Commentary

Neoadjuvant targeted therapy for advanced renal cell carcinoma: Where do we stand?

During the last two decades and until recently, there has been an annual increase of about 2% in the global incidence of renal cell cancer (RCC) while in Europe, the overall mortality rates for RCC increases again in recent years.[1] Surgical therapy remains the mainstay of therapy to achieve a cure in the management of RCC. For solitary renal tumors up to a diameter of 7 cm (T1), nephron-sparing surgery is the standard procedure, whereas radical nephrectomy is the necessary treatment for more advanced stages.[2]

Recent advances in molecular biology have led to the development of several novel agents for the treatment of metastatic RCC (mRCC). Vascular endothelial growth factor-pathway inhibitors (sunitinib, sorafenib, pazopanib, bevacizumab, axitinib) and mammalian target of rapamycin-inhibitors (everolimus and temsirolimus) has substantially improved the outcomes of patients with mRCC.[3] Moreover, the above molecules are increasingly being used preoperatively to achieve cytoreduction.

There are many advantages of administering molecular treatment with targeting molecules before planned definitive surgery to patients with non-metastatic RCC. First of all therapy is delivered at the earliest time-point, when the burden of micrometastatic disease is expected to be low. In addition tolerability of therapy is expected to be better before surgery rather than after, whereas patients with micrometastatic disease might respond to neo-adjuvant therapy and reveal a favorable pathological status. Moreover, a possible reduce of tumor size could make it more amenable to surgery.[4] Overtreatment of non-responders and those in the non-target population (i.e. patients without micrometastatic disease) is a major drawback in using neo-adjuvant therapy while delayed surgery might compromise the outcome in patients not sensitive to targeted treatment. In addition, hemorrhagic and wound healing issues have emerged and a significant increase in the incidence and severity of intraoperative adhesions have been shown in several studies.[5] The response of the primary tumor to the targeted molecular treatment seems to be unpredictable and relatively less compared with the metastatic tumor.

A period of presurgical targeted therapy may identify those patients with rapid disease progression prior to a planned nephrectomy or metastasectomy from which they may not benefit. In non-randomized prospective studies of presurgical therapy, up to 26% of patients progressed at metastatic sites prior to plann surgery. Those with intermediate risk and absence of progression had a more than 70% probability to survive 2 years or longer after nephrectomy.[6]

Sunitinib is the most potent agent which showed the maximum response in neo adjuvant treatment. Studies have shown that it caused the maximum reduction in the tumor size and the regression of tumor thrombus.[7] Moreover there is a report of complete radiological and histological regression of tumor with Sunitinib but the response is very unpredictable.[8]

Currently, there is no indication for neo-adjuvant or adjuvant therapy for RCC, outside controlled clinical trials.[2] The small number of patients in this study limit the ability to widely extrapolate the results. Major methodological biases preclude any firm conclusion regarding the routine use of adjuvant therapy. However, this study adds to the body of literature suggesting that sunitinib based pre-operative therapy may have a role in renal cancer.

The optimal neo-adjuvant strategy remains to be determined. Predictive biomarkers are urgently needed in order to determine, which patients are more likely to benefit from neo-adjuvant pharmaceutical therapy.

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