Kidney Cancer 4 (2020) 1–2
DOI 10.3233/KCA-200003
IOS Press

Editorial

Nephrectomy Status in the Context of Cabozantinib Treatment

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In this issue of *Kidney Cancer*, further subgroup analysis is reported from the Phase III METEOR study, which previously established an overall survival (OS) and progression free survival (PFS) benefit with cabozantinib compared to everolimus in patients with previously treated, metastatic renal cell carcinoma (mRCC) [1]. Tannir et al. present results in this issue by patient's nephrectomy status [2]. The primary endpoint of PFS and secondary endpoints of OS and objective response rate (ORR) remained improved with cabozantinib regardless of nephrectomy status. In patients who underwent nephrectomy, median PFS was 7.4 months for cabozantinib versus 3.9 months with everolimus (hazard ratio [HR] 0.51, 95% confidence interval [CI] 0.41–0.64). Patients who had not undergone prior nephrectomy were found to have PFS of 6.6 months with cabozantinib versus 4.4 months with everolimus (HR 0.51, 95% CI 0.30–0.86). Similarly, OS and ORR were also improved with cabozantinib compared to everolimus in patients with prior nephrectomy and without.

This analysis was in part prompted by questions about the role of cytoreductive nephrectomy (CN) in mRCC patients, given advances in systemic therapy that have led to remarkable improvements in survival. Therefore, the accrual period of METEOR must be considered in the context of clinical data that later followed. At the time the study enrolled, our best data as to whether pursue CN came from the SWOG-8949 trial [3]. This Phase III study, which randomized patients to receive radical nephrectomy followed by interferon alfa-2b systemic therapy or interferon alfa-2b alone, established an OS benefit to nephrectomy.

Whether it is beneficial to pursue CN in patients with mRCC has now been rightly questioned on the basis of trials evaluating CN in the era of vascular endothelial growth factor tyrosine kinase inhibitors (VEGF TKIs). Two studies evaluated the role of CN in the context of treatment with sunitinib in the front-line setting: the Immediate Surgery of Surgery After Sunitinib Malate in Treating Patients with Metastatic Kidney Cancer (SURTIME) and the Clinical Trial to Assess the Importance of Nephrectomy (CARMENA) studies [4, 5]. Both studies were challenging to conduct and accrued slowly; the SURTIME trial did not meet its accrual goal. Nevertheless, the SURTIME trial found no difference between immediate or delayed CN [4]. Moreover, the CARMENA trial, which enrolled patients with intermediate and poor risk disease, demonstrated non-inferiority of sunitinib alone compared to CN with sunitinib [5]. Both studies indicate that CN may not be beneficial to patients in the modern treatment era.

Prior to these results, the decision to offer CN to patients with mRCC involved multidisciplinary discussion, taking into consideration patient's age, performance status, extent of metastatic disease and likelihood of local complications. Not all of these factors can be captured in clinical trials, as real-world analyses of CN have demonstrated [6]. The METEOR analysis provides another real-world evaluation of patients with mRCC undergoing nephrectomy, but with some notable differences.

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ISSN 2468-4562/20/$35.00

The study evaluates cabozantinib, which has shown notable differences to sunitinib in terms of efficacy [7]. Unlike studies specifically evaluating CN, this analysis is in patients with refractory mRCC. The study did not delineate whether patients had undergone nephrectomy in the localized setting or in the metastatic setting. While 85% of patients in METEOR had nephrectomy, a greater proportion of the nephrectomy group had favorable risk disease-thus, it is possible those patients underwent nephrectomy prior to developing metastatic disease. The subgroup analysis found that patients in the prior nephrectomy group did enjoy a numerically longer OS, but this too may in part be explained by overrepresentation of favorable risk patients in that group. The analysis did not include OS outcomes by risk stratification and by nephrectomy status and the study was not powered to look at this outcome.

Nevertheless, a significant proportion of patients in the study with intermediate and poor risk disease underwent nephrectomy. This is of significance because a major concern that has emerged in the current treatment era is that immediate CN may lead to delays in systemic therapy, hastening progression and preventing patients from subsequent treatment. From the METEOR analysis, we have some assurance that nephrectomies are undertaken judiciously enough that patients may still go on to receive more than one line of therapy and benefit from it. In the current era of immune checkpoint inhibitor-based therapies, a majority of patients enrolled in clinical trials underwent CN; thus, clinical studies to reevaluate the role of CN with the current standards of treatment are planned [8]. Yet, it is likely that careful consideration of CN for patients on a case-by-case basis will remain important.

FUNDING

This work was supported by the UC Davis Comprehensive Cancer Support Grant (NCI P30 CA093373) and the Paul Calabresi K12 Oncology Career Development Training Grant 2K12CA138464.

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