Letters to the Editor


The case study of the month presented by Karakiewicz et al gave an example of a patient who was downstaged from renal cell carcinoma with stage IV caval thrombus to stage II caval extension. The decision for neoadjuvant sunitinib treatment was based upon the patient’s refusal of sternotomy [1]. The risk of stage IV caval thrombi is not only related to surgical morbidity due to central bypass, hypothermia, and potentially cardiac arrest, but mainly to their ability to cause disseminated or fulminate lung embolism [2,3]. Also, the risk of acute Budd-Chiari syndrome was given. Thus urgent surgical treatment was indicated. The authors hypothesize that neoadjuvant anti-angiogenic therapy could have effectively downstaged the caval thrombus. Unfortunately no information about the lung is given, and the subsequent magnetic resonance imaging of the abdomen is not included. Thus shrinkage of the thrombus could have been observed as a consequence of dislocation of the thrombus. The patient was treated for two cycles with sunitinib. Surgery was performed 4 wk later. It would be interesting to know whether the primary tumor of the kidney did grow again. So far no data exist to prove neoadjuvant therapy effective, but nephrectomy in advanced disease has the benefit of prolonged overall survival. Thus, designing a study protocol in the future is not easy. In locally advanced but surgically resectable disease no evidence of beneficial systemic therapy exists so far. Thus randomization seems to be impossible. So far, in patients with metastatic disease the study protocols did stratify the patients according to their nephrectomy status. As a consequence, subgroup analysis for building any hypothesis on the efficacy of the kinase inhibitors is impossible. In first-line therapy with kinase inhibitors the response rate of 31% of patients with partial remission and no complete remissions with sunitinib seems to be too low to achieve a benefit with neoadjuvant treatment in the majority of the cases, thus any protocol would need to compare early versus late nephrectomy in matched metastatic patient cohorts [4]. Nephrectomy still should be performed immediately if technically possible in patients with localized disease. Single case experience in this setting should not be the basis for a protocol in a large number of patients. Also, we still do not know what the effects of kinase inhibition on surgical morbidity will be. In our own metastatic patients who received surgical procedures we have experienced a higher tendency of bleeding and wound-healing complications. Thorough patient selection will be the challenge of future renal-cell cancer treatment, especially for neoadjuvant patients.

Conflicts of interest: The author has nothing to disclose.

References


We would like to thank Dr. Staehler for his interest in our recently released manuscript [1]. Dr. Staehler has raised several important points related to the use of neoadjuvant targeted therapy in the context of locally advanced, surgically resectable renal cell carcinoma (RCC): (1) the importance of timely surgical management of renal masses with vena cava thrombi, (2) the risk of embolization, (3) the effect of targeted therapy on the primary tumour, (4) the response rates to Sutent in randomized clinical trials and expected response rates in the neoadjuvant setting, and (5) the need for protocols to prospectively investigate the safety, feasibility, and efficacy of targeted therapies in the neoadjuvant setting.

Regarding the first point, we agree with Dr. Staehler that surgery is the standard of care for RCC with vena cava thrombi. Surgery needs to be planned and executed within the shortest delay possible to ensure resectability and to avoid the risk of embolization, as stated in the second point. Although the risk of embolization is real, there are no data on actual cases of spontaneous or intraoperative embolization and of secondary lung metastases. In the current case, the patient remains free of pulmonary metastases at 10 mo after surgery (see Fig. 1). Regarding the third point, the primary tumour did demonstrate shrinkage from 10.6 to 8.3 cm after two cycles of therapy. Unfortunately, we do not have imaging that would allow us to ascertain size fluctuations during the rest periods. Indeed, continuous therapy might represent a better alternative and may avoid the unnecessary fluctuations in tumour and/or thrombus size. Despite the encouraging results observed in the subject described in our case report, Dr. Straehler is absolutely correct in stating that responses will not be recorded in all the cases. Indeed, a proportion of patients may be unnecessarily exposed to targeted therapy, its toxicity, and the risk of potential embolic events related to the presence of the thrombus during the weeks of therapy, despite the absence of response. Unfortunately, there are no known criteria for predicting radiographic response to Sutent in the context of established metastatic disease, nor in the context of neoadjuvant therapy [2–4]. The ideal frequency (weekly, biweekly, monthly, and so forth) and the type of imaging (CT vs MRI) are unknown. Ideally, those and other points related to the safety, feasibility, and efficacy of neoadjuvant therapies should be examined in prospective trials. Ongoing trials of sorafenib, sunitinib, and of the bevacizumab/erlotinib combination confirmed their feasibility without untoward intraoperative or postoperative complications [5].

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