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Targeted agents in metastatic Xp11 translocation/*TFE3* gene fusion renal cell carcinoma (RCC): a report from the Juvenile RCC Network

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Background: Xp11 translocation renal cell carcinoma (RCC) is an RCC subtype affecting 15% of RCC patients <45 years. We analyzed the benefit of targeted therapy [vascular endothelial growth factor receptor (VEGFR)-targeted agents and/or mammalian target of rapamycin (mTOR) inhibitors] in these patients.

Patients and methods: Patients with Xp11 translocation/*TFE3* fusion gene metastatic RCC who had received targeted therapy were identified. Nuclear TFE3 positivity was confirmed by reviewing pathology slides. Responses according to RECIST criteria, progression-free survival (PFS), and overall survival (OS) were analyzed.

Results: Overall, 53 patients were identified; 23 had metastatic disease, and of these 21 had received targeted therapy (median age 34 years). Seven patients achieved an objective response. In first line, median PFS was 8.2 months [95% confidence interval (CI) 2.6–14.7 months] for sunitinib ($n = 11$) versus 2 months (95% CI 0.8–3.3 months) for cytokines ($n = 9$) (log-rank $P = 0.003$). Results for further treatment (second, third, or fourth line) were as follows: all three patients receiving sunitinib had a partial response (median PFS 11 months). Seven of eight patients receiving sorafenib had stable disease (median PFS 6 months). One patient receiving mTOR inhibitors had a partial response and six patients had stable disease. Median OS was 27 months with a 19 months median follow-up.

Conclusion: In Xp11 translocation RCC, targeted therapy achieved objective responses and prolonged PFS similar to those reported for clear-cell RCC.

Key words: interferon, pediatric renal cell carcinoma, sunitinib, targeted agents, TFE3, translocation renal cell carcinoma, Xp11.2

introduction

Xp11 translocation renal cell carcinoma (RCC) is an RCC subtype that was introduced in 2004 as a genetically distinct entity into the World Health Organization classification of renal tumors [1]. It accounts for at least one-third of pediatric RCCs and for 15% of RCCs in patients <45 years of age [2]. It is characterized by translocations, such as Xp11.2 translocations, which induce gene fusions involving the *TFE3* transcription factor gene. A diagnosis of Xp11 translocation RCC is confirmed by immunohistochemistry using antibodies against TFE3 (C-terminal part of transcription factor binding to IGHM enhancer 3), as native TFE3 is not detected in normal tissues. Little is known about the natural history of the disease, but there is increasing evidence to indicate that patients with metastatic Xp11 translocation RCC have aggressive disease that usually presents at an advanced stage [2–8].

Xp11 translocation RCC usually has a mixed papillary architecture with nested patterns of clear and/or eosinophilic cells and calcified foci. Most of these tumors are positive for CD10 and α-methylacyl-coenzyme A racemase (p504s) but negative for the epithelial markers EMA, AE1–AE3, and CK7 [3]. Two-thirds of the tumors show E-cadherin and vimentin overexpression, indicating new cell type-specific activities of TFE3 and TFEB (native transcription factor EB) due to gene fusion [3, 9].

Currently, the standard of care for metastatic renal cell carcinomas (mRCCs) in a first-line setting is administration of

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tyrosine kinase inhibitors (TKIs) targeting vascular endothelial growth factor receptor (VEGFR). Mammalian target of rapamycin (mTOR) inhibitors are used as second-line treatment when TKIs have failed or as first-line treatment in poor-risk patients [10].

The major clinical efficacy trials of these agents have not established the percentage of patients with Xp11 translocation mRCC and thus drug efficacy in patients with this tumor subtype. The goal of our study was to carry out a retrospective analysis of the data for patients with Xp11 translocation mRCC who received VEGFR-targeted agents and/or mTOR inhibitors. The efficacy of first-line cytokine treatment, when administered to these patients, was also analyzed.

