Response to systemic therapy in Fumarate hydratase-deficient Renal cell carcinoma

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Abstract

Background

Fumarate hydratase-deficient (FHdef) renal cell carcinoma (RCC) is a rare entity associated to the hereditary leiomyomatosis and RCC syndrome, which predisposes to cutaneous/uterine leiomyomas and to RCC. Data on efficacy of systemic treatment in FHdef RCC is limited.

Patients and methods

We performed a multicenter retrospective data analysis of FHdef RCC patients to determine the response to systemic treatments. The primary endpoints were disease control rate (DCR) and objective response rate (ORR), time to treatment failure (TTF), and overall survival (OS). The two latter were estimated using the Kaplan-Meier method.

Results

Twenty-four FHdef RCC patients were identified and 21 under systemic therapy were included in the analysis: 10 received cabozantinib, 14 sunitinib, 9 other antiangiogenics (AA), 3 erlotinib-bevacizumab (E-B), 3 mTOR inhibitors and 11 immune checkpoint blockers (ICB). ORR/DCR for treatments were respectively: 50%/80% for cabozantinib, 43%/57% for sunitinib, 63%/76% for others AA, 30%/60% for E-B, whereas ORR/DCR were 0%/30% for mTOR inhibitors and 18%/36% for ICB. Median TTF was 11.6 months for patients treated with AA, in global, whereas for mTOR inhibitors and ICB was 4.4 months and 2.7 months, respectively (p=0.0078). Median OS from start of first systemic treatment was 44.0 months (95%CI: 13.0-95.0).

Conclusion

We report the largest retrospective study of FHdef RCC patients treated with systemic therapy with a remarkably longer median OS of 44.0 months, exceeding previous reported data. Our results suggest that AA may be superior to ICB/mTOR inhibitors in this population. Cabozantinib is an option with a 50% ORR and 80% DCR.

Keywords: Hereditary leiomyomatosis; non-clear cell RCC; type 2 papillary RCC; FH mutated RCC; FH-deficient RCC; antiangiogenics; immunotherapy; rare tumors.

Highlights

- Hereditary Leiomyomatosis and RCC is a rare autosomal dominantly inherited disorder confering susceptibility to develop cutaneous, uterine leiomyomas and an aggressive type of RCC.
- Patients with pRCC shoud be offered an oncogeneticics consultation.
- Patients with nccRCC, including pRCC should be enrolled in prospective trials.

- Antigiogenics may be superior to ICB and mTOR inhibitors in the FHdef RCC population.
- FHdef RCC is an aggressive disease, however we reported a remarkably longer median OS of around 4 years suggesting that these patients also benefit from new therapeutic options.

Introduction

Fumarate hydratase-deficient renal cell carcinoma (FHdef RCC) is a rare subtype of RCC that is associated with the hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome. This syndrome is a rare autosomal dominant disease that can confer uterine and cutaneous leiomyomas in addition to an aggressive form of RCC[1, 2]. The risk of developing RCC for HLRCC patients is around ≈19-32% [1, 3], however due to its rarity the worldwide incidence is still unknown. These tumors are characterised by a negative immunohistochemistry (IHC) for FH. However, some patients may show FH expression loss by IHC in the absecence of germline mutation. These cases are recognised as a different entity, " FH deficient RCC", and can be due to either two somatic mutations or one somatic mutation associated to loss of heterozygozity, and in this case there is no heriditary syndrome[2, 4].

From a morphological perspective, FH-deficient RCC used to be described as a type 2 pRCC, however it may present in the shape of a wide spectrum of different histological subtypes including, but not limited to, pRCC, collecting duct carcinoma, high grade, or unclassified RCC[5]. HLRCC is characterized by a germline mutation in the fumarate hydratase (FH) gene. This gene is located at 1q42.3-q43, and encodes a Kreb's cycle enzyme catalyzing the formation of L-malate from fumarate [6, 7]. This protein is a key enzyme in the energetic metabolism. FH deficient tumors are associated with increased intracellular levels of fumarate which promotes the inhibition of the prolyl hydroxylases leading to the stabilization and accumulation of the hypoxia inducible factor HIF1α. Accumulation of HIF α leads to an uncontrolled expression of angiogenic genes such as the vascular endothelial growth factor (VEGF)[1]. In addition, these increased fumarate levels induce a metabolic shift to dependence on higher glucose consumption using aerobic glycolysis[1]. In contrast to other inherited RCC susceptibility syndromes, kidney tumors associated to HLRCC are usually solitary and

unilateral and have a highly aggressive behavior, with around 80% being metastatic at diagnosis according to some series [3].

