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Do anti-angiogenic therapies prevent brain metastases in advanced renal cell carcinoma?

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Abstract. **Background.** We analyzed renal cell carcinoma (RCC) brain metastasis (BM) risk factors and compared BM occurrence in metastatic RCC (mRCC) treated with or without anti-angiogenic agents (AA). **Methods.** Data from all consecutive metastatic RCC patients (patients) treated in a french cancer center between 1995 and 2008 were reviewed. Patients had histologically confirmed advanced RCC without synchronous BM at the time of metastasis diagnosis. AA were sorafenib, sunitinib and bevacizumab. We also included patients treated with mTor inhibitors, temsirolimus and everolimus, as they also demonstrated anti-angiogenic activities. Characteristics of the two groups treated with or without AA were compared with a Fisher exact test. Impact of AA on overall survival (OS) and cumulative rate of brain metastasis (CRBM) was explored by Kaplan-Meier method. **Results.** One hundred and ninety-nine patients with advanced RCC were identified, 51 treated with AA and 148 without AA. The median follow-up duration was 40 months. BM occurred in 35 patients. Characteristics between AA treated and non-AA treated groups were unbalanced and favoring better prognostic factors in AA treated group. Median OS was 24 months. AA treatment was not associated with a lower CRBM (HR = 0.58 [0.26-1.30], $P = 0.187$). Median survival free of BM was 11.8 months, CI95% (4.95-18.65) in the group without AA treatment and 28.9 months in the AA group, CI95% (18.64-39.16). Alkaline phosphatase (AP) was an independent prognostic factor for BM ($P = 0.05$). In multivariate Cox model, after adjustment to AP, AA did not improve the CRBM (aHR = 0.53 [0.22-1.32]). **Conclusion.** In this retrospective study, AA did not decrease significantly the CRBM. Elevated AP was a predictive factor for BM in mRCC. ▲

Key words: renal, cancer, brain, metastasis, anti-angiogenic, targeted therapies

Background

One-third of renal cell carcinoma (RCC) is diagnosed with a metastatic stage at the time of diagnosis [1] and 30 to 50% of patients undergoing curative surgery will develop metastases [2, 3]. Among the different sites of distant metastases in RCC, brain metastases (BM) occur in 2 to 17% of patients [4, 5]. In a cohort of 2,724 patients diagnosed with solid tumors analyzed by Schouten *et al.*, kidney cancer is ranked second, after lung cancer, in term of highest cumulative incidence of BM at 5 years [4]. As a metastatic location, the central nervous system (CNS) has a poor prognosis. Overall survival (OS) after a diagnosis of RCC BM ranges from 3 to 14 months [5-7]. CNS is also a particular metastatic site considering the difficulty to achieve long-lasting response with medical treatments. The specificities of brain tissue and its blood-brain barrier (BBB), highly expressing multidrug resistance transporters, can alter antitumoral drugs distribution in brain tissue [8]. BBB integrity can also be altered within the tumor, with new vasculature highly permeable, favoring crossing of BBB by treatment. Nevertheless, high-pressure difference of interstitial fluid between the tumor and normal brain limits the drug accumulation in brain tumor, even in case of BBB compromised, and enhances drug diffusion to surrounding tissue and out of the brain [8].

Anti-angiogenic agents (AA), blocking various aspects of the VEGF pathway have demonstrated clear antitumor activity and have emerged as a milestone in the management of metastatic RCC (mRCC). Among

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AA approved, sunitinib and sorafenib are both multi-targeted tyrosine kinase inhibitors (TKI) [9, 10]. The combination of bevacizumab, humanized monoclonal antibodies neutralizing the major isoforms of VEGF-A and interferon has also shown superiority to interferon alone [11]. The mammalian target of rapamycin (mTOR) inhibitors, temsirolimus and everolimus also showed antitumor activities in the same setting [12]. The mTOR protein is a protein kinase involved in the phosphatidylinositol 3-Kinase (PI3K)/AKT signaling pathway with a central role in the control of cell growth, survival and also angiogenesis [13].