patients and methods

patients

Patients with Xp11 translocation RCC were selected from the kidney tumor registries of the Juvenile RCC Network (period January 2000–July 2008), which includes eight hospitals in France (Institut Gustave Roussy, Hôpital Européen Georges Pampidou, Institut Curie, Centre René Goducheau, Hôpital Cochin, Hôpital Foch, Hôpital de la Pitié-Salpétrière, and Institut de cancérologie de la Loire) and one cancer center in the United States (Our Lady of Mercy Hospital Cancer Center, Bronx, NY). Selection criteria were immunohistochemically detected nuclear TFE3 expression and/or cytogenetically proven Xp11 translocation RCC, as well as treatment by VEGFR-targeted agents and/or mTOR inhibitors. Treatment was either within a reported clinical trial (expanded access program of sunitinib [11], pivotal trial of sunitinib versus interferon-α [12], sorafenib treatment approaches in renal cancer global evaluation trial (TARGET) [13], and everolimus renal cell cancer treatment with oral RAD001 given daily (RECORD) 1 trial in patients who failed TKI treatment [14]) or through direct access once the drugs had received marketing approval. The targeted agents were administered according to the dose and schedule defined in the main clinical trials assessing the efficacy of these agents [12–14]. Prior treatment with interferon-α and/or interleukin 2 was allowed. The data collated included pretreatment disease characteristics, first metastases, baseline biochemical variables, prior therapy, first date of treatment, best response to treatment, date of progression, and date of death or last follow-up.

assessment

All objective responses and treatments until death or loss to follow-up were noted. Patients were seen by their physician every treatment cycle until the end of treatment. Laboratory tests and clinical examinations were carried out at baseline and every 6–8 weeks. Tumors were assessed by physical examination and computed tomography scans at baseline and every two treatment cycles (about every 8–12 weeks). The radiological examinations carried out at baseline (before treatment) and at each follow-up were retrospectively reviewed. Tumor response and disease progression were documented using the RECIST criteria [15]. Complete and partial responses were confirmed at least 4 weeks apart. Patients were retrospectively divided into two groups according to the first-line treatment they had received (cytokines or sunitinib).

pathology review and cytogenetics

The pathology reports of patients <35 years of age and/or with atypical histology and/or with cytogenetically proven Xp11 translocation RCC were selected (Figure 1). The gross pathologic features of all the tumors were noted.

Hematoxylin-eosin-saffron-stained sections and immunostaining by antibodies directed against TFE3 and TFEB were reviewed independently by two pathologists (PC and VM). Only nuclear TFE3 labeling was taken into account [3]. The tumors were considered to be TFE3 positive when labeling was moderate to strong, whether nondiffuse or diffuse. Tumors with nondiffuse (<10% of the cells) and weak intensity labeling were excluded in the absence of proven translocation by cytogenetic analysis.

For the cytogeneric analysis, karyotypes from culture cell tumor metaphases were prepared and analyzed as described previously [16].

statistical analysis

Survival curves were constructed by the Kaplan–Meier method and compared by the log-rank test. All *P* values were two-sided. Progression-free survival (PFS) was measured from the date of initiation of mTOR or VEGFR-targeted treatment to the time of progression at any site or death from any cause. PFS values were compared by Fisher's exact test. Overall survival (OS) was measured from diagnosis until death from any cause. First-line treatments (cytokines, sunitinib) were compared by the chi-square test with Yates' correction for categorical data or the Mann–Whitney test for quantitative or ordinal data.

results

patient characteristics

The flowchart describing patients with immunohistochemically proven Xp11 translocation RCC is shown in Figure 2. Among the 53 selected patients, 23 (43%) had metastatic disease and translocation mRCC confirmed by TFE3 immunostaining.

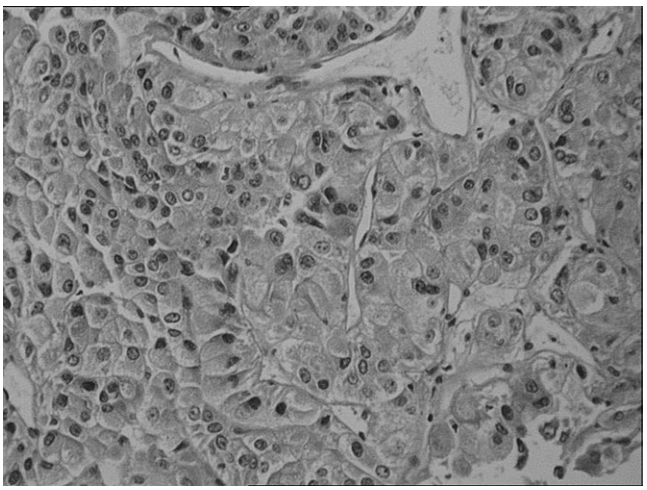

Figure 1. TFE3 carcinoma: papillary and nested pattern with clear and eosinophilic cells.

