Adjuvant treatment for high-risk renal-cell carcinoma: the jury is still out.

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Renal cell carcinoma (RCC) is a heterogeneous disease (1) with considerable variation in its natural history. Surgery remains the most important curative option for localized disease (2), however, up to 30 % of patients will develop metastases after a potentially curative nephrectomy (3). Several prognostic factors, such as histologic subtype, pathological Fuhrman grade, tumor dimension or extension and lymph node involvement permit to stratify patients according to prognostic models able to predict the risk of recurrence (4).

Adjuvant systemic therapy following nephrectomy has been used to reduce relapse rates and improve survival in high-risk patients. Interferon-alpha and interleukin-2 were the first agents to be investigated but failed to improve these end points (5, 6). Recently, the impressive efficacy of VEGFR tyrosine kinase inhibitors (TKIs) in advanced stages led to the investigation of these agents in the adjuvant setting (7). Up to now, four studies have been reported. Three of them, ASSURE, PROTECT and ATLAS showed no improvement in disease-free survival (DFS) and overall survival (OS) after one year of sunitinib, sorafenib, pazopanib or axitinib over placebo as adjuvant treatment in patients with localized RCC in high risk of relapse after nephrectomy (8-10). In contrast, S-TRAC met its primary endpoint to improve DFS (HR 0.76; 95 % CI 0.59-0.98; p=0.03) in patients receiving one year of sunitinib over placebo after a radical nephrectomy (11). Several reasons have been offered to explain these contradictive results (12). Among them, the lower exposure to the studied agents for dose and duration in the ASSURE and PROTECT trials has been suggested as being important in this respect. It is exactly, because of this speculation why the paper by Staehler et al (13), published in this issue of Ann Oncol offers valuable information.

Staehler et al report original data of the S-TRAC trial on treatment interruption, modification and discontinuation, therapy management and patient reported outcomes (PROs) on global health status and quality of life (GHS/QoL). They conclude that proactive management of side effects helped to maintain a higher than that reported in the other trials percentage of patients on treatment, while the deterioration on PROs was not clinically meaningful. We believe that some of the results and the conclusions are worth discussing further.

We fully concur with the first conclusion. Efforts for prevention and aggressive management of side effects cannot be overemphasized in the context of treatment with VEGFR TKIs. This is particularly important in the adjuvant setting. This study offers convincing evidence that patients receiving adjuvant TKIs are less tolerant to low or moderate toxicities, which, nevertheless, affect their QoL, compared to patients with active disease. High-grade hypertension, which is normally asymptomatic and treatable, did not affect QoL. On the contrary, low grade but symptomatic and not effectively treatable toxicities, were the cause of permanent discontinuation of therapy in 40% of cases. Similarly, palmar-plantar dysaesthesia, which is

mainly associated with patients' perception of severity, was reported as more severe than expected from metastatic setting.

In spite of clearly being more successful that other adjuvant studies to maintain exposure to sunitinib, S-TRAC still reported premature discontinuation of sunitinib in 44% of patients, mainly due to side effects (40% of which grade 1-2, as already mentioned). PROs have emerged as an important tool for the assessment of patients' perception of toxicity and they have been appropriately used in this study. They showed deterioration during therapy, indicating a detrimental effect of adjuvant sunitinib on GHS/QoL. The authors argue that this effect was not significant by using the clinically important difference (CID) scale (14,15). Not disregarding the importance of trying to quantify PROs, this scale was developed in different settings twenty years ago. The impact of CID score on patients' compliance could have been further supported if a correlation between this score and the probability of treatment modification or discontinuation had been sought. Such finding was not reported. Therefore, to our opinion, findings related to CID scale should not override the main QoL analysis results. On the contrary, we believe that these results relate quite convincingly the fairly poor compliance with the side effects of therapy, which was perceived by patients as significant and led many of them to discontinue it.

This last point generates the important question: "What is the benefit for which patients in the adjuvant setting should be encouraged to tolerate the undoubted and so accurately described in this paper side-effects of sunitinib?" At a median follow up time of 5 years, no evidence of OS improvement or reduction of risk of death was observed in the S-TRAC trial for the sunitinib arm (16). Currently, the role of angiogenetic inhibitors in adjuvant setting in RCC remains under debate. As a consequence, FDA and EMA have given different opinions on the approval of sunitinib as adjuvant treatment: FDA is in favor, while EMA is not. In addition, guidelines on adjuvant treatment divided: NCCN in favor (17), EAU against (18).

Data on the subject will continue to emerge. Other clinical trials assessing the role of targeted therapies have completed the accrual but no data are yet available. The SORCE study investigated the duration of adjuvant treatment comparing sorafenib for one year versus sorafenib for three years over placebo, while the EVEREST trial tested the role of everolimus compared to placebo (19,20). In addition, several trials testing new immunotherapy agents, inhibiting the interaction between the programmed cell death-1 (PD-1) receptor with its ligand (PD-L1) are in progress. Studies in advanced disease have suggested a more favorable toxicity profile compared to that of TKIs, suggesting that compliance of patients receiving adjuvant therapy might be improved.

In conclusion, the field of systemic adjuvant therapy in high-risk resected RCC is still evolving. Currently, inclusion in a clinical trial represents the best management option. If no clinical trials are available, motivated high-risk patients can be informed about available evidence and make shared decisions with their physicians. In this context, the data presented in the paper in discussion represent a valuable tool for decision-making and patients' counselling.

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Funding

No funding was received

Disclosure

AB: Honoraria Advisor Bayer, BMS, EUSA, Ipsen, Novartis, Pfizer

GP: Honoraria from Pfizer, Bayer, Bristol, Ipsen.

SP: Honoraria from Novartis, AZ, Roche.

PS, EV honoraria Advisor Ipsen, Novartis, Pfizer

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