The treatment landscape of metastatic RCC has greatly improved during the last 20 years with a median overall survival (OS) exceeding 30 months with immune checkpoint blockade (ICB) combinations and antiangiogenics (AA)- ICB combinations [8, 9]. However, all pivotal trials leading to the approval of new therapies enrolled ccRCC patients, because they are more frequent. Indeed, non clear cell RCC (nccRCC), represents around 25% of RCC. First prospective trials in nccRCC used to mix all these rare patients as a single entity, whereas recent data from biology and clinical data demonstrated that each subtype is a singular disease. Few trials focussed on pRCC patients. Drugs as everolimus, sunitinib, dual kinase inhibitor targeting VEGF receptor and MET pathway as foretinib, crizotinib and the selective MET inhibitor savolitinib have been investigated[10–16]. Response rates (RR) were below 15%, except for type 1 pRCC patients with MET germline alterations. Recently, the AXIPAP trial investigated axitinib showing a RR of 28.6% for metastatic pRCC population, with an enhanced RR of 35.7% in the type 2 pRCC subgroup[17]. Overall, trials demonstrated that VEGF targeted agents seem to be superior to mTOR inhibitors. However, the size of the trials or the methodology prevent from drawing strong conclusions on the efficacy.

Among pRCC, FHdef RCC is a particular carcinoma with no standard therapy approved. Currently the best therapeutic option is still unclear.

Given the lack of evidence on the efficacy of systemic therapies in this population, we conducted a multicenter retrospective study in advanced FH-deficient associated RCC under systemic treatedment to help treatment decision-making.

Methods

Study design and population

In February 2020, we performed a collaborative multicenter retrospective review of all metastatic FHdef RCC patients treated within the French genito urinary group (Groupe d'Etude des Tumeurs Urogenitales (GETUG)) and the University Hospital 12 de Octubre. Eligibility criteria included adult patients who had measurable disease by the Response Evaluation Criteria of Solid Tumors (RECIST) and received systemic treatment for an advanced FHdef RCC. Status of FH deficiency tumors was

determinated by using local immunohistochemistry (IHC) (defined as FH negative and/or 2-succinocysteine [2SC] positive) in high grade or with papillary pattern, or papillary RCC type 2 tumors [5]. In some patients with FH deficient tumors germline mutations were confirmed when the germline status could be assessed. Standardized chart review collected date of diagnosis, age at diagnosis, gender, date of nephrectomy, date of first metastasis, type of metastatic site at initiation of systemic treatment, and prognostic factors according to the International Metastatic RCC Database Consortium (IMDC) risk model. No central pathology review was provided. All patients had regular CTscanner evaluation based on local practice. The response by RECIST was determined locally.

Statistical analyses

The patient's characteristics (sex, age at diagnosis, Karnofsky Performance Scale (KPS), site of metastases, IMDC risk group, prior nephrectomy, grade, number of line and type of systemic therapy were described (median and interquartile range [IQR] for continuous variables and absolute and relative frequencies for categorical variables) for the global population and for the different treatment groups. Median follow up from the date of first-line therapy was estimated using the reverse Kaplan-Meier (KM) method. The different types of systemic treatment and lines of treatment were reported. Different systemic treatments were classified into six different groups: ICB, cabozantinib, sunitinib, erlotinib-bevacizumab combination (E-B), mTOR inhibitors and "others AA". Patients treated with pazopanib, axitinib or sorafenib were included in the group "other AA" given the small number of patients. Patient characteristics were also reported and compared. Best response was determined by local assessment every 8-12 weeks according to RECIST 1.1 criteria as complete response (CR), stable disease (SD) and progressive disease (PD). Objective response rate (ORR) was defined as CR+PR and disease control rate (DCR) as CR+PR+SD. DCR and ORR were compared between the different treatment groups using the Fisher's exact test. The time to treatment failure was defined as the time from the start of first line therapy to the discontinuation of treatment for any reason, including disease progression, toxicity and death. Patients with no treatment failure were censored at the date of last follow-up. These two time-to-events were estimated by using KM method and median with its 95% confidence interval (CI) was reported. We compared TTF and OS between IMDC prognostic groups (log-rank test) and the six different systemic treatment groups,

previously mentioned (stratified log-rank test). For the latter, no interpretation can be performed based on the KM estimation considering the observational design of the study. The cut-off date for the analysis was May 25, 2020. The statistical analyses were performed with SAS software 9.4 (SAS Institute).

Results

Patient's and tumors characteristics

We identified 24 FHdef RCC patients from 7 centers in two countries (France and Spain). Among them, 21 patients had received systemic treatment for metastatic disease and were included in the analysis. Patients had been diagnosed from January 2005 to January 2019. Patient and tumor characteristics are described in Table 1. A list with the germline mutations identified can be find in the suplemmentary material (Table 3). The different types of systemic treatment are reported in Table 2. Almost half of the patients (47.6%) were metastatic at diagnosis. All patients except one, that only received first line nivolumab/ipilimumab combination, received at least one line of AA treatment (95.2%, n=20). Three (14.3%) patients received mTOR inhibitors and 3 (14.3%) patients received the E-B combination, and 11 (52.4%) patients received ICB. Median age at diagnosis was 37.7 (IQR: 20.0-61.0) years with similar frequencies of men and women (men: 47.6%, n=10; women: 52.4%, n=11). Most patients had a nephrectomy (71.4%). Median time from diagnosis to metastasis was 7.0 months (95% CI: 0.0-18.0) and median time from metastasis to first line treatment was 2.0 months (95% CI: 1.0-3.0). In this cohort, abdominal lymph nodes and lung nodes were the most common site of metastases at first metastasis diagnosis, followed by bone and liver (Table 1). The IMDC risk model prognosis groups were favorable, intermediate and poor in 33.3% (n=6), 50.0% (n=9) and 16.7% (n=3) patients respectively (3 had missing data). Nine patients (42.8%) received at least three lines of systemic treatment.

