Original Article

Vascular Endothelial Growth Factor-Targeted Therapy for the Treatment of Adult Metastatic Xp11.2 Translocation Renal Cell Carcinoma

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BACKGROUND: Adult "translocation" renal cell carcinoma (RCC), bearing transcription factor E3 (*TFE3*) gene fusions at Xp11.2, is a recently recognized, unique entity for which prognosis and therapy remain poorly understood. In the current study, the authors investigated the effect of vascular endothelial growth factor (VEGF)-targeted therapy in this distinct subtype of RCC. **METHODS:** A retrospective review was conducted to describe the clinical characteristics and outcome of adult patients with metastatic Xp11.2 RCC who had strong TFE3 nuclear immunostaining and received anti-VEGF therapy. Tumor response to anti-VEGF therapy was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The Kaplan-Meier method was used to estimate progression-free survival (PFS) and overall survival (OS) distributions. **RESULTS:** Fifteen patients were identified, of whom 10, 3, and 2 received sunitinib, sorafenib, and monoclonal anti-VEGF antibodies, respectively. The median follow-up was 19.1 months, the median age of the patients was 41 years, and the female:male ratio was 4:1. Initial histologic description included clear cell (n = 8 patients), papillary (n = 1 patient), or mixed clear cell/papillary RCC (n = 6 patients). Five patients had received prior systemic therapy. Five patients had undergone fluorescent in situ hybridization analysis and all demonstrated a translocation involving chromosome Xp11.2. When treated with VEGF-targeted therapy, 3 patients achieved a partial response, 7 patients had stable disease, and 5 patients developed progressive disease. The median PFS and OS of the entire cohort were 7.1 months and 14.3 months, respectively. **CONCLUSIONS:** Adult-onset, translocation-associated metastatic RCC is an aggressive disease that affects a younger population of patients with a female predominance. In the current study, VEGF-targeted agents appeared to demonstrate some efficacy. ***Cancer*** **2010;116:5219–25.**

KEYWORDS: vascular endothelial growth factor (VEGF), sunitinib, adult translocation renal cell carcinoma (RCC), targeted therapy, kidney cancer.

Translocation carcinomas of the kidney were first described in children and adolescents and are usually considered indolent, even if diagnosed at an advanced stage in this population of patients.[1] Various cytogenetic translocations have been shown to be tumor specific, with the vast majority of these translocations involving the transcription factor E3 (*TFE3*) gene located on Xp11.2. The TFE3 protein encoded by this gene interacts with transcription regulators such as E2F3, SMAD3, and lymphoid enhancer-binding factor-1 (LEF-1), and is involved in transforming growth factor (TGF)-beta-induced transcription, playing important roles in cell growth, proliferation, and osteoclast and macrophage differentiation.[2] The most common translocations involve an alveolar soft part sarcoma locus (*ASPL*)-*TFE3* or renal cell carcinoma (RCC) papillary 1 gene (*PRCC*)-*TFE3* fusion.[2,3]

Xp11 translocation RCCs have recently been included as a separate entity in the 2004 World Health Organization classification of renal tumors.[4] Although these tumors comprise at least one-third of pediatric RCCs, to our knowledge far fewer adult cases have been reported.[5] Given the degree to which these tumors overlap morphologically with clear cell

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and/or papillary RCC, many cases of adult Xp11.2 translocation RCC may be misclassified as clear cell or papillary RCC, and thus the true incidence of this entity may in fact be underestimated.[6] In the past few years, several reports of adults with translocation RCC having an aggressive clinical course have emerged.[7-9]

An improved understanding of the molecular pathways implicated in the pathogenesis of RCC has led to the development of specific targeted therapies to treat this disease. Conventional/clear cell RCC is characterized by inactivation of the von Hippel-Lindau (VHL) tumor suppressor gene, which results in the dysregulation of hypoxia response genes, including an overproduction of vascular endothelial growth factor (VEGF), which promotes tumor growth and progression. In patients with advanced RCC, substantial clinical activity has been reported with VEGF inhibition, leading the US Food and Drug Administration to approve multiple drugs such as sunitinib, sorafenib, pazopanib, and bevacizumab.[10] Clinical trials using these drugs mainly include patients with clear cell histology, based on the role of the VHL gene in this subtype, although clinical activity has been reported in patients with non-clear cell histology.[11,12]

To our knowledge, there are no established effective therapies for metastatic Xp11.2 translocation RCC, although single case reports have recently reported a response to sunitinib.[13,14] Therefore, we performed a retrospective multicenter review of patients with advanced translocation RCC who were treated with VEGF-targeted therapy to assess the clinical features and treatment outcome of this particular RCC subtype.

