Clinical, pharmacodynamic and pharmacogenetic evaluation of docetaxel plus prednisone in combination with metronomic cyclophosphamide and celecoxib as first line treatment in castration resistant prostate cancer

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Context. Docetaxel is currently the standard first-line cytotoxic treatment in metastatic castration-resistant prostate cancer (mCRPC). Docetaxel has been combined with various agents, which demonstrated additive or synergistic activity in preclinical studies, in an effort to further improve outcomes, but to date, overall survival has not been extended compared with docetaxel plus prednisone. Metronomic chemotherapy has been extensively studied for its anti-angiogenic property in preclinical model, and several phase II trials on prostate cancers have demonstrated its clinical activity and good toxicity profile.

Purpose. The aims of the present study were to evaluate the clinical activity, and the pharmacodynamic/pharmacogenetic profile of the new schedule of docetaxel plus prednisone in combination with metronomic cyclophosphamide and celecoxib, as first-line treatment in advanced hormone-refractory prostate cancer patients.

Experimental design and methods. From March 2006 to April 2010, 41 patients received docetaxel (60 mg/m^2 i.v. every three weeks up to 12 cycles) and, from day 2, prednisone 10 mg/day, celecoxib 400 mg/day and metronomic cyclophosphamide 50 mg/day continuously until disease progression. Plasma vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) were detected by ELISA at different time points. Blood samples were collected at day 1 (pre-treatment) for DNA extraction. Real-time PCR–SNP analysis of VEGF-A [-2578A/C (rs699947), -1154A/G (rs1570360), -634C/G (rs2010963) and 936C/T (rs3025039)] were performed using an ABI PRISM 7000 SDS and validated TaqMan SNP genotyping.

Results. In 39 evaluable patients we observed a PSA decrease ≥ 50% in about 82% of patients with a median time to progression of 12.3 months. Main grade 3 adverse events were: neutropenia (5%), thrombocytopenia, diarrhoea, stomatitis and onycholysis (2.5%). Median progression-free survival (PFS) and overall survival were 14.9 months (95% confidence interval, 9.2-15.3 months) and 33.3 months (95% confidence interval, 23-35.6 months), respectively. A significant increase of PFS was found in those patients who, after the first cycle of treatment, had plasma levels of VEGF >129 pg/ml (16.5 *vs.* 11.1 months, p=0.042) and of bFGF >13 pg/ml (20.8 vs. 12.2 months, p=0.0314). Moreover, patients with the VEGF -1154AA genotype showed a significant shorter PFS (11.1 months) if compared to the VEGF -1154AG/GG patients (23.7 months; p=0.0028).

Conclusion. The combination of docetaxel and metronomic cyclophosphamide plus celecoxib and prednisone was effective in patients with mCRPC and showed favorable toxicity. The -1154A/G VEGF polymorphism, VEGF and bFGF plasma levels after the first cycle of chemotherapy may represent useful pharmacogenetic/pharmacodynamic markers to predict a better outcome. Randomized phase III clinical trials are urgently needed to verify these preliminary findings.