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Données inter-régionales sur le séquençage et l'utilisation en pratique clinique du cabozantinib dans la prise en charge du carcinome hépatocellulaire à partir de la base de données RaPiDo et de la cohorte CHIEF

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AVERTISSEMENT

La faculté n'entend donner aucune approbation aux opinions émises dans les thèses : celles-ci sont propres à leurs auteurs.

Short terms

AFP: Alphafoetoprotein

BCLC: Barcelona Clinical stage Classification

BMI: Body mass index

CHIEF : Carcinome Hépato cellulaIRe En France

CI : Confidence intervall

CR : Complete response

EASL: European Association for the Study of Liver

EMT: Epithelio-mesenchymal transition

HCC hepatocellular carcinoma

HCV: Hepatitis C virus

MELD : Model for End-stage Liver Disease

OS: Overall survival

PD : Progression disease

PFS: Progression-free survival

PPE: Palmoplantar erythrodysthesis

PR : Partial response

RaPiDo: RAcourcissement Personalisé des Investigations en vue d'une Décision Oncologique

SBRT : Stereotactic body radiation therapy

SD : Stable disease

TKI: Tyrosine-kinase inhibitor

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RESUME

Contexte: Le cabozantinib, nouvel inhibiteur de tyrosines kinases, a obtenu une extension d'AMM pour le traitement du CHC en 2nd ligne après sorafenib en 2018 après la communication des résultats de l'étude de phase 3 CELESTIAL. A ce jour, peu de données d'utilisation et de séquençage des différents traitements médicaux du CHC en pratique clinique quotidienne sont disponibles. Dans notre étude, nous avons décrit le profil des patients de la "vraie vie" recevant du cabozantinib, dans le but d'évaluer le séquençage et l'usage en pratique clinique du cabozantinib et de comparer nos résultats à ceux de CELESTIAL.

Patients et méthodes : Nous avons mené une étude observationnelle rétrospective incluant des patients du CHRU de Lille via une extraction de la base RaPiDo et des patients de la cohorte nationale CHIEF entre Juin 2018 et Janvier 2021. Les données complémentaires de suivi cliniques, biologiques et morphologiques ont été saisies de manière prospective.

Résultats: Soixante-quatorze patients ont été inclus. Il s'agissait principalement d'hommes (84%) avec un antécédent de cirrhose (38% liée à une consommation excessive en alcool et 21% d'origine alcoolique et métabolique). Le CHC était classé BCLC C dans 85% des cas. On retrouvait une différence entre les 2 groupes (RaPiDo et CHIEF) au niveau des caractéristiques des patients mais les caractéristiques des CHC étaient similaires. Le cabozantinib était prescrit dans le cadre de l'AMM dans 31 % des cas. La durée moyenne de traitement était de 5,1 mois. Le taux de réponse objective était de 4% et le taux de contrôle de la maladie de 22%. Quarante pourcents des patients ont arrêté le traitement pour intolérance. Les effets secondaires mis en évidence étaient l'asthénie, la diarrhée et la décompensation de cirrhose. Le diabète et l'antécédent d'effets secondaires sous sorafenib étaient des facteurs de risques associés à la survenue de grade ¾.

Conclusion : Cette étude observationnelle est, à notre connaissance, l'unique à décrire l'utilisation et le séquençage du cabozantinib depuis l'obtention de l'AMM en 2018 en France. Nous avons mis en évidence une utilisation fréquente du cabozantinib en dehors de son AMM mais avec des taux de réponse objective et une médiane de survie globale similaires aux données de l'étude d'enregistrement CELESTIAL.

SUMMARY

Background: Cabozantinib, a novel tyrosine kinase inhibitor, obtained a label for the treatment of HCC as 2nd line after sorafenib in 2018 after the publication of the CELESTIAL study. To date, few data in terms of utilization and sequencing in daily clinical practice are available. In our study, we described the profile of "real life" patients receiving cabozantinib, with the aim to evaluate its time sequencing and use in clinical practice and compare our results with those of CELESTIAL.

Patients and methods: We conducted a retrospective observational study including patients from the Lille University Hospital via an extraction of the RaPiDo database and patients from the national CHIEF cohort between June 2018 and January 2021. Additional clinical, biological and morphological follow-up data were prospectively captured.