Table 1. Baseline patients' characteristics

Characteristics	All patients (n=21) N (%)
Age at diagnosis (years) median IQR	37.7 (20.0-61.0)
Sex	
Male	10 (47.6)
Female	11 (52.4)
Country	
France	20 (95.2)
Spain	1 (4.8)
Cutaneous leiomyomas	
Yes	4 (19.0)
No	17 (80.9)
Uterine leiomyomas	
Yes	7 (33.3)
No	14 (66.7)
FH mut	
Molecular diagnosis	15 (71.4)
Immunohistochemistry	1 (4.8)
Both	4 (19.0)
Unknown*	1 (4.8)
Germline mutation	
Yes	19 (90.5)
No	1 (4.8)
Not analysed	1 (4.8)
Metastatic at diagnosis	
Yes	10 (47.6)
No	11 (52.4)
KPS at start of 1st line	
≥ 80%	16 (76.2)
<80%	5 (23.8)
Location of metastases	
Lung	8 (38.1)
Bone	7 (33.3)
Liver	6 (28.6)
Brain	0 (0.0)
Lymph nodes	
Abdominal	6 (28.6)
Supradiaphragmatic	2 (9.5)
Both	4 (19.0)
IMDC risk group	
Favorable	6 (28.6)
Intermediate	9 (42.9)
Poor	3 (14.3)
Missing	3 (14.3)
Prior nephrectomy	
Yes	15 (71.4)
No	4 (19.0)
Missing	2 (9.5)
Grade	
I	1 (4.8)
II	1 (4.8)
III	5 (23.8)
IV	5 (23.8)
Missing	9 (42.9)

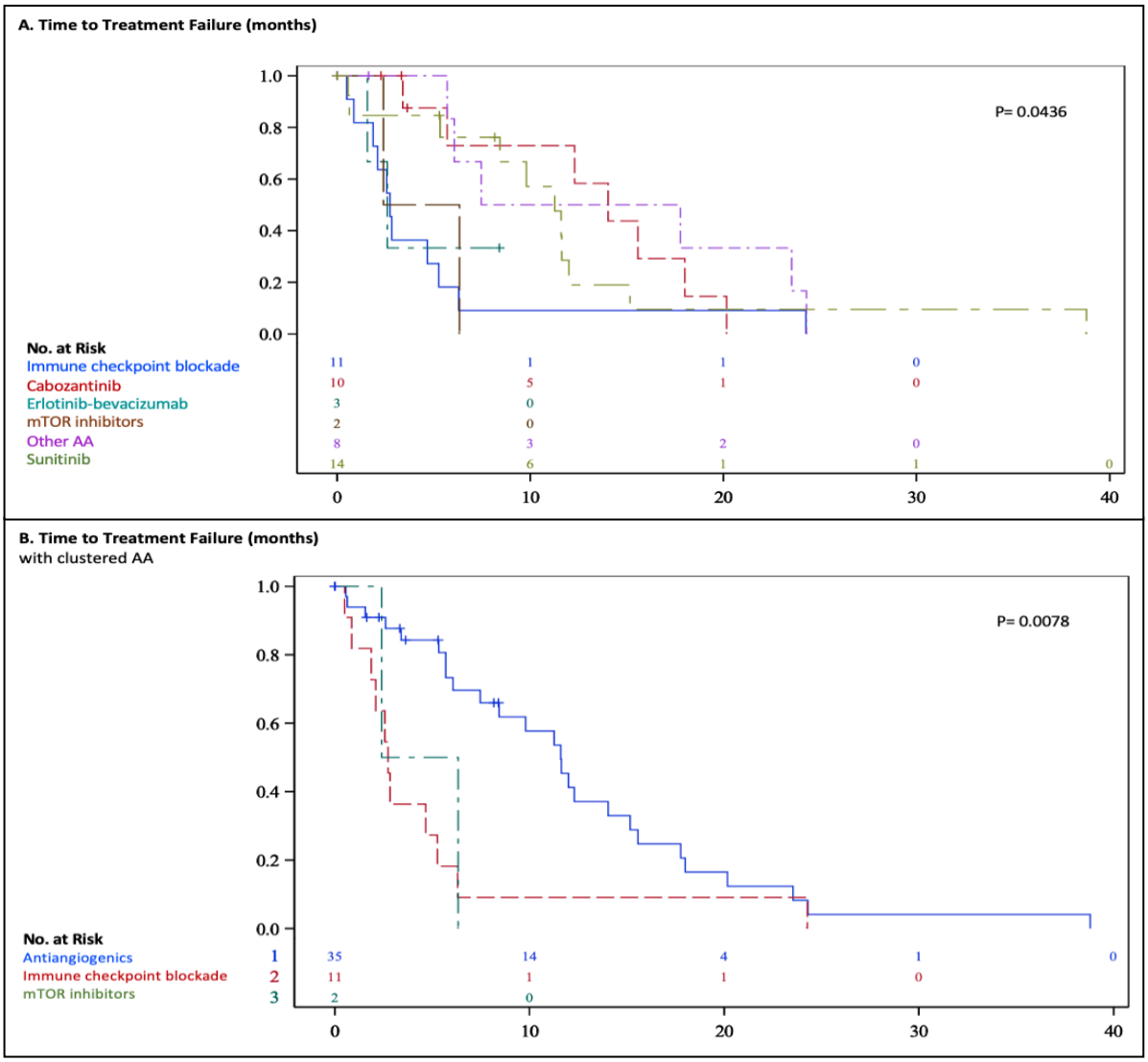
*IMDC: International Metasatatic Renal Cell l Carcinoma Database Consortium, IQR: Interquartile range. FH mut: Fumarate hydratase mutation. KPS: Karnofsky Performance Status Scale. * highly suspicious (clinical presentation) but not yet confirmed.*

