Multidrug and toxin extrusion 1 and human organic cation transporter 1 polymorphisms in patients with castration-resistant prostate cancer receiving metformin (SAKK 08/09).


Abstract

Background:

This study was initiated to explore the impact of organic cation transporter 1 (OCT1) and multidrug and toxin extrusion transporter 1 (MATE1) genetic polymorphisms on toxicity, and clinical activity of metformin in patients with castration-resistant prostate cancer (CRPC).

Methods:

The SAKK 08/09 trial included 44 patients with CRPC to receive single-agent metformin 1000 mg two times a day until disease progression or unwanted toxicity. Drug pathway-associated gene polymorphisms of OCT1 (rs622342) and MATE1 (rs2289669) were assessed. The primary objective of this study was to define the relationship between mutations in OCT1, MATE1 and progression-free survival (PFS) at 12 weeks absolute PFS and PSA response in consenting patients of SAKK 08/09. The secondary objective of this study was to analyze the association between mutations in OCT1, MATE1, metformin-related toxicity, PSA response at 12 weeks and overall survival.

Results:

Thirty-six patients were evaluable for pharmacogenetic analysis. Homozygous carriers of the polymorphic OCT1 C-allele had no metformin-related toxicity as compared with 41.9% for any metformin-related toxicity in carriers of at least one wild-type A-allele (P=0.07). Disease progression according to RECIST (Response Evaluation Criteria In Solid Tumors) was significantly more frequent in homozygous carriers of the polymorphic OCT1 C-allele (80%) as compared with carriers of at least one wild-type A-allele (28.6%) (P=0.002). Disease progression according to RECIST was also more frequent in carriers of at least one polymorphic MATE1 A-allele (44%) as compared with homozygous carriers of the wild-type G-allele (12.5%) (P=0.07). OCT1 and MATE1 were not associated with PFS.

Conclusions:

The polymorphic OCT1 C-allele has been shown to be associated with less metformin-related toxicity and a higher risk of tumor progression in patients with CRPC receiving metformin as an anticancer treatment. Polymorphisms in metformin drug transporters are attractive molecular markers to serve as potential predictors of efficacy in future clinical studies.