Results: Seventy-four patients were included. They were mainly men (84%) with a history of cirrhosis (38% related to excessive alcohol consumption and 21% of alcoholic and metabolic origin). HCC was classified as BCLC C in 85% of cases. There was a difference between the 2 groups (RaPiDo and CHIEF) in terms of patient characteristics but the characteristics of the HCC were similar. Cabozantinib was prescribed on-label in 31% of cases. The mean duration of treatment was 5.1 months. The objective response rate was 4% and the disease control rate was 22%. Forty percent of patients discontinued treatment due to intolerance. The main side effects were asthenia, diarrhea and decompensation of cirrhosis. Diabetes and a history of side effects with sorafenib were risk factors associated with the occurrence of grade ¾.

Conclusion: This observational study is, to our knowledge, the only one to describe the use and sequencing of cabozantinib since the label obtained in 2018 in France. We found frequent use of cabozantinib off-label but with objective response rates and median overall survival similar to data from the CELESTIAL study.

Introduction

Hepatocellular carcinoma (HCC) is the 4th most common cancer and the 3rd leading cause of cancer death worldwide. It is responsible for approximately 9000 deaths per year in France with an increasing prevalence (1). This increase in prevalence is mainly due to 1/ a decrease in competitive mortality related to an improved management of other complications of cirrhosis (2) 2/ hepatitis C virus (HCV) epidemic in the 80's leading to cirrhosis 20 years thereafter and 3/ increase in obesity and metabolic syndrome prevalence a known risks factor of HCC (3). The management of HCC is complex and depends on many parameters gathered in the BCLC classification (4). The European Association for the Study of the Liver 2018 recommendations, based on the BCLC classification, make it possible to establish a detailed therapeutic strategy adapted to the different stages of HCC (figure 1). The BCLC C stage is defined by multinodular carcinoma, portal invasion or extrahepatic spread associated with a preserved liver function and a good general condition. Systemic treatment such as tyrosine-kinase inhibitors (TKI) or immunotherapy are the standard-of care for patients with advanced HCC classified as BCLC C.

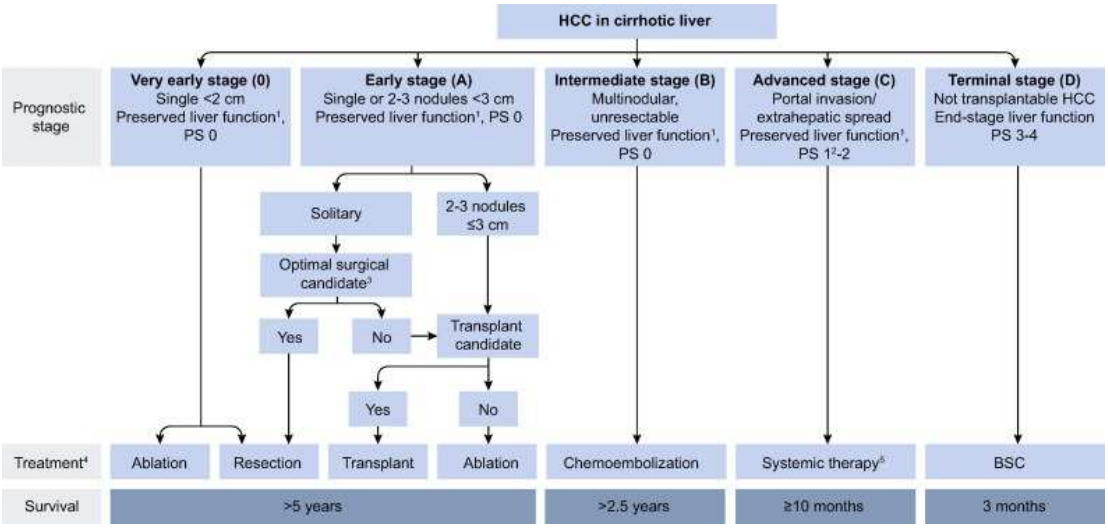


Figure 1: *EASL 2018, guidelines for HCC according to BCLC classification*

Sorafenib, historical treatment of HCC, is an inhibitor of the RAF/MEK/ERK 1-2 pathway among others and provides a modest benefit in terms of overall and progression-free survivals (5). Numerous studies have investigated the reason for the progression under sorafenib and thus the escape from the treatment. Xiang's team found that overactivation of the MET pathway was a poor prognostic factor in patients treated by sorafenib (6). We also have the proof that hypoxia induced by anti-angiogenic drugs promotes the overexpression of MET (7). In another study, Xiang et al. demonstrated that EGR1 is over-expressed due to hyper activation of the PI3K pathway, a pathway parallel to the one inhibited by sorafenib (Figure 2). This overactivation is in fact due the proto oncogen MET (8). As a result, MET appears to have a major role in acquired resistance to sorafenib in patients treated for HCC.