Time to treatment failure and Overall survival in all population

Median TTF (mTTF) from the date of treatment initiation to discontinuation was for all patients treated with AA treatments (cabozantinib, sunitinib, "other AA" group and erlotinib-bevacizumab) 11.6 months (95% CI: 6.1-15.2) with 26 events (Figure 1A).

More specifically, mTTF was 14.0 months (95% CI: 3.4-18), 11.6 months (95% CI: 0.6-12.0), 17.7 months (95% CI: 5.7-24.3), 5.5 months, for cabozantinib, sunitinib, other AA and erlotinib-bevacizumab combination, respectively. Median TTF for patients treated with either mTOR inhibitors or ICB was significantly shorter than in those treated with AA: mTTF was 4.4 months (95% CI: 2.4-6.3) and 2.7 months (95% CI: 0.9-5.3) respectively (p=0.0078) (Figure 1B). We reported unadjusted KM curves between the different treatment groups only for description. Median TTF for all treatment types and lines was 9.8 months (95% CI: 2.6-15.6), 6.0 m and 7.5 months in favourable, intermediate and poor risk group respectively (p=0.78).

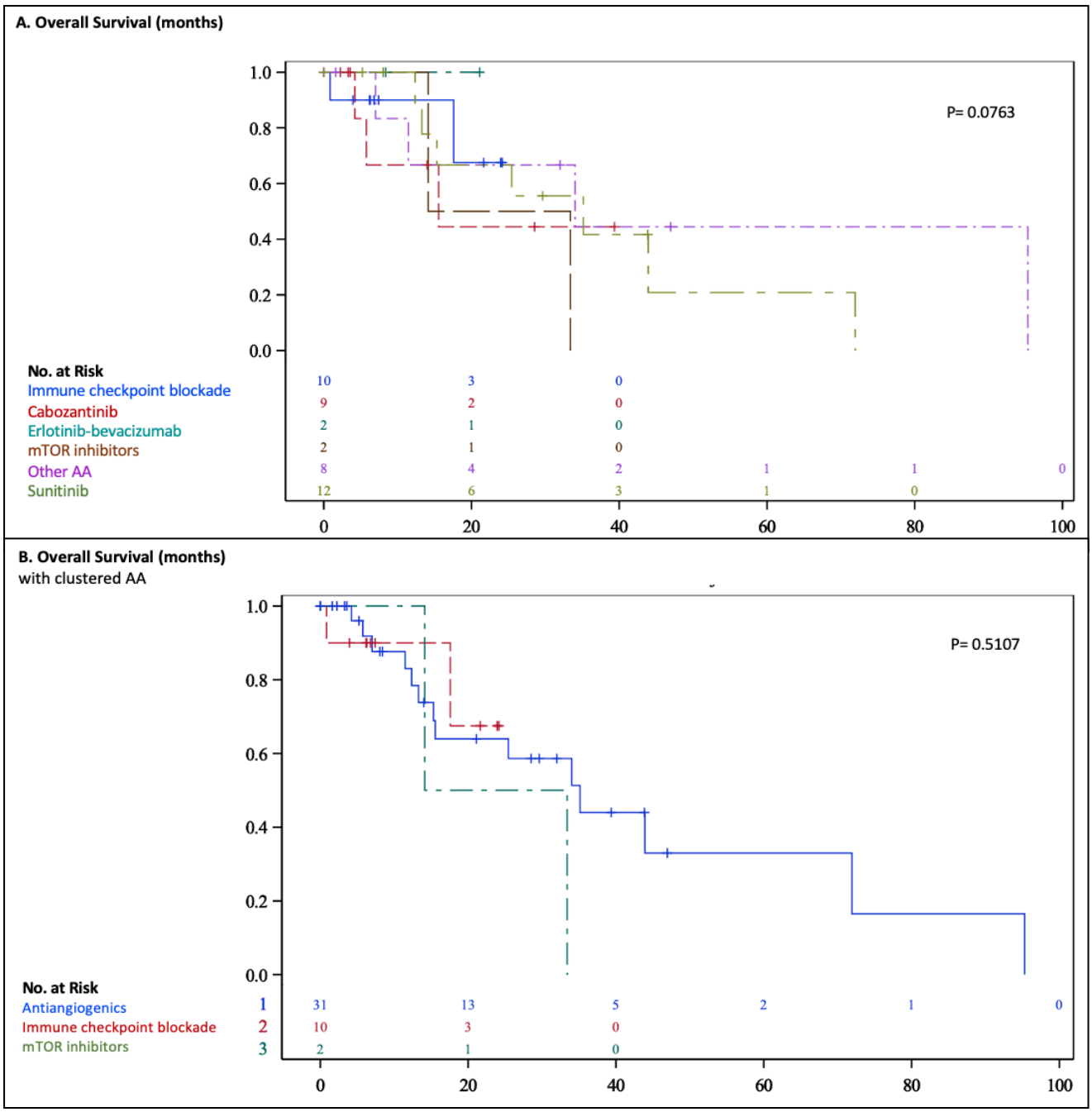
Figure 1. Unadjusted Kaplan-meier curves for TTF between the different treatment groups. A) All treatment groups. B) All antiangiogenics clustered into one group.



