8.4; $P = .026$). Also, assessing the type of second-line regimen, the multivariate analysis showed that second-line RDI was an independent prognostic indicator of TTF (HR, 1.7; 95% CI, 1.0-2.9; $P = .040$) and OS (HR, 2.7; 95% CI, 1.3-5.7; $P = .009$) in patients treated with everolimus. In this group, the median TTF and OS of patients with RDI < 0.7 were 2.4 and 11.1 months, and those with RDI ≥ 0.7 were 5.3 and 25.9 months, respectively. **Conclusion:** The results suggest that second-line RDI may be a prognostic predictor for patients with mRCC treated with second-line targeted therapy, particularly in both the International Metastatic Renal Cell Carcinoma Database Consortium poor-risk group and everolimus-treated group.

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Introduction

Although the incidence of renal cell carcinoma (RCC) is still increasing at a rate of 2% to 3% per decade in most countries, the stabilization of mortality trends has been achieved in many highly developed countries.[1] Up to 30% of patients have advanced or metastatic RCC (mRCC) at diagnosis, and the historic 5-year survival rate is approximately 10% after systemic relapse.[2] In recent years, the outcome of patients with mRCC has been improving owing to the use of novel agents, including tyrosine kinase inhibitors (TKIs), mammalian target of rapamycin inhibitors (mTORIs), and immune checkpoint inhibitors, which are more effective compared with the previous standard immunotherapies.[3-6] However, patients receiving targeted therapy often experience dose delays and reductions due to several factors, including poor performance status and adverse events (AEs), leading to modification of the medication dose received.

Relative dose intensity (RDI) is a simple index for evaluation of the amount of drug administered per unit time, expressed as a ratio of the planned dose or standard regimen. Retrospective studies have shown that incidence of severe AEs was significantly correlated with lower dose intensity in patients with advanced mRCC treated with TKIs, and that low-dose intensity and treatment discontinuation were correlated with shorter patient survival.[7,8] Although 1 study reported a correlation between the RDI of sunitinib and all-cause mortality in the first-line targeted therapy,[8] others reported that first-line RDI may predict favorable progression-free survival (PFS), but not mortalities like overall survival (OS).[7,9,10] While such discrepancies may be owing to the variety of sequential treatments in this malignancy, no study yet examines the impact of RDI on subsequent mortality in the second-line targeted therapy. Thus, we retrospectively investigated the association between second-line RDI and mRCC outcome after the failure of first-line targeted therapy.

Methods

After gaining approval from the institutional review board, a total of 7 Japanese institutions, consisting of Keio University Hospital and 6 affiliated institutions, provided data on 311 consecutive patients who received first-line targeted therapy of either TKIs or mTORIs for mRCC. Pre-treatment assessment of patient performance and blood data were performed just before second-line targeted therapy induction. We included patients who had received prior immunotherapy before first-line targeted therapy in our population.

Patients generally began any of the targeted therapies at the recommended starting dose (eg, sunitinib, 50 mg once daily orally; everolimus, 10 mg once daily orally), although lower starting doses were used in some cases, according to physician judgement. Dose intensity was defined as the cumulative dose received divided by the duration of the therapy. RDI was determined as dose intensity divided by the optimal or recommended daily dose for 4 weeks from the targeted treatment initiation.[7,8] Patients were followed up every 2 to 4 weeks after the initiation of the targeted therapies. Follow-up consisted of history, physical examination, routine blood work, and chest radiography. Radiographic evaluations of computerized tomography (CT) were generally performed every 3 months, while additional CTs and elective bone scans were performed when clinically indicated.

The purpose of the study was to evaluate overall survival (OS) and time to treatment failure (TTF). OS was defined as the time from second-line targeted therapy initiation to the date of death from any cause or date of censorship from last follow-up. TTF was defined as the time between second-line targeted therapy initiation and progression, drug cessation, death, or censorship from last follow-up. Progression was determined according to clinical criteria indicating that continuation of treatment was impossible or by radiographic criteria according to the Response Evaluation Criteria in Solid Tumors 1.1.[11]

We obtained outcome and survival data retrospectively, while the cause of death was determined by the attending physicians, chart reviews corroborated by death certificates, or by death certificates alone at each institution. Laboratory values were standardized according to the institutional upper and lower limits of normal values. Values are presented as medians and interquartile range or confidence interval (CI) for continuous variables and frequency with percentage for categorical variables. The variables of different groups were compared using the chi-square test or the Mann-Whitney U test, as appropriate. To predict the outcome in patients with mRCC treated with targeted therapy, we stratified patients into 3 groups using 6 factors of the first-line therapy (ie, time from diagnosis to treatment, Karnofsky performance status, hemoglobin, neutrophil count, platelet count, and corrected calcium) based on the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model.[12,13] Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model with stepwise forward selection to identify factors associated with OS and TTF. The level of significance was set at $P < .05$. Statistical analysis was performed using the SPSS version 23.0 statistical software package.

Results

Among total patients, we enrolled 168 patients who were treated with second-line TKIs (n = 82) or mTORIs (n = 86) after failure of the first-line targeted therapy. The median follow-up of the cohort was 18.1 months (interquartile range, 8.7-32.0 months) after second-line targeted therapy. Table 1 shows the characteristics of the 168 patients treated with second-line targeted therapy. The median patient age at the second-line targeted therapy induction was 65 years, and 121 (72.0%) of the patients were men. A total of 125 (74.4%) and 57 patients (33.9%) had prior nephrectomy and immunotherapy, respectively. In total, 86 (51.2%), 45 (26.8%), 21 (12.5%), 4 (2.4%), 11 (6.5%), and 1 (0.6%) patients were treated with sunitinib, sorafenib, axitinib, pazopanib, temsirolimus, and everolimus as a first-line targeted therapy, respectively. On the other hand, everolimus was most frequently used in the second-line setting, in 77 (45.8%) patients, and 38 (22.6%), 23 (13.7%), 20 (11.9%), 9 (5.4%), and 1 (0.6%) patients were treated with axitinib, sunitinib, sorafenib, temsirolimus, and pazopanib, respectively, as a second-line therapy. Fifty-six patients started to treat with the reduced dose (ie, 20, 7, 14, and 15 patients treated with everolimus, axitinib, sunitinib, and sorafenib). Regarding the IMDC criteria, 33 (19.6%), 88 (52.4%), and 33 patients (19.6%) were stratified into the favorable-, intermediate-, and poor-risk groups at the time of first-line targeted therapy.