MATERIALS AND METHODS

Patient Cohort

Patients aged $\geq$18 years with metastatic RCC who underwent clinical evaluation at 4 cancer centers in the United States (Dana-Farber Cancer Institute, Beth Israel Deaconess Medical Center, Karmanos Cancer Institute, and The University of Texas M. D. Anderson Cancer Center) and were treated with VEGF-targeted agents between 2005 and 2009 were the subjects of this retrospective review. Patients had not received prior VEGF-targeted therapy, and had to have pathology slides available for review to be included in this study. A total of 15 patients were identified who met these parameters.

At the time of the initiation of anti-VEGF treatment, all but 1 patient had detailed history and physical examinations, as well as baseline laboratory parameters such as blood counts and chemistries, including lactate dehydrogenase, allowing them to be stratified into the Memorial Sloan-Kettering Cancer Center (MSKCC) risk groups[15] and the recent prognostic groups by Heng et al.[16] In addition, pretreatment tumor status was evaluated with computed tomography scans of the chest, abdomen, and pelvis. Data collected included standard pretreatment disease characteristics, baseline biochemical parameters, prior non-VEGF-targeted therapies, first date of treatment, best response to treatment including tumor measurement data, date of disease progression, and date of death or last follow-up. This study was approved by the Institutional Review Board at each institution.

Pathologic Analysis

Slides were retrieved and reviewed by expert genitourinary pathologists from each corresponding institution. In cases with a suspicious diagnosis based on morphology, the incidence of Xp11.2 translocation RCC was investigated by immunostaining for TFE3, a highly sensitive (>95%) and specific (>95%) marker of Xp11.2 translocation carcinomas.[6] For immunohistochemistry (IHC), slides were incubated with the polyclonal antibody to TFE3 (Clone P-16, dilution of 1:600; Santa Cruz Biotechnology, Santa Cruz, Calif) after antigen retrieval. Cases were included if they demonstrated only strong nuclear immunoreactivity (readily apparent at low-power magnification [$\times$40]) for TFE3 by IHC. When available, cytogenetic analysis and/or fluorescent in situ hybridization (FISH) was performed using home-brew, dual-color, break-apart probes containing RP11-528A24 (specific for the 5′ end of TFE3) and RP11-8A2 (specific for the 3′ end of TFE3).[17]

Statistical Analysis

Objective response was defined using Response Evaluation Criteria in Solid Tumors (RECIST) for all patients.[18] Median survival was defined as the time from the initiation of treatment to the date of death or censoring at the time of last follow-up. Progression-free survival (PFS) was defined from the initiation of treatment to the date of disease progression, death, or censoring at the time of last follow-up. Survival distributions were estimated using the Kaplan-Meier method.[19] All tests of statistical significance were 2-sided. All data analyses were conducted using SAS statistical software (version 9.2; SAS Institute, Inc, Cary, NC).

RESULTS

Patient Characteristics

Table 1 summarizes patient characteristics. Fifteen patients were included in this analysis. The median age at the time of the initiation of therapy was 41 years (range, 18-65 years). The initial stage of disease was stage I in 2 patients (13%), stage II in 1 patient (7%), stage III in 4 patients (27%), and stage IV in 8 patients (53%). Twelve of the 15 patients (80%) were female. Initial histologic classification of the renal tumors included clear cell (n = 8 patients), papillary (n = 1 patient), or mixed clear cell/papillary (n = 6 patients) RCC. The median tumor size at the time of surgery was 8 cm (range, 2-11.4 cm). One-third of patients had received prior systemic therapy (2 had been treated with immunotherapy with high-dose interleukin-2, 1 patient had received chemotherapy, 1 patient had received a vaccine, and 1 patient had been treated with temsirolimus). One of the patients, who received immunotherapy, was treated subsequently with a MET inhibitor (ARQ-197). Twelve patients (80%) had undergone a prior nephrectomy. The most common sites of metastatic disease included the lymph nodes (13 of 15 patients; 87%), bone (7 of 15 patients; 47%), lung (6 of 15 patients; 40%), liver (3 of 15 patients; 20%) and brain (2 of 15 patients; 13%). Two or more sites of metastatic disease at the time of the initiation of therapy were found in 12 of 15 (80%) patients. At the time of therapy initiation, 11 patients (73%) were found to have an Eastern Cooperative Oncology Group performance status of 0 or 1. The median time from the initial diagnosis to metastatic disease was 3.2 months (range, 0-30.2 months). Only 3 patients presented with metastatic disease >1 year after their initial RCC diagnosis. MSKCC and Heng risk groups were favorable, intermediate, poor, and missing in 2, 9, 3, and 1 patients and in 2, 10, 2, and 1 patients, respectively.