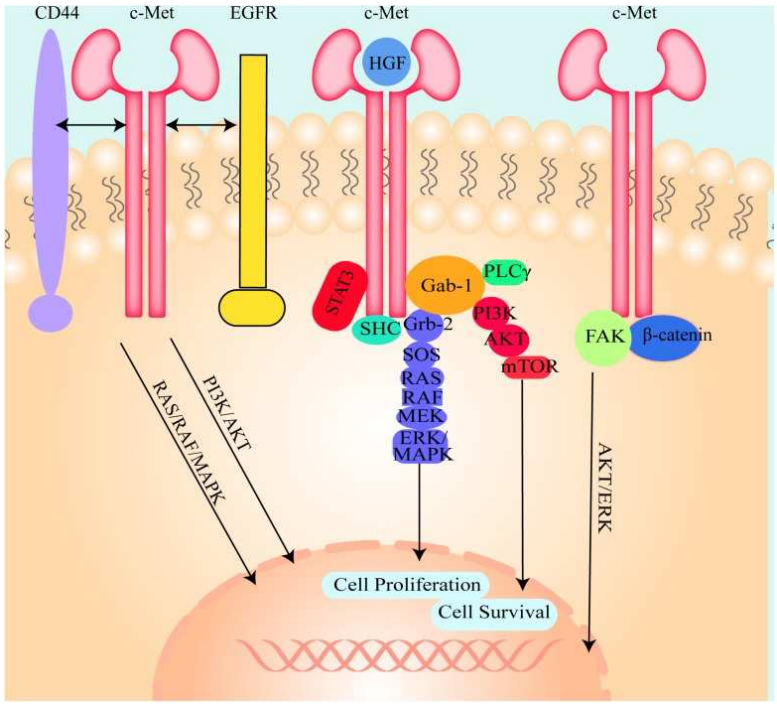


Figure 2 adapted from (9)
On the left side: MET has co-factors that can influence its activation (EGFR, CD44).
In the middle: different signaling pathways that the activation of MET allows
On the right side: another pathway that can be activated by MET

Cabozantinib is a tyrosine kinase inhibitor initially developed in medullary thyroid cancer (10) and in clear cell renal cell carcinoma (11-12). Its targets include the following tyrosine kinases: MET EGFR, AXL, RET, KIT and FLT 3. One of the most interest of cabozantinib is to inhibit the MET pathway. Indeed, the proto-oncogene MET is a molecule that contains the Hepatocyte Growth Factor (HGF) receptor and has a demonstrated role in the activation of mitosis, promotes the epithelio-mesenchymal transition (EMT) and allows an increase in HCC mobility to facilitate metastatic invasion. Furthermore, it is known that MET is over-expressed in 20 to 40% of cancer cells (9). The demonstration of the involvement of these different proteins in the development of HCC has led to the development of different targeted therapies which, until 2020, were in the first place in the treatment of advanced HCC. As a result, cabozantinib effectiveness in the treatment of 2nd line HCC can be derived from its main action on MET which is over-activated in HCC that has been exposed to sorafenib as explain above (13-14).

In 2018, the CELESTIAL trial is showing benefit of the cabozantinib in 2nd line therapy in patients progressing with sorafenib (13). This multi-center, international study of more than 700 patients demonstrated a benefit in terms of overall survival (OS) and progression-free survival (PFS), results reinforced by the power of the study. The median age of the population was 64 years, and 80% of the patients were male and 50% Caucasian' origin. The general condition of the patients was particularly well preserved (with more than 95% of ECOG 0 or 1 patients). One of the particularities of the population was that the viral origin predominated in the cirrhosis etiologies to more than 50% compared with only 20% for the alcohol-related etiology whereas, in France the etiology of cirrhosis is dominated by excessive alcohol consumption (14). The daily dose was initially 60 mg/d but the results show that the median dose in the study was

35.8 mg/d. Grade 3 and 4 side effects were experienced by 58% of the patients (compared to only 10% of the patients who were treated with placebo). Serious side effects included: hand-foot syndrome, hypertension, diarrhea and hyper-bilirubinemia.

As in many pivotal trials, the study population was distant from our target population, which can weaken external validity. In our study, we aimed to describe the profile of "real-life" patients receiving cabozantinib, which would allow us to compare with the CELESTIAL results and evaluate the sequencing and clinical practice use of cabozantinib in daily clinical practice.

