Good response to second-line bevacizumab and interferon-α in a sunitinib-refractory patient with metastatic renal cell carcinoma

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In recent years with the development of targeted agents such as bevacizumab, sunitinib, sorafenib, temsirolimus, and everolimus, the treatment of metastatic renal cell carcinoma has changed dramatically. In clinical practice, sunitinib and bevacizumab are reserved for first-line treatment, but despite various guidelines, optimal treatment is still uncertain. We present, for the first time, a case of a good response to second-line bevacizumab and interferon-α in a patient who failed classical sunitinib treatment. ***Anti-Cancer Drugs*** **21:210–213 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Renal cell carcinoma (RCC) is diagnosed in about 120 000 patients in Europe and the United States every year and is estimated to have caused 13 010 deaths in the United States in 2008 [1,2]. Among several histological types of RCC, the most common is clear-cell renal carcinoma and one-third of patients present with metastatic disease [3].

Metastatic RCC (mRCC) is resistant to classical cytotoxic chemotherapy while immunotherapy with either interleukin-2 or interferon-α (IFN-α) results in modest overall response rates (from 10 to 20%) and in durable complete responses in only 6% of patients [4,5]. An improved understanding of the biology of RCC resulted in the development of novel targeted agents such as multitargeted receptor tyrosine kinase inhibitors (TKIs), sunitinib and sorafenib; the vascular endothelial growth factor (VEGF) ligand-binding monoclonal antibody bevacizumab; and the mammalian target of rapamycin kinase inhibitors temsirolimus and everolimus. Numerous guidelines have been drawn but the best therapy is still uncertain; however, in clinical practice, sunitinib and bevacizumab are reserved for first-line treatment in good and intermediate Memorial Sloan-Kettering Cancer Center (MSKCC) risk score patients, whereas sorafenib was approved as second-line treatment in cytokine-refractory patients.

We present, for first time, the case of a patient with mRCC who had a good response to second-line bevacizumab and IFN-α after failing the standard first-line sunitinib.

Case report

In November 2006 a 67-year-old woman presented with gross hematuria and abdominal pain; imaging studies revealed a localized right renal tumor and she was subjected to right nephrectomy; the subsequent pathological examination and staging showed clear-cell renal carcinoma with moderate histological differentiation (grade 2) and stage pT3aN0M0. The MSKCC risk score was intermediate because of anemia. For 1 year the patient remained in good clinical condition and imaging studies did not show signs of disease recurrence. In December 2007 a chest computed tomography (CT) revealed multiple nodules in both lungs with mediastinal lymphadenopathy. The subsequent cytological examination showed this to be a RCC recurrence. Immediately, she started therapy with sunitinib (50 mg daily) for 4 weeks followed by 2 weeks without treatment; after 2 months of treatment a chest and abdominal CT showed a partial response (according to Response Evaluation Criteria in Solid Tumors) but she also presented grade 3 mucositis and grade 3 skin toxicity (according to the National Cancer Institute's common toxicity criteria, version 3.0) that forced a reduction in sunitinib dosing by 50%. After 5 months of further treatment a CT for restaging showed progression in number and size of the pulmonary and lymph nodal metastases (maximum diameter of 2.6×2 cm). Thus, sunitinib treatment was discontinued; sorafenib was not considered as an appropriate second-line treatment because of its possible toxicity, in particular cutaneous rash, similar to sunitinib that was so badly tolerated. Therefore, after 4 weeks of