Patients received the oral small molecules multityrosine kinase inhibitors sunitinib (N = 10 patients) and sorafenib (n = 3 patients), or the intravenous monoclonal antibodies against the VEGF ligand (bevacizumab; n = 1 patient) or against the VEGF receptor (ramucirumab; n = 1 patient).

Table 1. Patient Characteristics (N = 15)

Baseline Characteristics	No.
Gender	
Male	3
Female	12
Nuclear grade	
2	1
3	8
4	4
Missing	2
Initial stage of disease	
I	2
II	1
III	4
IV	8
Prior nephrectomy	12
ECOG performance status	
0	4
1	7
2	3
Missing	1
>1 metastatic site	12
Site of metastasis	
Lung	6
Lymph nodes	13
Brain	2
Bone	7
Liver	3
Anti-VEGF regimen used	
Sunitinib	10
Sorafenib	3
Bevacizumab	1
Ramucirumab	1
MSKCC risk group	
Favorable	2
Intermediate	9
Poor	3
Missing	1
Heng risk group	
Favorable	2
Intermediate	10
Poor	2
Missing	1
Prior systemic therapy	
Immunotherapy	2
Gemcitabine	1
Vaccine	1
Temsirolimus	1
Prior metastatectomy	6 (3 bone, 2 lymph node, and 1 lung)

ECOG indicates Eastern Cooperative Oncology Group; VEGF, vascular endothelial growth factor; MSKCC, Memorial Sloan-Kettering Cancer Center.

Pathology Results

All 15 patients were found to have strong TFE3 nuclear positivity in their tumors. Cytogenetic investigation reported 5 samples were available for review. Two samples exhibited a t(X;17) (1 of them with additional

Figure 1. Fluorescence in situ hybridization analysis demonstrating a translocation involving chromosome X is shown.

chromosome aberrations), 1 sample exhibited a t(X;3), and 2 karyotypes were interpreted as being normal/non-diagnostic (1-2 grown culture cells metaphases only). FISH analysis was performed in 5 cases and all 5 (including 1 case with "normal cytogenetics") demonstrated a translocation involving the X chromosome (Fig. 1).

Treatment Outcome

Using RECIST criteria, 3 patients had an objective response, for an overall response rate of 20%. All responders who were treated with sunitinib (n = 1 patient), sorafenib (n = 1 patient), and ramucirumab (n = 1 patient) achieved a partial response(PR). The duration of response was 7 months, 13 months, and 27 months, respectively. Seven patients achieved stable disease, 4 of whom had tumor shrinkage ranging from −9% to −24%. The median tumor shrinkage was −4.5% (range, 48% shrinkage to 67% growth).

Figure 2 shows survival distributions for the 15 patients. At a median follow-up of 19.1 months, the median PFS and OS for the entire cohort were 7.1 months (95% confidence interval [95% CI], 1.7-27 months) and 14.3 months (95% CI, 2.7 months to not reached), respectively. All deaths were related to disease. There were no differences with regard to PFS or OS ($P > .2$) noted between patients treated with sunitinib versus those not treated with sunitinib; however, these results should be viewed with caution because of the small numbers of patients studied and the heavy censoring.

Prior and Subsequent Therapies

Three patients who developed disease progression after initial VEGF-targeted therapy subsequently received temsirolimus, an intravenous mammalian target of rapamycin (mTOR) inhibitor, and all were found to have developed progressive disease at their first restaging evaluation. Before receiving VEGF-targeted therapy, none of the patients who received immunotherapy, vaccination, or chemotherapy experienced a response. The patient who received a MET inhibitor experienced stable disease for 7 months before developing disease progression.

