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Addition of Bevacizumab to Temsirolimus in Kidney Cancer Patients

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Key Words
Renal carcinoma · Treatment · Combination · Temsirolimus · Bevacizumab

Abstract
Treatment of metastatic kidney cancer has changed dramatically in the past years with the use of VEGF-targeted therapies and mTOR inhibitors. However, resistance occurs. We report here two cases of patients who benefited, both on disease control and side effects, from the addition of bevacizumab to temsirolimus, after progression on the mTOR inhibitor alone.

Introduction

Treatment of metastatic kidney cancer has changed dramatically over the past years with the use of VEGF-targeted therapies and mTOR inhibitors. However, resistance occurs. We report here two cases of patients who benefited from the addition of bevacizumab to temsirolimus.

Case 1

A 48-year-old man presented with several episodes of loss of consciousness in 2005. The MRI showed 2 hypervascular brain lesions. The CT scan showed a small right kidney tumour. He underwent right partial nephrectomy. Pathological examination of the surgical specimen showed a pT3aNx grade II clear cell carcinoma. The brain metastases were treated with gamma-knife radiosurgery.

In 2006, he developed lung metastases and mediastinal lymph nodes. In March 2007, the mediastinal lymph nodes increased and he was started on sunitinib (50 mg 4 weeks on treatment and 2 weeks off). He had a partial response. In April 2008, the mediastinal lymph nodes increased and he developed lymphangitic carcinomatosis and required oxygen. He was switched to temsirolimus (25 mg IV/week). The lesions were stable but the lymphangitic infiltration was extensive and the patient still experienced dyspnoea. Bevacizumab was added to temsirolimus in July 2008. He improved dramatically, his oxygen

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consumption decreased. On the CT scan the mediastinal lymph nodes and the lymphangitic carcinomatosis lesions improved. However, he progressed again in March 2009 and died in April 2009.

Case 2

A 54-year-old man presented with hematuria revealing a left kidney tumour in January 2004. He underwent a left radical nephrectomy. The pathological examination showed a pT2 clear cell carcinoma, Furman grade II tumour. In March 2005, he progressed with liver and lung metastases and he was enrolled in the phase III study comparing interferon to sunitinib. He had slowly progressive disease on interferon and crossed over to sunitinib in March 2006. He had a partial response. In July 2008, the lung and liver lesions were stable but he developed peritoneal carcinomatosis with ascitis. He was started on temsirolimus: ascitis was less abundant, the other lesions were stable. However, he became anaemic requiring blood transfusions. There were probably several causes to his anaemia (a side effect of temsirolimus and the disease). In January 2009, the liver lesions increased and he was started on a combination of bevacizumab (10 mg/kg every 2 weeks) and temsirolimus (20 mg IV weekly). His general condition improved, the anaemia disappeared, the lesions were stable and the ascitis much less abundant. He felt that he had fewer side effects on the combination treatment than on temsirolimus alone. However, in July 2009, he progressed and died in August 2009.

Discussion

These two cases show the effect of adding bevacizumab to temsirolimus for patients who were progressing on the mTOR inhibitor. Treatment of metastatic kidney cancer has changed dramatically in the past years with the use of VEGF-targeted therapies and mTOR inhibitors. The VEGFR tyrosine kinase inhibitor, sunitinib, is usually used in the first-line setting. Another tyrosine kinase inhibitor or an mTOR inhibitor can be used in the second-line setting, after progression on initial treatment. Mechanisms of resistance are not fully understood. Resistance to VEGF pathway inhibition can be caused by upregulation of alternative pro-angiogenic factors (FGF, angiopoietin…), inadequate target inhibition or enhanced receptor signalling [1]. Increasing VEGF blockade by combining therapies could be an interesting option in that case. There are a few cases in the literature of patients who were progressing on sunitinib and who benefited from the adjunction of bevacizumab; however, the first data show that these combinations are very toxic [2].

mTOR is formed of two multiprotein complexes: mTORC1 and mTORC2. Rapamycin and current mTOR inhibitors inhibit mTORC1 and not mTORC2. Inhibition of mTORC1 leads to compensatory activation of PI3K and AKT. This could drive upregulation of mTORC2 and further activation of Akt and HIF2α. This could therefore lead to increase of expression of HIF2α target genes, such as VEGF. Combining VEGF-blocking agents with mTOR inhibitors could contribute to reversing resistance when used in a sequential manner. However, results from the TORAVA phase II randomized trial show no improvement of non-progression rates with the upfront combination of bevacizumab and temsirolimus but increased toxicity leading to a high drop-out rate [3].

There is no data in the literature on why patients should feel fewer side effects when adding bevacizumab to temsirolimus. However, some reports already mention the development of polyglobulia with anti-angiogenesis agent. This effect may correct a pre-existing anaemia [4–6].

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