FGFR inhibitor induced peripheral neuropathy in patients with advanced RCC

Most patients with advanced renal cell carcinoma (RCC) respond poorly to cytokine therapy, and, until recently, the median survival for patients with metastatic disease was reported to be ~13 months [1]. Inhibition of angiogenesis has emerged as an important therapeutic strategy in a variety of solid tumors. This is particularly true in patients with metastatic RCC, who could potentially benefit from three approved angiogenesis inhibitors that target vascular endothelial growth factor (VEGF) signaling (bevacizumab, sunitinib, and sorafenib). There are now five targeted agents, i.e. sorafenib, sunitinib, temsirolimus [2], bevacizumab (in combination with interferon), and everolimus, that have been shown to improve the outcome in patients with metastatic clear cell renal cell carcinoma, in randomized controlled trials (RCTs). Different other targets seem to be interesting in RCC such as mesenchymal-epithelial transition factor, Tie, or fibroblast growth factor receptor (FGFR) [3].

A 64-year-old male, treated for hypertension (ramipril, furosemide, and nebivolol), uncomplicated type 2 diabetes (glimepiride), and gammopathy of unknown significance, was diagnosed with localized RCC. Physical examination was normal and he was treated with total nephrectomy. Three years later, the patient developed lung metastases and was treated in first line with immunotherapy. After failure of immunotherapy, he was included in the phase III randomized trial comparing sunitinib versus placebo and presented a partial response. After 18 cycles of treatment, tumor evaluation showed a progressive disease. The patient was enrolled in the phase III randomized trial comparing RAD001 versus placebo and presented a stable disease during 8 months but disease progressed with significant mediastinal lymph nodes. He was included in a phase I protocol with a multitarget tyrosine kinase inhibitor against vascular endothelial growth factor receptor (VEGFR) 2 and FGFR. FGFR inhibitor TKI258 is a broad-targeted-profiled RTK inhibitor active against these three receptor tyrosine kinases [VEGF and fibroblast growth factor (FGF)] involved in tumor cell growth. The most common adverse events were predominantly mild to moderate [3]. Physical examination was normal at the enrolment in the phase I study as routine laboratory investigations except for the inflammatory syndrome. No new treatment was added. After 2 months of treatment, the patient developed pain and grade I dysesthesias in the sole of the feet. The patient presented mild peripheral neuropathy symptoms with numbness and pain. An electromyogram demonstrated a distal axonal evolutive neuropathy which was predominantly sensitive. As the symptoms involved all the feet, gabapentine was added which alleviated significantly the pain allowing the continuation of the phase I. Tumor evaluation showed stable disease after 6 months and the patient is still ongoing. The neurologic symptoms remain controlled with gabapentine. The diabetes or the monoclonal gammopathy of undetermined significance did not worsen during this period.

Peripheral neuropathies are a common side-effect of various chemotherapy regimen such as cisplatin, taxane, and antimicrotules agents [4]. Progress has been achieved in the management of cancer with the advent of targeted therapies, in particular, in metastatic RCC. Nevertheless, targeted therapies can inhibit major pathways in normal or noncancerous cells leading to unexpected off-target side-effects. FGF is known to be an essential growth factor for neurons [5] and the inhibition of FGFR seems to induce neurotoxicity.

The imputability of the new inhibitor of FGFR/VEGFR2 is highly likely as peripheral neuropathy has not been described with RAD001 and no other treatment was prescribed simultaneously. Physical examination was normal before the inclusion in the phase I; the new drug is the lone new event occurring in this patient and is therefore probably involved in the neuropathy.

The existence of comorbidities which can be complicated by peripheral neuropathy such as diabetes and monoclonal gammopathy of undetermined significance here could have a worsening effect on the neuropathy in this patient.

In conclusion, this is the first report of peripheral neuropathy in advanced RCC patients treated with VEGFR and FGFR inhibitors. Oncologists should be aware of this new side-effect of FGFR inhibitors in patients.

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