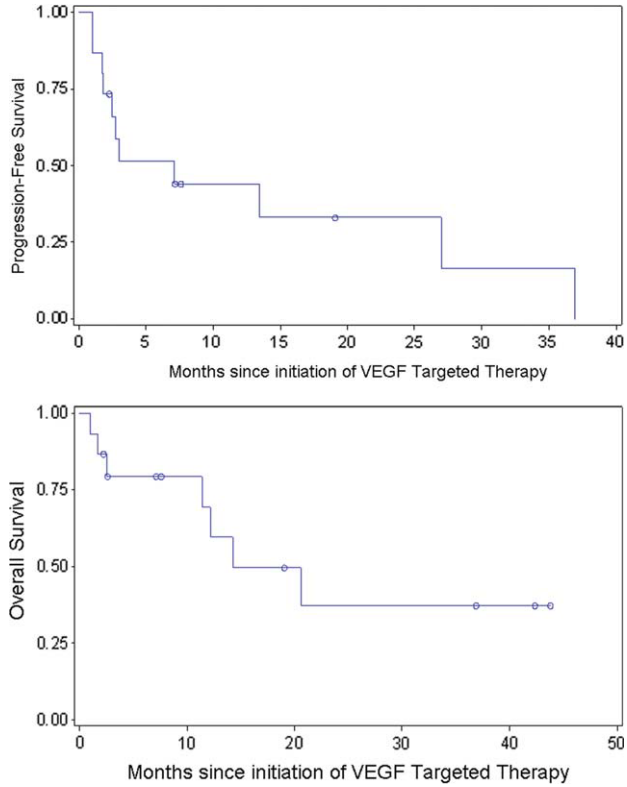

Figure 2. (*Top*) A progression-free survival of 7.1 months was reported for 15 patients with advanced Xp11 translocation renal cell carcinoma who were treated with vascular endothelial growth factor (VEGF)-targeted therapy. (*Bottom*) An overall survival of 14.3 months was reported for 15 patients with advanced Xp11 translocation renal cell carcinoma who were treated with VEGF-targeted therapy

DISCUSSION

To our knowledge, this is 1 of the largest studies published to date reporting on targeted therapy for adult patients with metastatic translocation Xp11.2 RCC. Although several targeted agents have been approved for the treatment of advanced RCC, allowing oncologists to treat all RCC subtypes, clinical trials have for the most part been conducted in patients with clear cell histology (the most common subtype), with some limited experience reported in

patients with non-clear cell subtypes such as papillary and chromophobe RCC.[11] Prior reports from the literature suggest that patients with Xp11.2 translocation RCC do not benefit from immunotherapy or chemotherapy, although these studies included <5 patients with advanced disease. To our knowledge, to date there has not been a reported case with a significant response to those therapies.[9,20,21] In contrast, 2 case reports[13,14] have shown that sunitinib may have significant activity in patients with translocation RCC.

The results of the current study demonstrated that VEGF-targeted therapy can be of benefit in adults with metastatic Xp11.2 RCC, as evidenced by a response rate of 20% and a median PFS of 7.1 months. However, based on the small number of patients in the current study and the finding that responses occurred with 3 different drugs, it is impossible to make definitive conclusions regarding the best VEGF-targeted agent for patients with this disease.

A recent multicenter study from several French centers reported on 21 patients with metastatic Xp11.2 RCC who were treated with VEGF and mTOR-targeted therapies.[22] Patients treated with sunitinib were found to have a median PFS of 8.2 months if they received therapy before treatment with sunitinib, and 11 months if they were previously treatment-naive. Patients treated with sorafenib had a median PFS of 6 months, whereas patients treated with temsirolimus had a median PFS of 3 months. Seven patients (33%) experienced objective responses. All patients treated with sunitinib and 1 patient treated with temsirolimus achieved responses. With a median follow-up of 19 months, the median OS was reported to be 27 months.[22] The efficacy data in the French series are somewhat higher than in the current report, which could be because of case selection bias or the fact that they did not restrict their study to adult patients. In fact, 5 patients in the French series (24%) were aged <18 years. As shown in multiple reports, patients with adult Xp11.2 RCC tend to have a more aggressive disease course than their pediatric counterparts.[7,9]

