TREATMENT OF METASTATIC RENAL CARCINOMA PATIENTS WITH THE COMBINATION OF GEMCITABINE, CAPECITABINE AND BEVACIZUMAB AT A TERTIARY CANCER CENTRE

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Treatment options for advanced RCC have dramatically multiplied in relatively few years, rendering a once orphan disease an ‘overcrowded’ one, with six molecularly targeted agents that have proved to benefit patients from different treatment settings within randomized controlled phase III trials [1–7].

Despite these successes, advanced RCC should still be regarded as incurable. Besides the highly perceived problem of how best exploiting all the agents presently available, i.e., how best sequencing them, another emerging issue is that of those patients who have failed more than one anti-vascular endothelial growth factor (receptor) [VEGF(R)] inhibitor, as well as an mammalian target of rapamycin (mTOR) inhibitor.

Indeed, with the exception of those 20–25% of unlucky patients with advanced RCC who unfortunately and dramatically will not respond to any of the available treatments, an increasing number of patients will ultimately receive several lines of active, molecularly targeted treatments.

Consequently, also increasing is the number of patients who, after receiving three, four, or more lines of treatment, are still candidates to further treatment options.

This intriguing preliminary report by Jonasch *et al*. suggests that a combination of the anti-VEGF monoclonal antibody bevacizumab plus two relatively old chemotherapeutic agents (i.e., capecitabine and gemcitabine) endowed with some (even though limited) activity against kidney cancer [8,9] could benefit patients with advanced RCC, mainly from the intermediate- and poor-risk groups according to the Motzer’s classification [10], already pre-treated also with tyrosine kinase inhibitors.

Furthermore, the authors selected individuals to receive the combination of capecitabine, gemcitabine and bevacizumab based on the presence of aggressive tumour characteristics, including multiple negative risk factors, multiple sites of disease, sarcomatoid features, and refractoriness to anti-angiogenic therapies.

The rationale for this courageous choice lies in some provocative preclinical works suggesting that remodelling of the endothelium occurring over time, with resistant subsets of endothelial cells replacing those who are dependent on VEGF signalling, being responsible for the development of resistance to anti-angiogenic agents [11].

In such a hypothetical scenario, the use of agents that may alter epithelial tumour function and decrease paracrine

factor secretion may potentiate the activity of anti-angiogenic therapy, or re-sensitise tumour cells (as well as endothelial cells) to their action.

Furthermore, interest in the use of traditional cytotoxic chemotherapy in advanced RCC has bounced back because of a recent provocative finding from a phase III trial of immunotherapy [12]; indeed, we have seen that the use of chemotherapy after a first progression on immunotherapy was significantly associated with a longer time from first progression to death.

Should chemotherapy, eventually given in association with anti-VEGF(R) drugs, be revitalized in RCC in the peculiar setting of molecularly targeted agents-refractory patients? Realistically, it is too early to say, but the experience of Jonasch *et al*. deserves attention and, especially, warrants further studies.

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