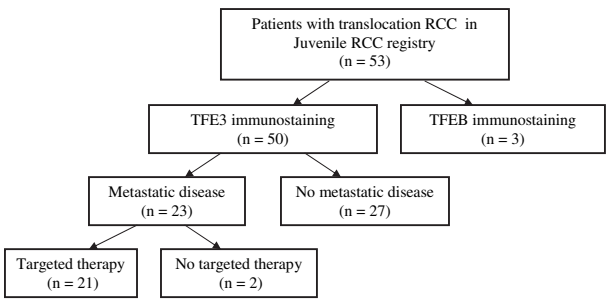

Figure 2. Patient flowchart.

Twenty-one (39%) were assessable for response as they had received targeted therapy. Their characteristics are given in Table 1. Of these 21 patients, 15 had metastases at presentation and 6 developed distant metastasis within 1 year of nephrectomy (range 2–9 months). Treatments received were sunitinib ($n = 14$), sorafenib ($n = 8$) or mTOR inhibitor ($n = 7$). Median patient age was 34 years (range 2–45 years). The male : female sex ratio was ~1 : 1. The median time from metastasis to treatment was relatively short (2.2 months, range 0.1–9.1 months). All patients had undergone nephrectomy. Nine patients (43%) had received prior systemic cytokine therapy. The Karnofsky performance status score was ≥80% in 95% of patients. All patients belonged to intermediate-risk ($n = 15$) or poor-risk ($n = 6$) groups according to Memorial Sloan–Kettering Cancer Center criteria [17]. The first metastatic sites were the mediastinal ($n = 15$) and/or para-aortic ($n = 16$) lymph nodes, lung ($n = 12$), liver ($n = 4$), and bone ($n = 2$). Most of the patients had a mixed papillary histology with clear and eosinophilic cells and calcifications.

Cytogenetic analysis was carried out in four cases, with data available in three cases. Three cases had specific Xp11.2 translocations: one case displayed t(X;1)(p11.2;q21.2), one case t(X;17)(p11.2;q23), and one case t(X;17)(p11.2;q25), t(5;17)(q23;q25). In one patient, array comparative genomic hybridization analysis showed Xp11 translocation and isolated tetrasomy of chromosome 6 in 18% of nuclei. In another, translocation *ASPL-TFE3* was confirmed by RT-PCR.

The overall objective response rate for the entire population (VEGFR-targeted and/or mTOR inhibitors) was 33% (7 of 21 patients). There were nine deaths (43%). With a median follow-up of 19 months, the estimated median OS was 27 months (range 12–43 months). Only one patient had grade IV neutropenia. For the other patients, the main symptoms of treatment toxicity were grade I or II neutropenia, fatigue, rash, and diarrhea.

Table 1. Baseline demographic and clinical characteristics

Characteristic	Number of patients	Percentage of patients
Sex		
Male	10	48
Female	11	52
Age, years		
Median	34	
Range	2–45	
≤34	11	52
>34	10	48
ECOG performance status		
0	20	95
1	1	5
Prior nephrectomy	21	100
Prior radiation therapy	0	0
Common sites of metastases		
Mediastinal lymph nodes	15	71
Para-aortic lymph nodes	16	76
Lung	12	57
Liver	4	19
Bone	2	9
Number of disease sites		
1	4	19
2	6	29
≥3	11	52
Hemoglobin		
Within normal limits	10	48
< Normal	11	52
MSKCC risk factors		
0 (favorable)	0	0
1–2 (intermediate)	15	71
≥3 (poor)	6	29

ECOG, European Collaborative Oncology Group; MSKCC, Memorial Sloan–Kettering Cancer Center.