Patients and methods

This is a retrospective observatory study of practice including patients with HCC who had been treated with cabozantinib between June 2018 and January 2021. We used our local data base ‘RaPiDo’ (RAcourcissement Personalisé des Investigations en vue d’une Décision Oncologique) dedicated to biliary and hepatic carcinoma and we did an extraction with the key words following: « cabometyx », « cabozantinib ». The other part of the patients has been extracted of the national cohort called CHIEF (Carcinome Hépato cellulaIRe En France) with the key word « cabozantinib ».

Data were extracted from files (for RaPiDo group) and case report form (for CHIEF group) and completed by phone call to private labs and general practitioners for lost to follow-up. The following characteristics were retrospectively recorded for each patient: gender, age at introduction of cabozantinib, weight, size, body mass index (BMI), history of arterial hypertension, type 2 diabetes, smoking status, treatments before cabozantinib, dosage, and tolerance. Then, after the introduction of cabozantinib, we recorded clinical and biological (alphafoetoprotein and bilirubin) parameters for each medical visit, the RECIST status if available and the presence of side effects.

Results are expressed as means ± SD or median (IC 95%). Student's t-test or Mann–Whitney U-test for nonpaired values was used to compare means of groups for quantitative variables, assuming or not Gaussian distribution, respectively. For qualitative variables, chi-square test or Fisher's exact test was employed. Kaplan–Meier survival curves were constructed. The statistical analysis were performed using NCSS version 9.

Results

I. Patient characteristics

Among the 44 patients extracted from the RaPiDo database, 9 patients died before being able to begin treatment and 1 patient was treated within the framework of the EXILIXIS study without access to its data. In total, we included 34 patients who received cabozantinib from RaPiDo and 40 patients from the CHIEF cohort. The final cohort included 74 patients (figure 3).

The main characteristics of the population' study are summarized in table 1. Briefly, there were 84% of males, with a median age at 66 years. Eighty two percent had cirrhosis, related to excessive alcohol consumption in 38% of cases. Median MELD score was at 8 (CI 95% [7-10]). Seventy percent of patients were Child Pugh class A and 28% class B. Forty percent of them experienced a history of cirrhotic decompensation (mainly ascites and digestive bleeding).

Figure 3. Flow chart.