Recently, Gore *et al*. showed retrospectively some activities of AA on brain metastases in a large cohort of mRCC patients all treated with sunitinib. Among the 213 evaluable patients, 26 (12%) had an objective response in the BM [14]. Nevertheless, in a French prospective phase II study, sunitinib demonstrated no objective response in the brain metastases. The primary endpoint of this study was to determine the objective response rate in the brain after two courses of sunitinib in patients diagnosed with mRCC and BM non pretreated non-operable [15]. From 2009 to 2011, 17 patients were enrolled. One patient diagnosed with cerebral hemorrhage died before treatment start and 16 patients were evaluable after two cycles. Best responses on CNS were stabilization of the disease in five patients and no objective response was observed. Twenty grades greater or equal to three adverse events were observed in 12 patients and one toxic death was reported (peritonitis with gastric perforation). However, no neurological complication related to sunitinib was registered.

We performed charts analysis of all consecutive patients referred to our cancer center with a diagnosis of metastatic RCC to determine RCC BM risk factors and to compare BM occurrence in patients treated with or without AA. Our main objective is to analyze if AA can prevent or delay the occurrence of BM in advanced RCC.

Patients and methods

Patients and collected data

Retrospectively, data from all consecutive mRCC patients treated in the Northern France Cancer Center (Centre Oscar-Lambret, Lille) between 1995 and 2008 were reviewed. All patients had a metastatic and histologically confirmed RCC. Bellini duct, urothelial and neuroendocrine carcinoma, nephroblastoma and sarcoma were excluded (148 patients). The metastatic work-up consisted of computerized tomography (CT) of the chest and abdomen, cranial CT or MRI and bone scan. Brain imaging, brain CT scan with contrast or brain MRI, were part of the baseline work-up for more than 95% of the patients. Patients with BM at diagnosis of the primary tumor or at the diagnosis of first metastases were excluded (24 patients), even patients diagnosed with BM surgically treated who will subsequently receive specific medical treatments. Brain imaging was repeated if patients presented with neurological symptoms. Patients were treated with best supportive care with or without immunotherapy (Interferon, interleukin 2 or both), chemotherapy (vinblastine, gemcitabine), bisphosphonate or targeted therapies with AA depending on drugs available at the time of diagnosis, co-morbidities and the performance status. AA included sorafenib, sunitinib, bevacizumab, temsirolimus, or everolimus. Data collected included: patients characteristics (age, gender, occurrence of deep vein thrombosis [DVT], history of arterial hypertension), tumors features (side, size, histology subtype, presence of sarcomatoid component, Fuhrman grade, pT, pN, capsular rupture of lymph nodes, lymphovascular invasion [LVI]), extension of the disease (number of metastatic sites, metastases location, presence of local relapse, occurrence of brain metastasis, interval time diagnosis to first metastasis), biology (natremia, protidemia, albuminemia, calcemia, corrected calcemia, lacticodehydrogenase [LDH], alkaline phosphatase, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin, neutrophil, lymphocyte) and treatment. Platelet count was also collected, but due to high number of missing data, it is not reported.

Endpoints

The primary endpoint was to compare the cumulative rate of brain metastasis (CRBM) in RCC patients treated with AA *versus* without AA. The secondary endpoints were to determine risk factors for BM and OS analysis.

Statistical analysis

The description of the population was based on median and extreme values for continuous parameters and frequency for categorical parameters. The continuous parameters have been categorized according to the observed median values. The characteristics of the two groups treated with or without AA were compared with a Fisher exact test.

The OS, survival free of brain metastasis and the CRBM were established from the date of the first extra cerebral metastasis until the date of death (OS), the diagnosis of brain metastasis (survival free of brain metastasis and CRBM) or until the last follow-up. The impact of treatment with AA on OS and CRBM was explored by Kaplan-Meier method. We took into account the differences between patients having received AA and those having not received AA. We identified potential confounders as parameters with significant different repartition in both populations and significantly correlated to CRBM. We subsequently conducted an adjusted analysis using Cox model.