clinical outcomes on first-line treatment

First-line treatment was as follows: sunitinib ($n = 11$, 52%), cytokines ($n = 9$, 43%), and temsirolimus ($n = 1$, 5%) (Table 2). The median PFS was 8.2 months in the sunitinib group [95% confidence interval (CI) 2.6–14.7 months] versus 2 months in the cytokine group (95% CI 0.8–3.3 months) (log-rank $P = 0.003$). One complete response was observed in the sunitinib group. A partial response was observed in 3 of 11 patients (27%) in the sunitinib group and in 1 of 9 patients (11%) in the cytokine group. Stable disease was observed in six patients (55%) in the sunitinib group and in two patients (22%) in the cytokine group. Six patients on cytokines (67%) but only one patient on sunitinib (10%) progressed within 2 months. At the time of analysis, the median OS rate was estimated at 17 months in the cytokine group and had not been reached in the

Table 2. PFS[a] on first-line treatment

	Number of patients	Median PFS (months)	P[b]
Treatment			
Cytokine	9	2	0.003
Sunitinib	11	8.2	
Sex			
Male	9	6.1	0.54
Female	11	4.9	
Age, years			
≤34	11	4.9	0.68
>34	9	5.5	
Number of disease sites			
≤2	10	3.9	0.35
≥3	10	6	
Hemoglobin			
Within normal limits	12	6	0.51
< Normal	8	4.9	
MSKCC risk factors			
1–2 (intermediate)	14	5.2	0.92
≥3 (poor)	6	4.9	
Time from diagnosis to treatment, months	2.2 (0.1–9.1)		

[a]From treatment initiation to progression or death.
[b]Exact log-rank test (from StatExact); significance level <0.05.
PFS, progression-free survival; MSKCC, Memorial Sloan–Kettering Cancer Center.

sunitinib group. The single patient treated with mTOR inhibitor achieved stable disease over 6 months.

clinical outcomes after failed first-line treatment

Eleven patients received second-line treatment, and 6 patients received third- and fourth-line treatment with targeted agents. Three patients received sunitinib, eight patients sorafenib, and seven patients mTOR inhibitors (four temsirolimus, three everolimus). The three patients on sunitinib achieved a partial response with a median PFS of 11 months (range 5+ to 15 months). Seven of eight patients treated with sorafenib had stable disease with a median PFS of 6 months (range 3 to 29+ months), and only one patient had progressive disease. One patient on mTOR inhibitors achieved a partial response lasting 15 months. Interestingly, this patient had progressed under cytokine, sunitinib, and sorafenib therapy. The six remaining patients had stable disease; median PFS was 3 months (range 3–15 months).

The clinical characteristics of the patients and their clinical outcomes on treatment by targeted agents are reported in Table 3.

discussion

This is, to our knowledge, the first assessment of the clinical efficacy of targeted agents in patients with Xp11 translocation/*TFE3* gene fusion mRCC apart from a case report in a 23-year-old male which found no clinical evidence of activity [4].

Our patients with Xp11 translocation mRCC displayed aggressive disease with a median PFS of 2 months when receiving a cytokine-based regimen and an 11% response rate. On the other hand, 33% of patients showed an objective response to VEGFR-targeted and/or mTOR inhibitor treatment. The PFS for first-line sunitinib was 8.2 months, and similar to that for clear-cell RCC, indicating that response to targeted therapy does not depend on RCC subtype. However, cautions must be considered regarding these results because of the retrospective type of the study. Recently, sunitinib has also been shown to be effective in alveolar soft part sarcoma, a rare chemoresistant soft tissue sarcoma, which harbors the same t(X;17) (p11.2;q25) translocation as detected by TFE3 immunostaining [18].

PFS in patients on first-line sunitinib was better than in those receiving cytokines. Second-, third- ,or fourth-line treatment by VEGFR-targeted agents achieved a median PFS of >6 months. Seven patients are still progression free after >5 months of treatment. Sunitinib seems to be effective as 7 of 14 treated patients achieved a partial ($n = 6$) or complete ($n = 1$) response. No patient experienced a partial response on sorafenib, although all patients received sorafenib beyond the first line; median PFS was 6 months. Two girls aged 2 and 9 years, who received an age-adjusted dose of sunitinib and sorafenib respectively, experienced a partial response for 15 months and