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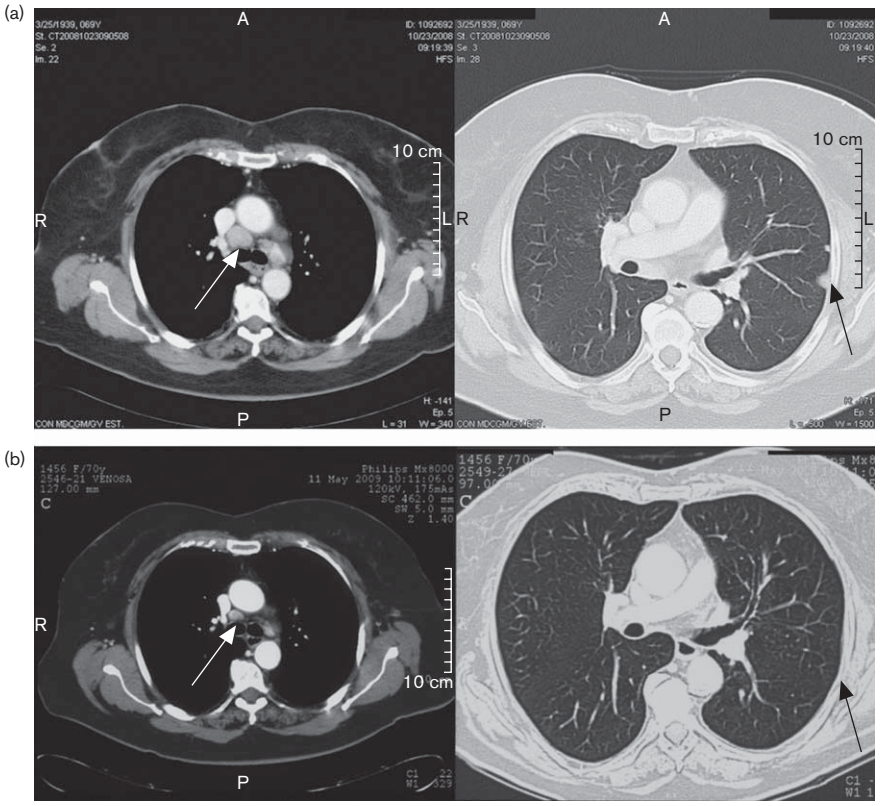
Fig. 1



Computed tomography images of the patient before (a) and after 8 months from second-line bevacizumab and interferon-α treatment (b).

her earlier treatment we decided, under compassionate use circumstances, to start therapy with bevacizumab (10 mg/kg) every 2 weeks and IFN-α 3 MIU three times weekly. Two months later we performed a chest CT that showed a partial response (Response Evaluation Criteria in Solid Tumors) of pulmonary lesions and mediastinal lymph nodes; because of this response the woman continued treatment. Eight months after starting the second-line therapy a chest and abdomen CT documented a further partial response (see Fig. 1): no more evidence of pulmonary lesions and further reduction of mediastinal lymph nodes (maximum diameter of 1.5 × 1 cm). Furthermore, during this treatment the patient did not show significant toxicities and had always been in good clinical condition. The time elapsed since the start of first-line treatment to date was 16 months, the time since bevacizumab and IFN-α therapy to date was 8 months, and the time to progression after initial treatment was 7 months.

Discussion

To our knowledge there are no studies with bevacizumab and IFN-α after first-line multitargeted TKIs.

Regarding first-line treatment, sunitinib and bevacizumab plus IFN-α are now advised for patients with good and intermediate MSKCC risk score although, recently, sunitinib was also seen to be active in poor-risk patients [6]. The two phase III studies, AVOREN [7] and CALGB [8] showed that median duration of progression-free survival was significantly longer in the group receiving the combination of bevacizumab (10 mg/kg every 2 weeks) and IFN-α (9 MIU three times weekly) (10.2 and 8.5 months, respectively) than it was in the IFN-α group (5.4 and 5.2 months, respectively), although, recently, data from American Society of Clinical Oncology 2009 [9,10] showed that the difference in terms of overall survival did not reach statistical significance. Moreover, Melichar *et al.* [11] performed a subgroup analysis showing that throughout IFN-α dose reduction it is possible to better manage the side effects with the same efficacy.

Similarly, temsirolimus has proven effective in first-line therapy for patients with poor prognostic criteria in a phase III trial [12]. With regard to second-line treatment, sorafenib seems effective in cytokine-refractory patients [13]; and in two phase II studies sunitinib showed clinical activity, as well [14,15]. Despite the fact that bevacizumab is not currently approved for second-line treatment, in a phase II study by Yang *et al.* [16] bevacizumab alone showed activity in cytokine-refractory patients.