After a median follow-up of 32.0 months (95%IC: 7.0-51.0) at the time of analysis, 10 (47.6%) patients had died from disease. Median OS from time of treatment initiation was 44.0 m (95%CI: 13.0-95.0). Median OS (mOS) from the date of specific treatment initiation in the population treated with AA was 35.1 months (95%CI: 15.3-71.9). Specifically, mOS was 15.6 months (95%CI: 4.2-36.0), 35.1 months (95% CI: 12.4 - 71.9), 34.0 months (95%CI: 11.4-95.3) and not reached (NR), for cabozantinib, sunitinib, "other AA" and the erlotinib-bevacizumab combination, respectively. Median OS for patients treated with mTOR inhibitors was 23.8 months (95%CI: 14.1-33.4) and NR for patients treated with ICB.

Unexpectedly, the median OS according to IMDC risk group was, 25.4 months (95%CI 11.5-71.9) in the favourable group and 34.0 months (95% CI: 7.0-NR) in the intermediate group. The poor prognostic group was not evaluable for OS due to lack of events (p=0.038).

Figure 2. Unadjusted Kaplan-meier curves for OS between the different treatment groups. A) All treatment groups. B) All antiangiogenics clustered into one group.



Response rate according to systemic therapy

Antiangiogenics (single agent and combinations)

Among patients treated with cabozantinib ORR and DCR was 50% and 80% respectively. Response rate was: CR 0% (n=0), PR 50% (n=5), SD 30% (n=3) and PD 10% (n=1) (one patient had missing data) (Table 3). Under sunitinib, ORR and DCR were 43% and 57% respectively. Response rate was: CR: 7% (n=1), PR: 36% (n=5), SD: 14% (n=2) and PD 21% (n=3) (three patients had missing data for evaluation of best response rate; Table 2). In the group treated with "other AA" ORR and DCR were 63% and 76% respectively. Response rate was: CR: 0% (n=0), PR 63% (n=5), SD 13% (n=1) and PD 0% (n=0) (two patients had missing data for best response rate evaluation; Table 2). Under E-B combination, ORR and DCR were 30% and 60% respectively. The responses were: CR 0% (0), PR 30% (n=1), SD 30% (n=1) and PD 30% (n=1).

Immune checkpoint blockers

Under ICB, ORR and DCR were 18% and 36% respectively. Response rate was: CR 9% (n=1), PR 9% (n=1), SD 18% (n=2) and PD 63% (n=7). The response with ICB trend to be inferior compared to AA. It did not reach statistical significance for ORR and DCR (p= 0.071 and p=0.106 respectively), with Fischer's exact test (Table 3).

mTOR inhibitors

Under mTOR inhibitors ORR and DCR were 0% and 30%, respectively. Response rate was: CR 0% (n=0), PR 0% (n=0), SD 30% (n=1) and PD 30% (n=1). The response rate with mTOR tended to be inferior to AA, but without reaching statistical significance (Table 3).

Table 2. Efficacy results according to systemic therapy (including by type of antiangiogenic).

Systemic therapy	N	Lineof therapy 1L%/>1L%	PR	CR	SD	PD	Missing **	ORR %	P-value	DCR %	P-value
Immune checkpoint blockers	11	36/64	1 (9)	1 (9)	2 (18)	7 (63)	0	18		36	
Cabozantinib	10	0/100	5 (50)	0 (0)	3 (30)	1 (10)	1	50		80	
Sunitinib	14	93/7	5 (36)	1 (7)	2 (14)	3 (21)	3	43	0.266	57	0.314
Other AA* (pazopanib, axitinib, sorafenib)	8	38/62	5 (63)	0 (0)	1 (13)	0 (0)	2	63		76	
mTOR inhibitors	3	0/100	0 (0)	0 (0)	1 (30)	1 (30)	1	0		30	
Erlotinib-bevacizumab	3	0/100	1 (30)	0 (0)	1 (30)	1 (30)	0	30		60	

* AA: antiangiogenics. ** Missing data for evaluation of best response according to RECIST 1.1. N: population. ORR: overall response rate. DCR: disease control rate. PR: partial response. CR: complete response. SD: stable disease. PD: progressive disease. mTOR: mammalian target of rapamycin.

Table 3. Efficacy results according to type of systemic therapy.

