Incidence and prognostic role of cumulative toxicity by tyrosine kinase inhibitors (TKI) in metastatic renal cell carcinoma (mRCC)

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Background: TKI related toxicities have been reported to be predictive and/or prognostic factors in patients affected by mRCC. We investigate the incidence and the prognostic role of cumulative toxicity in mRCC patients treated with sunitinib (SU) or pazopanib (PA).

Material and methods: mRCC patients treated at the European Institute of Oncology in Milan were reviewed for incidence of adverse events (AEs) such as hypertension, hand-foot syndrome and hypothyroidism during treatment. Cumulative toxicity was defined as more than one selected AE of any grade. Prognostic class was evaluated by IMDC (Heng) prognostic factors. The median PFS and OS were estimated by Kaplan-Meier method, correlation of prognostic factors with survival was evaluated by Cox analysis.

Results: 72 consecutive mRCC patients were evaluated. 87.5% of whom had partial or radical nephrectomy, 75% had clear cell RCC, and 62.5% were metastatic at diagnosis. Prognosis by IMDC was good in 57% of patients, intermediate in 40% and poor in 3%. ECOG performance status was 0 in 65%, 1 in 32% and 2 in 3% of patients. First-line treatment was sunitinib in 85% and pazopanib in 15% of patients. Any grade and high grade toxicity was present in 57% and 1.3% of patients for hypertension, in 43% and 0% for hypothyroidism and in 43% and 1.4% for hand-foot syndrome. Patients without selected AE were 23.6%, while 30.6%, 26.4, and 19.4% had one, two or all selected toxicity, respectively. The median follow-up was 30.6 months and the median PFS and OS was 12.4 and 61.2 months, respectively. Significant differences in PFS were found in patients experienced hypertension (p = 0.011) and hand-foot syndrome (p = 0.010) but not in patients experienced hypothyroidism (p = 0.12). In patients who experienced none, one or two toxicities in terms of hypertension and hand-foot syndrome, the median PFSs were 6.9, 15.3 and 29.0 months (p = 0.001), and the median OSs were 23.5, 35.1 and 81.1 months (p = 0.019), respectively. Cumulative toxicity was confirmed as prognostic factor for PFS (p = 0.001) and OS (p = 0.012) when compared to IMDC prognostic factors.

Conclusions: In the present study we report that the presence of cumulative toxicity (mainly hypertension and hand-foot syndrome), related to the use of SU and PA as first-line treatment in mRCC may select patients with a better PFS and OS.