Data from a phase III trial indicated that patients failing one or both TKIs enjoyed significantly longer progression-free survival with everolimus [17]; overall, numerous studies have shown that sequential therapy in RCC should provide a clinical benefit and a survival advantage to patients. Retrospective studies analyzed the sequence of TKIs [3,18,19] showing the lack of cross-resistance between them, a likely longer time of disease control with sorafenib followed by sunitinib treatment than vice versa, as well as showing clinical activity of sunitinib or sorafenib after bevacizumab treatment [20,21].

It is thought that different sequences of drugs can give different outcomes, and thus it is very important to know their mechanism of action to have the best impact. Over time, tumors tend to accumulate genetic mutations and express increasing numbers of abnormal receptors [22]. This suggests that a targeted agent that inhibits a single factor, such as bevacizumab, may be more effective as first-line treatment whereas multitargeted agents, such as sunitinib and sorafenib, should be used more actively as second-line treatment. In contrast, the optimal sequence of therapy may be influenced by numerous factors such as tolerability of therapy, MSKCC-risk score and plasma VEGF levels.

Plasma VEGF could be a candidate marker to predict clinical benefit for the treatment. Earlier studies have shown that serum VEGF is correlated with stage and recurrence after definitive local resection. Moreover, higher serum VEGF has also been associated with poorer outcome with sunitinib therapy [23]. It was shown that sunitinib modulates circulating VEGF pathway biomarkers increasing plasma VEGF-A levels with respect to baseline, in particular in patients who experience disease progression after the first two cycles of treatment [24]. In addition, recently, Escudier *et al.* [13] showed that both patients with high-VEGF and low-VEGF levels benefit from sorafenib as second-line treatment, although the high-VEGF patients may benefit more. Thus, patients with high plasma VEGF may benefit from a sorafenib treatment or second-line bevacizumab and IFN-α if they have disease progression during sunitinib therapy; likely, bevacizumab, by binding to VEGF, may inhibit the signaling pathway involved in sunitinib or sorafenib resistance. Unfortunately, in our case we did not analyze the plasma VEGF level, but, in conclusion, we showed a lack of cross-resistance between sunitinib and subsequent bevacizumab, and a possible role for bevacizumab and IFN-α treatment after failing TKI in specific patients; nevertheless, the reduced dose of IFN-α made it possible to obtain a good response and, at the same time, to reduce the multiple and serious side effects that, normally, could be caused by higher doses.

In contrast, in our case the patient received a reduced dosage of sunitinib. Activity of antiangiogenic therapy following failure of this line might not be an accurate demonstration of efficacy; however, we must also consider the extended period of treatment of this patient. It must also be said that the good response might be due to IFN-α alone; it is impossible to separate the effects of the two agents, bevacizumab and IFN-α.

Significant advances in the treatment of mRCC have been made during the past few years; however, prospective studies are needed to discern optimal treatment and provide a better understanding of the agents' mechanisms of action, as well as to develop biomarkers to predict clinical benefit to therapy.

References

1 Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 2007; **18**:581–592.

2 Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, *et al.* Cancer statistics, 2008. *CA Cancer J Clin* 2008; **58**:71–96.

3 De Reijke TM, Bellmunt J, van Poppel H, Marreaud S, Aapro M. EORTC-GU group expert opinion on metastatic renal cell cancer. *Eur J Cancer* 2009; **45**:765–773.

4 Horoszewicz JS, Murphy GP. An assessment of the current use of human interferons in therapy of urological cancers. *J Urol* 1989; **142**: 1173–1180.

5 Rosenberg SA, Yang JC, White DE, Steinberg SM. Durability of complete responses in patients with metastatic cancer treated with high-dose interleukin-2: identification of the antigens mediating response. *Ann Surg* 1998; **228**:307–319.

6 Gore ME, Szczylik C, Porta C, Bracarda S, Bjarnason GA, Oudard S, *et al.* Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. *Lancet Oncol* 2009; **10**:757–763.

7 Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, *et al.* Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* 2007; **370**:2103–2111.

