



Adjuvant therapy in renal-cell carcinoma: Is it prime time yet?

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More than 200,000 people worldwide are diagnosed with renal-cell carcinoma (RCC) each year, and almost one third of them will die from metastatic disease (1). Although 5-year survival rate for metastatic disease has increased from 34% in 1954 to 73% in 2011, it still remains low (8–10%) in metastatic setting (2). Although nephrectomy can be curative for the majority of patients presenting with localized disease, nearly 40% of patients initially diagnosed with stages II and III, will eventually relapse (3). Taking the above into consideration, development of an effective adjuvant treatment for patients in high-risk for relapse following nephrectomy is needed.

RCC is a highly vascular tumor and it represents an excellent target for antiangiogenic treatment due to the dominant role of the vascular endothelial factor (VEGF)/VEGF receptor (VEGFR) pathway in carcinogenesis and tumor expansion (4). This has led to the approval of different agents, targeting VEGF or VEGFR for the management of metastatic disease, such as sorafenib (5), sunitinib (6), pazopanib (7), axitinib (8), bevacizumab (9), cabozantinib (10) and lenvatinib (11). Improvement in progression free survival (PFS) and overall survival (OS) was shown in a series of different trials in patients with metastatic RCC (mRCC). For example, sunitinib (6) prolonged PFS by 6 months compared to interferon alpha (IFN- α) and achieved significantly higher response rates at 30–40%. PFS benefit was also achieved by axitinib over another inhibitor of the tyrosine kinase (TKI) of the VEGFR in the AXIS trial (8) in second line, while more recently cabozantinib prolonged OS compared to everolimus, another agent used in relapsed mRCC (10). In spite of these exciting results reported in metastatic disease,

the role of VEGF inhibition in the adjuvant setting after nephrectomy still remains unclear.

The recently published S-TRAC trial (12) investigated the efficacy and safety of sunitinib in preventing disease relapse in high risk patients with resected renal cell carcinoma were assessed. Accrual lasted from September 2007 to April 2011 and 615 patients with locoregional, high-risk clear-cell RCC (T3N0M0 or T4N0M0 or node-positive) were randomized in a 1:1 fashion to receive either sunitinib (50 mg per day) or placebo on a 4-week-on, 2-week-off schedule for 1 year or until disease recurrence, unacceptable toxicity, or consent withdrawal. The study met its primary endpoint: median duration of disease free survival (DFS) was longer in patients receiving sunitinib [6.8 *vs.* 5.6 years, hazard ratio (HR), 0.76; 95% confidence interval (CI), 0.59 to 0.98; *P*=0.03]. Toxicity profile of sunitinib was comparable to that reported in trials on metastatic setting. Adverse events grade 3 or more were reported in 63% of patients receiving sunitinib, but the rate of serious adverse events was similar in both arms. Treatment discontinuation due to toxicity was considerable and occurred in 28% of the patients.

S-TRAC results should be reviewed within the current environment of clinical research on adjuvant therapy in RCC. Apart for the S-TRAC, five more trials are addressing this issue (13–17). Only one has been reported yet: the ASSURE trial studied the adjuvant use of sorafenib and sunitinib in RCC (13). This trial showed no benefit in DFS and OS from the use of VEGFR TKIs. The SORCE trial focuses on treatment duration, administering sorafenib for 3 *vs.* 1 year (14). The PROTECT trial investigates the adjuvant use of pazopanib in clear-cell, >T2, grade 3–4

disease, but high discontinuation rates led to a protocol amendment to allow a lower dose of pazopanib (15). The ATLAS trial treats patients for three years with axitinib (16), while the EVEREST trial exploits the inhibition of a different pathway [the mammalian target of rapamycin (mTOR)], using everolimus in the adjuvant setting (17).

The reasons for the discrepancy between the results of S-TRAC and ASSURE are not clear. S-TRAC aimed at a higher-risk population than ASSURE. It included only patients with T3 and T4 node negative disease, whereas ASSURE also included patients with T2 and T1b Fuhrman Grade 3 and 4 N0M0 patients. Furthermore, ASSURE required negative surgical margins, whereas S-TRAC accepted microscopic (R1) residual disease. Presence of predominant clear cell histology was mandatory in S-TRAC but not in ASSURE. Clear-cell RCCs seem to be more dependent on the VEGF pathway, which may have underpowered the results of ASSURE.

Another factor contributing to the discordance between ASSURE and S-TRAC results may be the difference in the treatment dosage and compliance. ASSURE had a higher drop out due to toxicity (44%) compared to S-TRAC. This is surprising taking into consideration that an amendment in ASSURE clinical protocol allowed initiation with a lower level of sunitinib dosage (37.5 mg daily for 4 weeks on a 6-week cycle) for the first two cycles, which led to only 41% of patients receiving full dose of sunitinib during third cycle. On the other hand, S-TRAC initiated sunitinib in its full dose (50 mg daily for 4 weeks on a 6-week cycle) and 54% achieved to maintain this dose throughout treatment period. This may have increased efficacy, as suggested by previous studies, associating higher exposure to sunitinib with higher response rates (18).

Finally, progression was centrally assessed in S-TRAC but not in ASSURE. This factor may be of importance, since statistical significance difference in DFS between the two arms was observed only through independent assessment of progression in the S-TRAC trial.

The major question following the publication of the results of S-TRAC, is whether they should change the current practice of follow up after nephrectomy for localized RCC, regardless of the risk of relapse. Certain points should be taken into consideration. Whether DFS is the most appropriate endpoint for adjuvant therapy trials in the current treatment paradigm of RCC remains questionable. Many agents used in metastatic disease, sunitinib included, prolong survival. In that sense S-TRAC may be viewed as an early *vs.* late sunitinib study. For this reason, definitive

conclusion about the wide application of this strategy, should be drawn after maturation of OS data. The current median follow up of 5.4 years is not adequate, taking into consideration the natural history of RCC. Furthermore, no information regarding the use of sunitinib at relapse has been made available yet. Another important question is the way adjuvant sunitinib may influence sensitivity to VEGFR TKIs at relapse. Data from metastatic setting suggest reduction of efficacy of subsequent therapies after sunitinib failure. This was noted in both RECORD-1 and CheckMate-025 trial, where prior progression on sunitinib correlated with poorer outcome of second line treatment (19,20).

Finally, the most appropriate method for selection of patients in high-risk for relapse after nephrectomy remain elusive. The results of the Cancer Genome Project suggest that traditional pathological characterization may be further tuned by molecular markers (21).

In conclusion, S-TRAC represents an important study, underscoring the efficacy of VEGFR/VEGFR pathway blockade in the adjuvant setting of renal cell carcinoma. Further research to define the precise role of this strategy is required.

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