In the current series, we confirmed that advanced translocation RCC tends to have a strong female predominance and a high frequency of lymph node metastases, findings that are consistent with those of other large reports.[5,20] The current series, as well as others, did not address the incidence of Xp11.2 RCC in adults. The best way to do so would be to screen a large consecutive series of cases placed on a tissue microarray using IHC staining for TFE3.One Japanese study indicated that the incidence of Xp11 RCC in adults is <5%.[21] At this rate, one would predict that adult cases will ultimately outnumber pediatric cases, given that approximately 40,000 cases of adult RCC occur each year in the United States.[23] Moreover, it is likely that Xp11.2/TFE3 RCC continues to be underdiagnosed in adults because of its morphologic overlap with the more common RCC subtypes (clear cell and papillary) and because cytogenetic analysis is not routinely performed for all adult renal tumors as it is in those occurring in children. This point is illustrated in a case from the current series, in which a diagnosis of a mixed clear cell/papillary RCC was made before a TFE3 stain and FISH analysis confirmed the diagnosis of adult Xp11.2 RCC. The tumor was heterogeneous, comprised of epithelioid cells with prominent nucleoli and voluminous clear to eosinophilic cytoplasm with a papillary/nested architecture, as is typical for translocation RCC (Fig. 3).

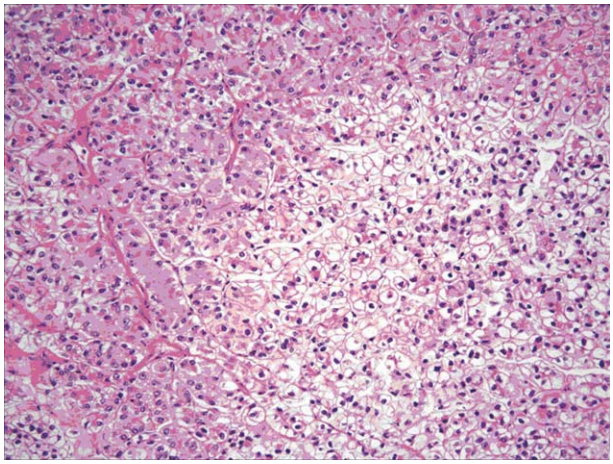

Figure 3. Histologic appearance of Xp11.2 translocation renal cell carcinoma is shown, demonstrating a nested/alveolar pattern with voluminous, eosinophilic/oncocytic cells (H & E, original magnification ×400).

The mechanism of efficacy of VEGF-targeted therapy in patients with Xp11.2 RCC is largely unknown. Using microarray profiling, the gene expression profile of Xp11.2 translocation RCC was found to be closer to that of alveolar soft-part sarcoma (ASPS), a sarcoma that is notoriously refractory to chemotherapy, than to clear cell RCC.[24] Although Xp11.2 translocation RCC likely arises in renal tubular epithelial precursors such as clear cell RCC, the underlying pathogenesis may be driven by the ASPS-TFE3 gene fusion shared with ASPS. Recently, 4 patients with metastatic ASPS were treated with sunitinib, with 2 patients demonstrating PRs and 1 patient achieving an ongoing response lasting >12 months.[25] Upstream

target analysis on fresh frozen tissue demonstrated a high level of activation of members belonging to the MET, RET, and platelet-derived growth factor receptor family. VEGF receptors were found to be activated in only 1 case.

In vitro, the ASPS-TFE3 fusion protein common to ASPS and the Xp11.2 translocation carcinomas transactivates the MET promoter, increasing MET mRNA expression.[26] Similarly, at the RNA level, ASPS has been shown to overexpress the gene for the MET receptor tyrosine kinase compared with other translocation-associated sarcomas.[27] Hence, MET is a potential therapeutic target in these neoplasms. A selective inhibitor of c-Met receptor tyrosine (ARQ-197) kinase has been shown to be safe and well tolerated in a phase 1 trial. ARQ-197 is currently being evaluated in a phase 2 clinical trial (NCT00557609) in patients with microphthalmia transcription factor-driven tumors, including translocation-associated RCC.[28]

In conclusion, adult-onset, translocation-associated metastatic RCC is an aggressive disease that often presents at an advanced stage and affects a younger population with a female predominance. VEGF-targeted agents demonstrated efficacy in this small retrospective series of 15 patients that to our knowledge constitutes 1 of the largest experiences in the treatment of this entity published to date. Nevertheless, we recognize the potential bias inherent to retrospective studies that precludes a definitive statement regarding whether VEGF-targeted agents should be the preferred therapy for patients with advanced stage Xp11.2 RCC. In addition, because of the heterogeneity of translocation RCC, even in adults, further genetic and epigenetic studies are needed to prioritize the discovery of rational targets for the development of more effective therapies.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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