8 Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Ou SS, *et al.* Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J Clin Oncol* 2008; **26**:5422–5428.

9 Escudier BJ, Bellmunt J, Negrier S, Melichar B, Bracarda S, Ravaud A, *et al.* Final results of the phase III, randomized, double-blind AVOREN trial of first-line bevacizumab (BEV) + interferon-a2a (INF) in metastatic renal cell carcinoma (mRCC). *J Clin Oncol* 2009; **27** (**Suppl; abstract 5020**):243s.

10 Rini BI, Halabi S, Rosenberg J, Stadler WM, Vaena DA, Atkins JN, *et al.* Bevacizumab plus interferon-alpha versus interferon-alpha monotherapy in patients with metastatic renal cell carcinoma: results of overall survival for CALGB 90206. *J Clin Oncol* 2009; **27** (**Suppl; abstract LBA5019**):18s.

11 Melichar B, Koralewski P, Ravaud A, Pluzanska A, Bracarda S, Szczylik C, *et al.* First-line bevacizumab combined with reduced dose interferon-alpha2a is active in patients with metastatic renal cell carcinoma. *Ann Oncol* 2008; **19**:1470–1476.

12 Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, *et al.* Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007; **356**:2271–2281.

13 Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Staehler M, *et al.* Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol* 2009; **27**:3312–3318.

14 Motzer RJ, Michaelson MD, Redman BG, Hudes GR, Wilding G, Figlin RA, *et al.* Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006; **24**:16–24.

15 Motzer RJ, Rini BI, Bukowski RM, Curti BD, George DJ, Hudes GR, *et al.* Sunitinib in patients with metastatic renal cell carcinoma. *JAMA* 2006; **295**:2516–2524.

16 Yang JC, Haworth L, Sherry RM, Hwu P, Schwartzentruber DJ, Topalian SL, *et al.* A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003; **349**:427–434.

17 Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, *et al.* Efficacy of everolimus in advanced renal cell carcinoma: a

double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008; **372**:449–456.

18 Szczylik C, Demkow T, Staehler M, Rolland F, Negrier S, Hutson TE, *et al*. Randomized phase II trial of first-line treatment with sorafenib versus interferon in patients with advanced renal cell carcinoma: final results. *J Clin Oncol* 2007; **25** (**Suppl; abstract 5025**):18s.

19 Dudek AZ, Zolnierek J, Dham A, Lindgren BR, Szczylik C. Sequential therapy with sorafenib and sunitinib in renal cell carcinoma. *Cancer* 2009; **115**:61–67.

20 Rini BI, Michaelson MD, Rosenberg JE, Bukowski RM, Sosman JA, Stadler WM, *et al*. Antitumor activity and biomarker analysis of sunitinib in patients with bevacizumab-refractory metastatic renal cell carcinoma. *J Clin Oncol* 2008; **26**:3743–3748.

21 Tamaskar I, Garcia JA, Elson P, Wood L, Mekhail T, Dreicer R, *et al*. Antitumor effects of sunitinib or sorafenib in patients with metastatic renal cell carcinoma who received prior antiangiogenic therapy. *J Urol* 2008; **179**:81–86.

22 Lea IA, Jackson MA, Li X, Bailey S, Peddada SD, Dunnick JK. Genetic pathways and mutation profiles of human cancers: site- and exposure-specific patterns. *Carcinogenesis* 2007; **28**:1851–1858.

23 George DJ, Michaelson MD, Rosenberg JE, Bukowski RM, Sosman JA, Stadler WM, *et al*. Phase II trial of sunitinib in bevacizumab-refractory metastatic renal cell carcinoma (mRCC): updated results and analysis of circulating biomarkers. ASCO Annual Meeting Proceedings Part I. *J Clin Oncol* 2007; **25** (**Suppl; abstract 5035**):18s.

24 Kontovinis LF, Papazisis KT, Touplikioti P, Andreadis C, Mouratidou D, Kortsaris AH. Sunitinib treatment for patients with clear-cell metastatic renal cell carcinoma: clinical outcomes and plasma angiogenesis markers. *BMC Cancer* 2009; **9**:82.