



Platinum Priority – Editorial and Reply from Authors

Referring to the article published on pp. 448–454 of this issue

Sunitinib Prior to Planned Cytoreductive Nephrectomy: Is This the New Litmus Test for Metastatic Renal Cell Carcinoma?

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There is currently a paucity of high-level evidence regarding the role of cytoreductive nephrectomy in the era of targeted therapy. Patients diagnosed with metastatic renal carcinoma are confronted with difficult treatment decisions regarding the optimal treatment strategy and the timing of surgery in relation to targeted therapy. Level 1 evidence from two randomized trials has demonstrated improved overall survival with cytoreductive nephrectomy in the immunotherapy era [1–3]. Current clinical guidelines recommend cytoreductive nephrectomy followed by systemic therapy for patients presenting with metastatic renal carcinoma in which the primary tumor is surgically resectable and where the treatment is individualized based on symptoms and extent of metastatic disease [4].

In this issue of the Platinum Journal, Powles et al report a pooled analysis of two single-arm, phase 2 prospective trials and evaluate the efficacy and outcomes of sunitinib prior to cytoreductive nephrectomy [5]. Although the authors previously reported safety with neoadjuvant sunitinib prior to cytoreductive nephrectomy [6], this investigation describes the outcomes for the 66 patients who received two or three cycles of sunitinib prior to surgery.

Two principal findings from this study help inform the debate regarding the optimal treatment strategy of targeted therapy and cytoreductive nephrectomy. First, patients who are in the Memorial Sloan-Kettering Cancer Center (MSKCC) intermediate risk group can achieve a lasting response with a median overall survival >2 yr compared with patients harboring poor-risk disease, for whom a markedly shorter median overall survival of 9 mo was observed. These results suggest that patient selection, particularly by MSKCC risk stratification, is paramount in identifying those patients who are most likely to benefit from targeted therapy prior

to cytoreductive nephrectomy. Second, the authors also observed that interruptions of sunitinib in preparation for surgery were associated with a high rate of disease progression. Although the study attempted to apply a rigorous protocol to minimize the time off of targeted therapy by reinitiating sunitinib within 2–3 wk following cytoreductive nephrectomy, there was considerable variation in the amount of time off of therapy following surgery. Consequently, 36% of the patients had disease progression by RECIST criteria and eight patients had new metastatic sites during the perioperative convalescence interval without sunitinib. Thus patients treated with sunitinib who plan to stop treatment for surgical intervention should be informed about the risk of disease progression. Although the authors acknowledge the need to validate their findings with a randomized trial, the results of this study suggest that cytoreductive nephrectomy may have limited efficacy in patients who experience disease progression following initiation of sunitinib or in patients with poor MSKCC risk.

To date, no level 1 evidence has evaluated the efficacy of cytoreductive nephrectomy and targeted therapy, whether neoadjuvant or adjuvant, in patients presenting with metastatic renal carcinoma. Proponents of cytoreductive nephrectomy have extrapolated the results from randomized trials of sunitinib and immunotherapy in patients who underwent previous nephrectomy and then developed metastatic disease and from the two randomized trials that set the current treatment paradigm of cytoreductive nephrectomy [1–3,7,8]. Currently, an ongoing phase 3 trial is recruiting patients presenting with metastatic renal carcinoma to be randomized to immediate cytoreductive nephrectomy followed by sunitinib or three cycles of sunitinib (4 wk of sunitinib and then 2 wk off) followed by

cytoreductive nephrectomy (ClinicalTrials.gov identifier NCT01099423) [9]. The results of this study will further define the role of cytoreductive nephrectomy and the optimal timing of targeted therapy.

Another consideration in ascertaining the role of cytoreductive nephrectomy in the targeted therapy era is the importance of patient selection. Although both clinical trials randomizing cytoreductive nephrectomy for metastatic renal carcinoma showed superior overall survival with surgery and interferon α -2b, it is important to evaluate the inclusion criteria of both trials to appropriately identify which patients are best suited to derive a survival benefit [1–3]. A recent large study also reported retrospective data from nine institutions on the benefit of cytoreductive nephrectomy in the contemporary targeted therapy era [10]. In this study, Choueri et al observed that cytoreductive nephrectomy was associated with a longer median overall survival compared with those patients treated with targeted therapy alone (19.8 vs. 9.4 mo; $p < 0.01$). Moreover, the subgroup analysis revealed that age, performance status (as measured by the Karnofsky score), and MSKCC risk stratification were independent clinical variables predictive of overall survival on multivariable analysis. Taken together, these studies suggest that when determining a treatment strategy for patients presenting with metastatic renal carcinoma, the timing of surgery and targeted therapy should be individualized based on age, performance status, MSKCC risk stratification, extent of metastatic disease, and proportion of tumor burden from the primary tumor relative to the metastatic sites. Ongoing clinical trials should help further define the optimal timing of cytoreductive nephrectomy in the targeted therapy era. Although this may leave more questions than answers, one important aspect of metastatic renal cell carcinoma should not be forgotten: Patients with resectable metastatic renal cell carcinoma are served best with radical nephrectomy and metastasectomy.

Conflicts of interest: The authors have nothing to disclose.

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doi:10.1016/j.eururo.2011.05.056

Platinum Priority

Reply from Authors re: Simon P. Kim, R. Houston Thompson. Sunitinib Prior to Planned Cytoreductive Nephrectomy: Is This the New Litmus Test for Metastatic Renal Cell Carcinoma? Eur Urol 2011;60:455–6

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We would like to thank Kim and Thompson for their incisive and detailed editorial. We are pleased they acknowledge the

DOIs of original articles: 10.1016/j.eururo.2011.05.028, 10.1016/j.eururo.2011.05.056

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importance of our data by asking whether presurgical targeted therapy with sunitinib is the new litmus test in previously untreated clear cell metastatic renal cell carcinoma (RCC) and the primary tumour in place [1].

The concept of presurgical therapy for patient selection in metastatic RCC is not new and has been recognized by others previously, based on retrospective data involving various targeted agents [2,3]. The overall survival data available from our study suggest that this may be the case in that a period of upfront sunitinib prior to planned nephrectomy may select out patients with primary refractory disease [4]. This approach results in a subpopulation with a favourable outcome, which is particularly apparent in the Memorial Sloan-Kettering Cancer Centre (MSKCC) intermediate-risk population. However, because we observed frequent temporary progression during the treatment break, these intriguing findings require robust evaluation before they become incorporated into treatment algorithms.