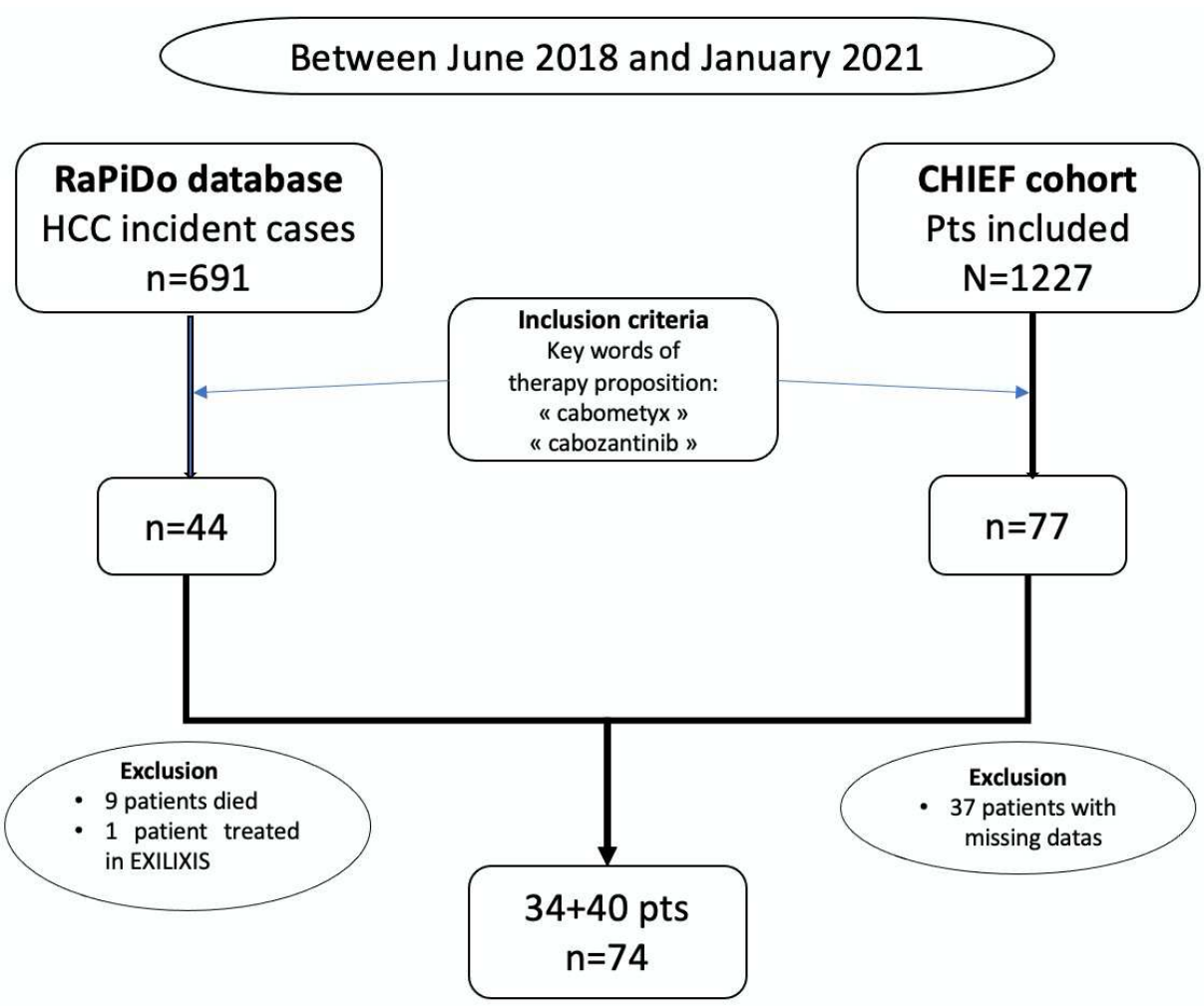


Table 1. Population characteristics at the introduction of cabozantinib (n=74)

	Nber (%)	**Median [CI 95%]**
Age (years)	72	66,2 [63,7- 68,5]
Gender :		
- Male	62 (84)	-
- Female	12 (16)	-
ECOG :		
- 0	23 (43)	-
- 1	29 (54)	-
- ≥ 2	2 (3)	-
BMI:	74	26,8 [25,2- 27,5]
Diabetes :	32 (44)	-
Arterial hypertension :	47 (64)	-
Tabaco :		
- No	18 (27)	-
- Former smoker	37 (54)	-
- Current smoker	13 (19)	-
Patients with cirrhosis :	61 (82)	-
Diagnosed by		
- Histological	28 (47)	-
- Radio-biological	27 (45)	-
- Non invasive	5 (8)	-
CHILD classification		
- A	35 (70)	-
- B	14 (28)	-
- C	1 (2)	-
MELD score	-	8 [7-10]
Past history of decompensation	23 (40)	-
- Ascites	17 (73)	-
- Encephalopathy	2 (8)	-
- Bleeding	4 (17)	-
- Jaundice/ AAH	1 (4)	-
Alcohol consumption :		
- Never	21 (28)	-
- Abstinent	40 (54)	-
- active	13 (18)	-
Main aetiology of hepatopathy:		
- Alcohol	24 (38)	-
- Metabolic	3 (5)	-
- Alcohol + metabolic	13 (21)	-
- Viral	10 (16)	-
- Others	13 (20)	- -

Others includes mixed etiologies (viral and alcohol, viral and metabolic), hemochromatosis or unknown.
AAH: Alcoholic Acute hepatitis

II. HCC characteristics

HCC characteristics are summarized in table 2. Briefly HCC belonged to BCLC C stage in 85% of cases and BCLC B stage in 15% of cases. Median number of nodules was at 5 and the median cumulative size of nodules was at 100 mm. Fifty three percent of patients had extrahepatic metastases (mostly lymph nodes 42%, pulmonary location 13%). Above the 35 patients who had histological proof of HCC, pathological analysis found 34% of well differentiated HCC, 51% moderately differentiated and 14% poorly differentiated (Table 3.).

Tableau 2. HCC characteristics at the introduction of Cabozantinib

	Nber	**Median [CI 95%]**
Number of nodules	61	5 [3 - 7]
Tumour size :		
- Size of the biggest nodule (mm)	55	60 [49 - 71]
- Cumulative size of nodules (mm)	55	100 [100 - 100]
Macroscopic tumoral thrombosis :		
- None	25 (62)	-
- Segmental	10 (25)	-
- Truncular	5 (13)	-
Metastasis location :	31 (53)	-
- Lymph nodes	13 (42)	-
- Pulmonary	4 (13)	-
- Adrenal	2 (7)	-
- Bone	2 (7)	-
- Peritoneal	2 (7)	-
- ≥ 2 locations	8 (25)	-
BCLC :		
- B	10 (15)	-
- C	58 (85)	-

Table 3. Histological HCC characteristics

	Nber	%
Differentiation degree :		
- Well	12	34
- Moderately	18	51
- Poorly	5	14

III. HCC management before cabozantinib

Fifty five percent of our patients received at least one loco-regional treatment (surgery, ablation, chemo-embolization or stereotactic body radiation therapy) before starting systemic therapy (Table 4.). Six patients underwent liver transplantation and then HCC recurrence.

