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

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Submitted Apr 15, 2012. Accepted for publication May 03, 2012.
doi: 10.3978/j.issn.2223-4683.2012.05.02
Scan to your mobile device or view this article at: http://www.amepc.org/tau/article/view/636/682

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 schedule 4/2 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 events 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.

Acknowledgements

None.

Footnote

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

References