Systemic therapy	N	Line of therapy 1L%/>1L%	PR	CR	SD	PD	Missing **	ORR %	P-value	DCR %	P-value
Immune checkpoint blockers	11	36/64	1(9)	1(9)	2(18)	7(63)	0	18		36	
Antiangiogenics	35	46/54	16(46)	1(3)	7(20)	5(14)	7	49	0.071	69	0.106
mTOR inhibitors	3	0/100	0(0)	0(0)	1(30)	1(30)	1	0		30	

** Missing data for evaluation of best response according to RECIST 1.1. N: population. ORR: overall response rate. DCR: disease control rate. PR: partial response. CR: complete response. SD: stable disease. PD: progressive disease. mTOR: mammalian target of rapamycin.

Discussion

The best therapeutic option for the systemic treatment of advanced FHdef associated RCC is still unclear. To date there is only one retrospective study evaluating the response of FHdef RCC to systemic therapy, a small Korean study reporting the response of this population under the E-B combination, from real-world-data (RWD) (n=10)[18]. In this context, we report a larger retrospective cohort including 21 metastatic FHdef RCC patients treated with systemic therapy. In our cohort, the efficacy of AA tended to be superior. Antiangiogenics, either single-agent or in combination (E-B), showed a stronger antitumor activity than with ICB or mTOR inhibitors, with a DCR of 69% for the overall AA compared to 36% and 30% for ICB and mTOR inhibitors, respectively. Among all AA, cabozantinib was associated with higher ORR

(50%) and DCR (80%) respectively, and mTTF was 14.0 months (95%CI: 3.4-18.0). MET alterations are commonly associated to type 1 pRCC and expressed around 46% in type 2 pRCC[19]. Recent data reported antitumor activity of MET inhibitors in pRCC with increased MET expression [12–14]. However, the ORR observed with cabozantinib in this study exceeds previous reported data from other retrospectives studies conducted in nccRCC populations enriched with pRCC [20, 21]. Concerning the efficacy of other antiangiogenics, the ORRs observed in our study are consistent with the results from Gleeson et al. [22]. The TTF in the AA group was associated with the longest TTF: mTTF was 11.6 months, compared to the 2.7 and 4.4 months of the ICB and mTOR groups (p=0.0078, log-rank). Combination E-B had a mTTF of 5.5 months, shorter than the median PFS reported in the AVATAR trial (21.1 months) and in the Korean retrospective study (13.3 months), however the number of patients (n=3) was small[18, 23].

Indeed, studies have already investigated safety and efficacy of bevacizumab, a VEGF inhibitor, and erlotinib, EGFR inhibitor which has been shown to revert the Warbug effect [24]. Indeed, the HLRCC-associated RCC carcinogenesis is characterized by the upregulation of the HIF-VEGF pathway and the shift to aerobic glycolysis due to the fumarate accumulation [1]. The ORR in the Korean cohort was 50%, however the median PFS was shorter in this cohort (13.3 months) than in the AVATAR trial [18, 23]. Only one clinical prospective trial, the AVATAR trial (NCT01130519), has reported data in this rare popualtion [23]. This phase II trial investigated the efficacy and safety of the erlotinib-bevacizumab combination (E-B) in 83 HLRCC-associated RCC and sporadic pRCC. The ORR and median PFS were 72.1% and 21.1 months, respectively in the HLRCC-associated RCC, compared to a 35% ORR and a mPFS of 8.8 months in the sporadic cohort [23]. However, the trial took 10 years to complete accrual, which could imply selection bias. Encouraging results were reported in the HLRCC group with a 64% objectif response rate (ORR) and a 21.1 months median PFS [17]. These data led to the recommendation of this combination by the NCCN Kidney Guidelines for the selected patients with advanced HLRCC [25]. Another HLRCC-associated RCC ongoing phase I/II trial (NCT02495103) study is investigating the effect of vandetanib, a dual VEGFR/EGFR inhibitor that reverses the metabolic phenotype associated to the FHmut tumors, in combination with metformin [26]. Metformin demonstrated synergy in combination with vandetanib in preclinical models of FH deficient tumors [27].

Advanced FHdef RCC is a poor prognosis disease. However, this cohort reported a longer median OS than those previously reported [18, 22, 23]. This may be explained because of the presence of long-term survivor (95 months) and because the population was heavily treated. Indeed, half of the patients received at least 2 lines of systemic therapy (42.8%). Patients treated with AA presented a median OS of 35.1 months. Median OS with everolimus was 23.8 months consistent with the RAPTOR trial results[11].