Table 3. Outcome according to treatment

Patient	Age (year)	Sex	Stage at diagnosis	TTR (months)	MSKCC score	First-line treatment			Follow-up (months)	Current status
						Drug	Response to treatment	PFS (months)		
1	26	Male	pT3aN2M1		Intermediate	Sunitinib	SD	3	15	Palliative care
2	15	Male	pT4pN2M0	8	Intermediate	Sunitinib	CR	–	16	Disease free
3	44	Female	pT3bN0M1		Intermediate	Sunitinib	PR	6	9	Deceased
4	28	Male	pT3N0M1		Intermediate	Sunitinib	SD	5	27	Deceased
5	46	Female	pT1aN0M0	8	Intermediate	Sunitinib	SD	18	27	Under treatment
6	16	Female	pT1bN2M0	9	Intermediate	Sunitinib	SD	8	20	Under treatment
7	36	Male	pT3N1M1		Intermediate	Sunitinib	PR	6	15	Palliative care
8	41	Female	pT4N2M1		Poor	Sunitinib	PD	–	3	Deceased
9	39	Male	pT3bN1M1		Poor	Sunitinib	SD	9*	8	Under treatment
10	34	Male	pT3N2M1		Intermediate	Sunitinib	SD	5*	6	Under treatment
11	43	Male	pT2N2M1		Intermediate	Temsirolimus	SD	6	13	Under treatment
12	2	Female	pT4N2M1		Poor	Sunitinib	PR	15*	17	Under treatment
13	18	Female	pT4N2M1		Intermediate	IFN-α	PD	–	8	Deceased
14	43	Female	pT3bN2M1		Intermediate	IFN-α	PD	–	41	Palliative care
15	16	Female	pT3bN2M0	2	Poor	IFN-α and IL-2	PD	–	15	Deceased
16	36	Female	pT3aN2M1		Intermediate	IFN-α and IL-2	PR	6	32	Deceased
17	43	Male	pT3aN2M1		Intermediate	IFN-α and IL-2	PD	–	8	Deceased
18	34	Female	pT1bN2M0	2	Intermediate	High-dose IL-2	PD	–	19	Deceased
19	33	Male	pT3bN0M1		Intermediate	High-dose IL-2	PD	–	13	Under treatment
20	9	Female	pT3N2M1	6	Poor	IFN-α and IL-2	SD	5	77	Under treatment
21	24	Male	pT3bN0M1		Poor	IFN-α and IL-2	SD	7	33	Deceased

TTR, time to recurrence; MSKCC, Memorial Sloan–Kettering Cancer Center; PFS, progression-free survival; pTNM, pathological tumor-node-metastasis; IFN, interferon; IL-2, interleukin-2; SD, stable disease; CR, complete response; PR, partial response; PD, progressive disease.

stable disease for 29 months. Both are currently progression free. There was no unexpected toxicity at the given dose in either patient. In general, the main symptoms of treatment toxicity were the same as for clear-cell RCC.

All patients who progressed on VEGFR-targeted therapy and were switched over to an mTOR inhibitor achieved stable disease. One patient even had a partial response lasting 15 months. Some form of targeted therapy should therefore not be discontinued in patients with Xp11 translocation mRCC. The mTOR inhibitors temsirolimus and everolimus target the PI3K/AKT/mTOR signaling pathways.

Half of our patients had one or two metastatic sites. Metastases affected mainly the mediastinal and/or para-aortic lymph nodes (76%) and lung (57%) as observed in phase III trials of sunitinib and sorafenib in patients with mRCC [12, 13].

A limitation of our study is the small number of patients and their diversity (children, adolescents, and adults). Because of the small number and heavy censoring, the PFS for targeted therapy should be viewed with caution. The main strengths of the study are the central pathology review with confirmation of TFE3 immunostaining by expert pathologists, multicenter patient accrual, and the participation of most patients in previously reported clinical trials assessing the activity of targeted agents in advanced or mRCC.

In summary, VEGFR-targeted therapies and mTOR inhibitors seem to be active in Xp11 translocation mRCC. Sunitinib appears to be more effective than cytokine. The observed objective response rate and PFS of targeted agents were similar to those reported for clear-cell mRCC. Prospective international studies on novel targeted agents are now needed to confirm these retrospective observations.

disclosure

The authors declare no conflicts of interest.

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