Table 4. First line HCC treatment before cabozantinib

	nber	**%**
Ablation	12	16
Surgery	17	23
Liver transplant	6	8
Chemo-embolization	28	38
Stereotactic body radiation therapy (SBRT)	7	9
Systemic therapy	33	45

Table 5 summarized the different systemic therapies before cabozantinib. Sixty-seven patients (90%) received sorafenib as first line therapy, with a mean duration of treatment of 6.8 months. Among them, 26% interrupt their treatment because of

adverse effects such as diarrhea, deterioration of general status, arterial hypertension or palmo-plantar erythrodyesthesia (PPE). Otherwise, 30 patients had been treated with regorafenib with a mean duration of treatment of 5.6 months. Others systemic therapy used before cabozantinib included lenvatinib, sunitinib, immunotherapy and chemotherapy.

Table 5. Therapeutic sequencing before cabozantinib

	Sorafenib	**Regorafenib**	**Lenvatinib**	**Immunotherapy**	**Others**
Nber (%)	67 (90)	30 (40)	6 (8)	16 (25)	7(9)
Line					
- 1st line	62 (92)	0 (0)	4 (67)	3 (19)	-
- 2nd line	4 (6)	24 (80)	-	8 (50)	-
- 3rd line	1 (2)	4 (13)	2 (33)	4 (25)	-
Duration of treatment (months) [CI 95%]					
- Mean	6.8 [4.2-9.3]	5.6 [3.4-7.8]	6.6 [1.6-11.5]	7.1 [4.4-9.8]	-
- Median	3.6 [3-5.2]	3.5 [2.6-5.2]	5.6[1.5-16.85]	5.2 [2.3-10.4]	-
Median dosage [CI 95%]	600 [400-800]	120 [80-160]	-	-	-
Adverse events	45 (75)	19 (63)	-	2 (12)	-
Reason for withdrawal					
- Intolerance	17 (26)	7 (24)	-	0 (0)	-
- progression	49 (74)	29 (76)	-	16 (100)	-

Adverse effects include: diarrhea, PPE, AEG, decompensation of cirrhosis. Other treatments included sunitinib (n=2), chemotherapy (n=5).

IV. Cabozantinib use

IV.1. Management

Cabozantinib was introduced on label for 22 patients (31%), starting median dosage was at 40 mg/d (CI 95% [20-40]). The mean duration of treatment was 5.1 months, with 40% of withdrawal for intolerance and 60% for progression (Table 7.).

The need of stopping or decreasing treatment concerned 13 patients (23%) at the first medical visit (within 1 month of treatment approximately).

Tableau 7. Use of cabozantinib

	Nber (%)	**Median [CI 95%]**	**Mean [CI 95%]**
On-label :	22 (31)	-	-
Off-label	50 (69)	-	-
Treatment line			
- **2nd line**	31 (43)	-	-
- **3rd line**	23 (32)	-	-
- **4th line**	10 (14)	-	-
- **5th line**	3 (4)	-	-
- **6th line**	1 (1)	-	-
- **Unknown**	4 (6)	-	-
Initiation dosage (mg/d)	-	40 [20-40]	32 [29-36]
Duration treatment (months)	-	4,3 [3,6-4,9]	5.1 [4,2-5,9]
Reason for withdrawal			
- Intolerance	19 (40)	-	-
- Progression	23 (60)	-	-

On-label means 2nd line treatment, OMS 0 or 1 and CHILD A.