As nccRCC patients, patients with FHdef associated RCC were initially excluded from RCC prospective clinical trials because of their rareness. Later, patients were included in few nccRCC trials as an homogenous entity, although this group is heterogenous both in terms of clinical outcomes and molecular biology. More recently, a number of phase II clinical trials were designed to address specific histological nccRCC subytpes such as the pRCC [11–14, 17]. A clinical trial investigated the activity of foretinib in pRCC, a multikinase inhibitor targeting MET, RON, AXL TIE-2 and VEGF receptor, based on the impressive long-term response from the phase I trial [12]. The 13.5% ORR obtained increased up to 50% in MET germline mutation carriers and the median PFS was 9.3 months. Another trial investigated the activity of savolitinib, a selective MET inhibitor, according to MET status[14]. The results were promising in the MET driven cohort with an ORR and median PFS of 18% and 6.2 months respectively, compared to the MET independent cohort (ORR: 0%, median PFS: 1.4 months). Unfortunately, the phase 3 trial presented at ASCO 2020 closed early due to futility[16]. Further understanding of the papillary subtype as an heterogenous disease and of the involvement of the MET pathway mainly in the type 1 subtype, suggested the rationale for the design of the biomarker-driven trial. The CREATE trial assessed the activity of crizotinib in 23 type 1 pRCC patients [13]. The ORR and the PFS at two years were impressive in the MET mutated group with 50% and 80% respectively, compared to 6% and 22% in the non-mutated group. According to these results, the phase II PAPMET trial, is currently investigating the efficacy of different MET inhibitors (cabozantinib, savolitinib, crizotinib and sunitinib)[28].

Some single-arm trials have investigated approved targeted therapies for ccRCC in the papillary population (Table 5). The phase II SUPAP trial investigated the efficacy of sunitinib in untreated pRCC patients [10]. Efficacy outcomes were similar for the type 1 and the type 2 pRCC subtypes, but were inferior than in ccRCC [10]. RAPTOR trial assessed everolimus as first-line therapy in pRCC; DCR was 66%, median OS was

21.4 months, despite a short median PFS of 4.1 months [11]. Data from RAPTOR were consistent with SUPAP trial, but survival outcomes were superior in the type 1 histology. More recently, AXIPAP trial, reported the activity of axitinib in pRCC [17]. Results were promising for the type 2 histology, with an ORR of 35.7% compared to the 7.7% of the type 1 group [17].

Immunotherapy has been investigated also in metastatic pRCC. The KEYNOTE-427 phase II trial, assessed an anti-PD1 (pembrolizumab) in previously untreated advanced ccRCC (cohort A) and non-ccRCC (cohort B), including 72% of pRCC. The results were promising with an ORR of 25.4% in the pRCC group [29]. The ongoing phase II randomized clinical trial, SUNNIFORECAST (NCT03075423), is currently enrolling and aims to explore the activity of nivolumab-ipilimumab combination versus sunitinib in the nccRCC population[30]. Furthermore, the combination of durvalumab (anti-PD-L1) and savolitinib was assessed in the phase I/II CALYPSO trial in an un-selected pRCC population showing encouraging results[15]. The ORR was 33%, the median PFS was 4.9 m and the median OS was 12.3 m, regardless of PD-L1 and MET expression (Table 5). The discovery of biomarkers, as the MET-driven subtype, led to improved clinical outcomes in this specific subpopulation. Therefore, efforts should go in this direction.

Our work is not without limitations inherent to its retrospective nature. Also, given the limited number of patients, results should be interpreted with caution; no multivariable analyses were performed. Moreover, the lack of central pathologic review and radiological review lead to some biases.

Conclusion

We reported the largest retrospective cohort to date of metastatic FHdef associated RCC under systemic therapy (N=21). Global collaborative networks should be pursued to improve the understanding of this rare disease and help treatment decision-making. We described the clinical outcomes of metastatic FHdef RCC under systemic treatment. Median OS from this cohort was surprisingly long, 44.0 months, exceeding previous data reported. This suggests the benefit of new drugs in this population. Indeed, 42.8% of patients received at least three lines of systemic treatments. This study may suggest the superiority of AA therapy over ICB and mTOR

inhibitors in this particular population. Specifically, cabozantinib seems to be a good option with an ORR and DCR of 50% and 80%, respectively. Further prospective studies based on the molecular biology of this tumor and global collaborations including larger number of patients are warranted.

Supplementary tables:

Table 1: Studies with FHdef RCC under systemic therapy

Table 2: Studies with patients with advanced pRCC under systemic therapy

Table 3: Germline *FH* mutations (Chr1-GRCh37- NM_000143.3)

Table 1: Studies with FHdef RCC under systemic therapy

Reference	Identification	Design	N	≥1 prior line (%)	Histology (N)	Treatment	ORR (%)	PFS (m)	OS (m)	Grade ≥ 3 AE (%)
Srinivasan et al. [23]	NCT01130519	Phase 2	83	32	HLRCC= 43 Sporadic= 40	Bevacizumab + Erlotinib	HLRCC= 72.1 Sporadic= 35	HLRCC= 21.1 Sporadic= 8.8	NA	49
[26]	NCT02495103	Phase 1/2	NA			Vandetanib + metformin	NA	NA	NA	NA
Choi et al.[18]		Retrospective	10	60	FHmut = 10	Bevacizumab + Erlotinib	50	13.3	14.1	20
Gleeson et al. [22]		Retrospective	32	NA	FHmut = 32	Several	mTOR/AA= 47 AA= 50 ICB= 0 mTOR= 0 ICB/VEGF= 100*	NA	Overall= 28.1	NA

Fhmut: FH mutated. NA: not available. *: 1 patient only. N: population. ORR: overall response rate. PFS: progression-free survival. M: months. OS: overall survival. AE: adverse events. HLRCC: hereditary leiomyomatosis and renal cell carcinoma syndrome. mTOR: mammalian target of rapamycin inhibitors. AA: antiangiogenics. ICB: immune checkpoint blockers. VEGF: anti-vascular endothelial growth factor .

