



The potential role of germline single nucleotide polymorphisms for selecting the ideal candidates for sunitinib therapy in patients with locally-advanced renal cell carcinoma

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Renal cell carcinoma (RCC) represents the eighth most common malignant cancer diagnosed in the United States (1). Despite a stage migration of RCC towards a more localized disease over the past decades, a considerable proportion of patients is still diagnosed with loco-regional disease. In case of organ-confined RCC, the overall prognosis for surgically treated patients is fairly good, with a 5-year cancer specific mortality (CSM)-free rate of 91% and for stage I (T1N0M0) and 74% for stage II (T2N0M0). Conversely, the 5-year CSM-free survival for patients treated with surgery alone for loco-regional disease remains unsatisfactory, with a 53% event-free rate for stage III RCC (T1-2N1M0 or T3N0-1M0) (2). Since the vascular endothelial growth factor (VEGF) pathway inhibitors have demonstrated improved survival in patients the metastatic RCC (3), the role of this medications has been explored in the adjuvant setting for patients with loco-regional RCC (4,5).

In the ASSURE trial no survival advantage emerged for adjuvant therapy with sunitinib or sorafenib over placebo in patients with locally advanced renal-cell carcinoma (4). However, the S-TRAC study, evaluating the role of sunitinib versus placebo, demonstrated the superior disease-free survival (DFS) in patients with locally advanced RCC at high risk of recurrence (5). This randomized, double-blind, phase III trial (ClinicalTrials.gov, NCT00375674) randomized patients (1:1) to receive sunitinib 50 mg/day or placebo on a 4-week-on/2-week-off schedule for 1 year

or until recurrence, diagnosis of secondary malignancy, unacceptable side effect, or withdrawal from the study. Of the 610 patients who consented to the study, 286 (46.9%; n=142 and 144, sunitinib and placebo, respectively) consented to the pharmacogenomic analysis and provided a blood sample that was subsequently genotyped. In the recent study by George *et al.*, the authors evaluated whether germline genomic mutations, in terms of single nucleotide polymorphisms (SNPs) were correlated with DFS and overall survival (OS) (6).

The rationale for this phenomenon is that SNPs can affect the pharmacokinetics, pharmacodynamics and the downstream signaling pathways of tyrosine kinase inhibitors (7).

The authors relied on the 286 patients who consented to genotyping. These patients were older, white, and were categorized in the UISS high-risk group with respect to the group that did not consent to receive genotyping.

Overall, the role of 11 SNPs (including specific SNPs in VEGFA, VEGFR1, and VEGFR3) was assessed with respect to DFS and OS. Three of the 11 SNPs demonstrated improved DFS with sunitinib treatment over placebo. Specifically, the genotypes C/C for VEGFR1 rs9554320, T/T for VEGFR2 rs2071559, and T/T for eNOS rs2070744 were associated with a longer DFS with sunitinib versus placebo treatment. These genotype did not deviate from the Hardy-Weinberg equilibrium $[(p^2 + q^2)=1]$. However, the

SNP VEGFR2 rs2071559 tended to segregate with VEGFR2 rs1870377 on chromosome 4 and the VEGFR1 rs9554320 SNP tended to segregate with VEGFR1 rs9582036 on chromosome 13. Yet, the linkage disequilibrium was not predictive of worse prognosis.

Overall, the hazard ratios for the three aforementioned SNPs ranged between 0.44 and 0.56, compared to 0.76 for the overall population. This suggests that there are subgroups of patients that are likely to respond better to sunitinib.

Yet, the authors acknowledged that some of the observations in the adjuvant setting appear to be divergent from the observations reported in the metastatic setting. If their findings are confirmed in future studies and if correlation with will be demonstrated, the implementation of genotyping for C/C for VEGFR1 rs9554320, T/T for VEGFR2 rs2071559, and T/T for eNOS rs2070744 should be implemented in clinical practice in an effort to identify better candidates for adjuvant Sunitinib. However, before implementing this information in clinical practice, the actual frequencies in the patient population with RCC of the three SNPs should be explored so as the estimated costs related to genotyping in all patients who is a candidate for adjuvant Sunitinib.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

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