Hypertension and clinical benefit of bevacizumab in the treatment of advanced renal cell carcinoma

Few predictive factors for efficacy of vascular endothelial growth factor pathway-targeted therapies have been identified. We studied whether bevacizumab treatment-related hypertension is associated with outcome. Forty-three consecutive patients with metastatic progressive renal cell cancer (RCC), of whom 41 had cytokine-refractory disease, were treated with bevacizumab [administered either 5 mg/kg every 2 weeks ($n = 37$) or 7.5 mg/kg every 3 weeks ($n = 6$)] from June 2004 to March 2007 in our hospital. We used this dose since it was widely used in the treatment of colorectal cancer at the time when RCC patients were accrued [1]. Blood pressure was measured before each bevacizumab infusion and antihypertensive medication was initiated or intensified whenever blood pressure was >150/100 mmHg.

The median age of the patients was 58 (range 43–77). Most ($n = 40$, 93%) patients had RCC with clear cell histology. The median duration of bevacizumab therapy was 4.8 months (range 0.1–16.3), time to progression 5.3 months [95% confidence interval (CI) 1.2–17.5], and overall survival 16.7 months (95% CI 1.4–28.0).

Twelve patients (28%) needed initiation ($n = 3$) or intensification ($n = 9$) of antihypertensive medication during bevacizumab treatment (group A). The rest of the patients (who had blood pressure 150/100 mmHg or less throughout the therapy) formed group B. There were no differences in the frequency of the most important prognostic factors of RCC between groups A and B ($P > 0.05$ for all comparisons) or in the frequency of grade III adverse events (hemorrhage, proteinuria). The median number of doses given in group A was 17 (range 6–32) and eight in group B (range 1–35). The median time to initiation of antihypertensive treatment or medication intensification was 2.8 months (range 1.3–13.3), and the mean blood pressure at the time of initiation or intensification of hypertension medication was 177.2/105.5 mmHg (Table 1).

Response to treatment was assessed according to the response evaluation criteria in solid tumors criteria. One (8%) patient had partial response (PR), 10 (83%) stable disease (SD), and one (8%) progressive disease (PD) as best response in group A, whereas in group B one (3%) patient had PR, 14 (45%) SD, and 16 (52%) PD as best response. Thus, significantly more patients in group B ($n = 16$) than in group A ($n = 1$) had PD as best response ($P = 0.0050$). The median time to disease progression was 8.1 months (95% CI 5.3–11.3) in group A versus 4.2 months in group B (95% CI 2.6–5.6; $P = 0.036$; Figure 1). However, overall survival was not different between the groups (median 19.4 versus 12.4, respectively; $P = 0.22$). Treatment-related ≥grade II proteinuria (>1000 mg/24 h; $n = 7$, 16%) did not correlate with time to progression or overall survival ($P = 0.73$ and 0.51, respectively) or with occurrence of hypertension ($P = 0.96$). Two of the three patients who required initiation of antihypertensive medication also developed grade II proteinuria.

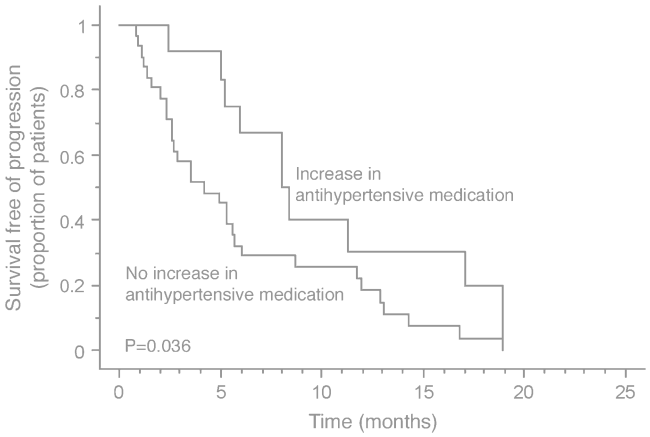

Figure 1. Time to progression by hypertension treatment during bevacizumab therapy.

Table 1. Systolic and diastolic blood pressure before and during bevacizumab treatment

Measure	Patients who had treatment for hypertension initiated or intensified, $n = 12$				Patients with no hypertension or no change in hypertension medication, $n = 31$		
	Baseline, mmHg, mean ± SD	1 month after start of therapy, mmHg, mean ± SD	At start of HTN therapy, mmHg, mean ± SD	1 month after start of HTN therapy, mmHg, mean ± SD	Baseline, mmHg, mean ± SD	1 month after start of therapy, mmHg, mean ± SD	3 months after start of therapy, mmHg, mean ± SD
SBP	144.7 ± 3.4	153.2 ± 4.4	177.2 ± 7.1	163.2 ± 4.4	140.6 ± 4.3	145.8 ± 4.2	144.6 ± 3.7
DBP	83.7 ± 2.8	89.1 ± 2.9	105.5 ± 1.8	93.9 ± 1.9	82.4 ± 2.1	83.1 ± 4.1	85.8 ± 3.9

SD, standard deviation; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Recently, patients with axitinib-related hypertension have been reported to have longer overall survival as compared with patients who did not develop hypertension [2]. Similar results have been published regarding sunitinib in RCC [3] and bevacizumab in pancreatic cancer [4]. Thus, treatment-related hypertension may predict outcome to antiangiogenic treatment, but these data require confirmation in prospective studies.

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