Table 2: Studies with patients with advanced pRCC under systemic therapy

Reference	Identification	Design	N	≥ 1 prior line (%)	Histology (N)	Treatment	ORR (%)	PFS(m)	OS (m)	Grade ≥ 3 AE (%)
Choueiri et al. [12]	NCT00726323	Phase 2	74	18.9	pRCC1	Foretinib	13.5	9.3	NR	NA
Schöfski et al. [13]	NCT02495103	Phase 2	23	39.1	pRCC	Crizotinib	MET+: 50 MET-: 6 MET?: 33	At 2y: MET+ 80% MET - 22%	At 2y: MET+ 80% MET - 30%	26
Choueiri et al. [14]	NCT02127710	Phase 2	109	41	pRCC	Savolitinib	MET driven: 18 MET ind: 0	MET driven 6.2 MET ind 1.4	14.1	47
Ravaud et al. [10]	NCT00541008	Phase 2	61	0	pRCC	Sunitinib	Type 1: 13 Type 2: 11	Type 1: 6.6 Type 2: 5.5	Type 1: 17.8 Type 2: 12.4	NA
Escudier et al. [11]	NCT00688753	Phase 2	Safety= 92 ITT=88 PP= 46	0	pRCC	Everolimus	1	Type 1: 7. Type 2:5.1	Type 1: 28.0 Type 2: 24.2	NA
Negrier et al. [17]	NCT02489695	Phase 2	44	0	pRCC	Axitinib	Type 1: 7.7 Type 2: 35.7	Type 1: 6.7 Type 2: 6.2	Type 1: NR Type 2: 17.4	54.5
Suarez-Rodriguez et al. [15]	NCT02819596	Phase 1/2	42	NA	pRCC	Savolitinib + Durvalumab	27 MET+: 40 PDL1+: 25	4.9	12.3	34
Choueiri et al.** [16]	NCT03091192	Phase 3	60	12	pRCC	Savolitinib (33) vs Sunitinib (27)	Savolitinib: 27 Sunitinib: 7.0	Savolitinib: 7.0 Sunitinib: 5.6	Savolitinib: NR Sunitinib: 13.2	Savolitinib 42 Sunitinib 81

pRCC: papillary RCC. pRCC1: pRCC type 1. NA: not available. NR: not reached. ITT: intention to treat. PP: per protocol. At 2y: at 2 years. ** Early terminartion due to poor acrural. ORR: overall response rate. PFS: progression-free survival. M: months. OS: overall survival. AE: adverse events.

Table 3: Germline *FH* mutations (Chr1-GRCh37- NM_000143.3)

Identification	Genomic change	cDNA change	Amino-acid change	2SC or FH IHC staining	FH Enzymatic dosage**	Classification
Patient 1	g.241667521del	c.929del	p.(Asn310Ilefs*19)	NA	NA	5
Patient 2	g.241676932C>G	c.349G>C	p.(Ala117Pro)	NA	41%	5
Patient 3	g.241665790C>T	c.1189G>A	p.(Gly397Arg)	NA	51%	5
Patient 4	g.241667532_241667538del	c.912_918del	p.(Phe305Leufs*22)	NA	NA	5
Patient 5	g.241663826C>T	c.1301G>A	p.(Cys434Tyr)	NA	45%	5
Patient 6	g.241665862T>C	c.1117A>G	p.(Asn373Asp)	NA	47%	5
Patient 7	g.241669315C>G	c.892G>C	p.(Ala298Pro)	NA	NA	3
Patient 8	g.241665861T>C	c.1118A>G	p.(Asn373Ser)	NA	39%	5
Patient 9	g.241671943C>T	c.698G>A	p.(Arg233His)	NA	NA	5
Patient 10	g.241676980G>A	c.301C>T	p.(Arg101*)	NA	Decreased[31]	5
Patient 11	Genomic deletion exons 3-5	c.268-?_738+?	p.Thr90-?_Gln246+?	NA	NA	5
Patient 12	g.241676932C>G	c.349G>C	p.(Ala117Pro)	NA	41%	5
Patient 13	g.241665790C>T	c.1189G>A	p.(Gly397Arg)	Yes	51%	5
Patient 14	No germline mutation identified					
Patient 15	g.241665798_241665803del	c.1176_1181del	p.(Ala393_Val394del)	Yes	NA	deletion en phase
Patient 16	Germline mutation identified but report not available					
Patient 17	Germline mutation identified but report not available					
Patient 18	g.241667359del	c.1091del	p.(Gly364Glufs*9)	NA	NA	5
Patient 19	Germline mutation identified but report not available					
Patient 20	No data regarding the presence or absence of germline mutation			Yes	NA	NA
Patient 21	Germline mutation identified but report not available			Yes	NA	NA

*: performed on PBMC of the patient himself or another carrying the same germline missense mutation. NA: not available (report not available but presence confirmed FH mutation or loss of FH expression by IHC). IGR: Institute Gustave Roussy. FH: fumarate hydratase. IHC: immunohistochemistry. 2SC: 2-succinocysteine.

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