IV.2. Efficacy and follow up

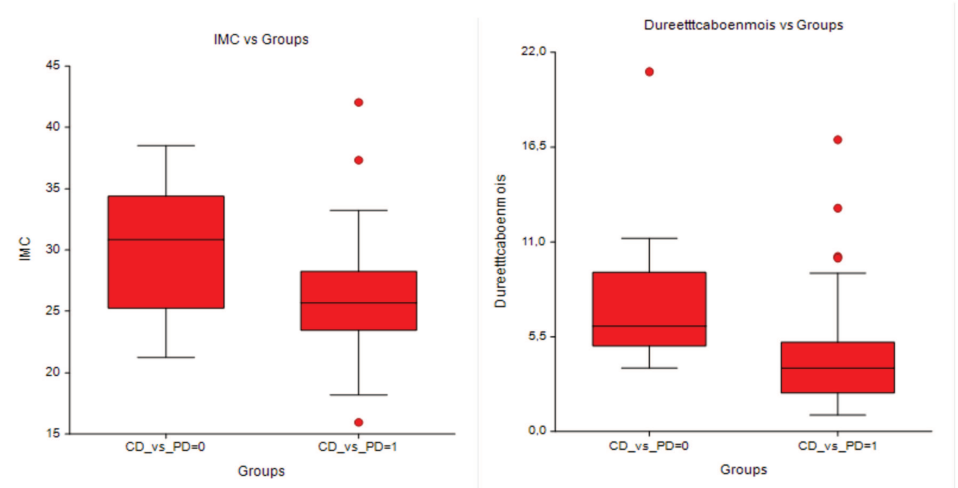
The follow-up of the patients is described in Table 8. Median dosages appear to be stable at 40 mg/d and throughout the follow up. Disease control (CR+PR+SD) declined from 71% (first evaluation) to 53% and then 22% at last news according to RECIST 1.1 criteria (CR n=1, PR n=3, SD n=7).

Tableau 8. Follow up

	1st visit n=58	2nd visit n=40	3rd visit n=23	Last news n=50
Mean duration of treatment (months)	0.7 [0.6-0.9]	2.7 [2.2-3.2]	6 [2.6-13.6]	4.9 [4.0-5.8]
Median dosage [CI 95%]	40 [20-40]	40 [40-60]	40 [20-40]	-
ECOG status				
- **0**	3 (9)	4 (11)	0	-
- **1**	25 (74)	23 (62)	8 (36)	-
- **2**	4 (12)	10 (27)	13 (59)	-
- **≥3**	2 (6)	0	1 (5)	-
Mean Bilirubin [CI 95%] (mg/l)	10 [7.6-13.6]	9 [6.5-12.6]	15 [10.9-22.1]	-
Mean Alphafoetoprotein [CI 95%] (ng/dl)	323 [56-1867]	272 [78-958]	185 [44-785]	-
Radiological response (RECIST 1.1)				
- **CR**	-	0	0	1 (2)
- **PR**	-	4 (13)	3 (16)	3 (6)
- **SD**	-	18 (58)	7 (37)	7 (14)
- **PD**	-	9 (29)	9 (47)	40 (78)
Side effects				
- **Grade ½**	21 (64)	16 (40)	12 (52)	-
- **Grade ¾**	10 (17)	7 (17)	9 (39)	-
Necessity of stopping or decreasing cabozantinib	13 (23)	21 (52)	19 (79)	-

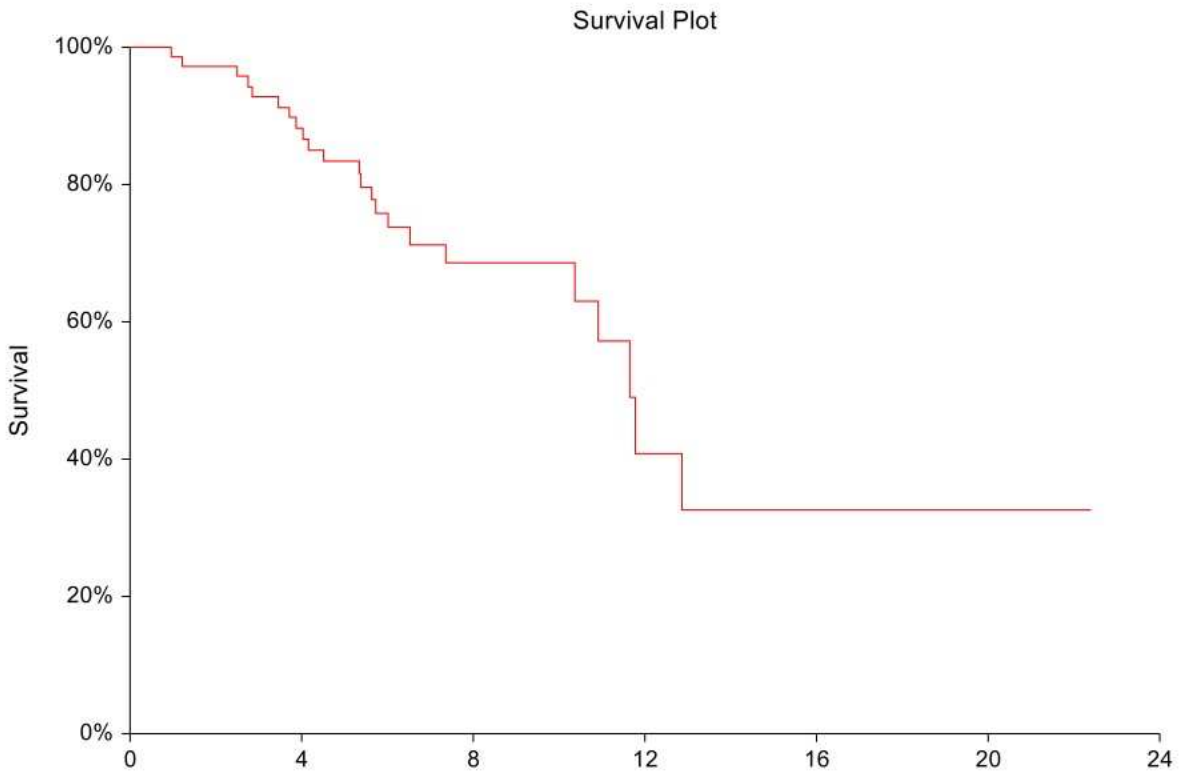
We identified only 2 predictive factors of disease control: a higher BMI (30.1±5 versus 26.1±4.7, p=0.01) and a longer duration of treatment (8.1±4.8 months versus 4.6±3.3, p=0.002) (figure 4).

