Editorial

Continuous or intermittent? On the dosing schedule of sunitinib for advanced renal cell carcinoma

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Sunitinib is globally approved for treatment of advanced renal cell carcinoma (RCC) at a dosage of 50 mg/day with four weeks on treatment and two weeks off, based on a randomized phase III trial in which its superiority over interferon alpha was established as first-line therapy for patients with metastatic RCC (1). On the other hand, continuous daily dosing of sunitinib at a dosage of 37.5 mg/day may be expected to provide consistent antitumor activity with a better safety profile compared with the 50 mg/day intermittent schedule according to two phase II trials (2,3). The recently published paper reported the result of a very interesting randomized phase II study called "Renal EFFECT Trial", in which the efficacy and safety of sunitinib was directly compared between the 50 mg/day intermittent schedule and the continuous 37.5 mg/day as first-line therapy for patients with advanced RCC (4).

In this study, patients with treatment-naïve, clear cell advanced RCC were randomly assigned in a 1:1 ratio to receive sunitinib 50 mg/day with four weeks on treatment and two weeks off (schedule 4/2) or 37.5 mg/day on a continuous daily dosing schedule (CDD), with 146 patients in each arm. The primary end point was time to tumor progression (TTP). As a result, although statistically not significant, a longer TTP and progression-free survival (PFS) was observed with the 4/2 schedule. Median TTP in the 4/2 schedule and CDD arms was 9.9 months (95% CI, 7.0 to 13.4 months) and 7.1 months (95% CI, 6.8 to 9.7 months), respectively (hazard ratio [HR], 0.77; 95% CI, 0.57 to 1.04; P=0.090). Median PFS was 8.5 months (95% CI, 6.9 to 11.1 months) and 7.0 months (95% CI, 6.0 to 8.7 months) in the schedule 4/2 and CDD arms, respectively (HR, 0.77; 95% CI, 0.58 to 1.02; P=0.070). No significant difference between the schedule 4/2 and CDD arms was observed in objective response rate (32% and 28%, respectively), stable disease rate (43% and 49%, respectively), or overall survival (median, 23.1 and 23.5 months, respectively).

Patient baseline characteristics were similar between both arms, although a slightly higher number of patients had a lower Karnofsky performance status, MSKCC poor risk disease, and liver metastases in the CDD arm compared with the schedule 4/2 arm. When analyzed by the MSKCC risk criteria, however, the relative increase in TTP with the 4/2 schedule was most pronouncedly shown in the favorable-risk (HR, 0.56; 95% CI, 0.29 to 1.07; P=0.075) rather than in the intermediate or poor-risk group. Moreover, in the multivariable analysis which assessed an independent relationship for each variable studied among a range of pretreatment clinical features, the trend for longer TTP (HR, 0.74; 95% CI, 0.53 to 1.01; P=0.061) and PFS (HR, 0.75; 95% CI, 0.55 to 1.02; P=0.071) with schedule 4/2 was observed. Predictors for TTP were baseline lung or bone metastases within the multivariable analysis.

What about safety and tolerability? Median treatment duration was five months (range, <1 to 26 months) and six months (range, <1 to 25 months) in the 4/2 schedule and CDD arms, respectively. There were no significant differences between both arms in incidence of commonly reported treatment-related adverse evens of any grade or grades 3 to 4. Eleven percent and 15% of patients discontinued treatment because of adverse events, 65% and 62% had at least one dose interruption, and 36% and 43% had a dose reduction in the 4/2 schedule and CDD arms, respectively. However, the median relative dose intensity of sunitinib was higher with the 4/2 schedule (91%) than CDD (78%), which suggests that maintaining the dose

may be more difficult in the continuous dosing regimen rather than in the intermittent. The presence of a certain off-treatment period in the regimen may be of value to maintaining the dose. This hypothesis may be sustained by the observation that patients on the 4/2 schedule showed a reversible on/off effect of self-reported fatigue and other symptoms, whereby the symptom scores were better at the beginning of each treatment cycle following the two-week break compared with scores of day 28. Finally, the 4/2 schedule was statistically superior to the CDD regimen in time to deterioration, a composite end point comprising death, progression, or disease-related symptoms (HR, 0.77; 95% CI, 0.60 to 0.98; P=0.034).

In conclusion, there was no benefit in efficacy or safety for 37.5 mg/day continuous dosing of sunitinib compared with 50 mg/day with four weeks on treatment and two weeks off. This paper emphasizes the importance of assessing new dosing strategies in randomized studies before implementing them in clinical practice.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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