Figure 4. IMC and treatment duration as predictive factors of control disease.



General status ECOG 1 declined during the follow up from 74% to 36% at the third visit (with a mean duration of treatment of 6 months). Overall survival was defined as the time from the introduction of cabozantinib to death or last news. Median overall survival is 11.5 months, illustrated by figure 5. Twenty three patients expired during the follow up. Causes of deaths were HCC progression in 85%, sepsis in 10% and decompensation of cirrhosis in 5% of cases.

Figure 5. Kaplan Meier analysis of overall survival.



Predictors of a better overall survival were: higher BMI (27.5±5 versus 25.1±4 p=0.04), duration of treatment (5.6±3 months versus 4.1±3 months p=0.02), cumulative size of HCC (97.3±36mm versus 128.8±64 mm p=0.04) and lack of portal thrombosis (65% versus 57% p=0.06).

IV.3. Tolerance

The mean adverse events related to cabozantinib are summarized in table 9. Forty percent of patients have definitively withdrawn their treatment. The more common adverse event were mainly fatigue (38%), diarrhea (32%), decompensation of cirrhosis (25%), and PPE (23%). Serious adverse events (grade 3 or 4) were fatigue and decompensation of cirrhosis (ascites in 73% and digestive bleeding in 15% of cases). Two predictors of grade ¾ adverse events at the first visit have been identified: presence of diabetes (70% versus 35%, p=0.04) and past history of adverse events with sorafenib (55% versus 44% p=0.004).

Tableau 9. Adverse events

	Nber (%)	**Grade 1/2**	**Grade 3/4**
≥ 1 side effect	74 (100)	48 (64)	26 (36)
Interruption of treatment because of side effect	19 (40)	-	-
Diarrhea	24 (32)	20 (27)	4 (5)
Fatigue	28 (38)	18 (24)	10 (13)
PPE	17 (23)	13 (17)	4 (5)
Hypertension	5 (6)	3 (4)	2 (2)
Nausea/Vomiting	9 (12)	7 (9)	2 (2)
Biological abnormalities	3 (4)	2 (2)	1 (1)
Decompensation of cirrhosis	19 (25)	10 (13)	9 (12)
- Ascites	14 (73)	-	-
- Encephalopathy	2 (10)	-	-
- Bleeding	3 (15)	-	-
- Jaundice/ AAH	0	-	-
Others	8 (10)	7 (9)	1 (1)

Biological damages include: increase in serum bilirubin level (n=3), increase in ALAT/ASAT (n=1), leucopenia (n=2), decrease in platelet count (n=1)
Others side effects include: cervical pain, bone pain, abdominal pain, mucitis, dysgeusia, tinnitus, dysphonia, pulmonary embolism (n=1).
Severity was graded according to National Cancer Institute Terminology Criteria for Adverse Events, version 4.0.

V .Comparison of the 2 groups of patients

The two groups of patients were quite different in terms of patient's characteristics and cabozantinib management (Table 10). Briefly, patients extracted from RaPido database were less often diabetics, smokers, with a more preserved liver function. HCC characteristics were similar except for the incidence of extra-hepatic metastasis. In terms of cabozantinib management, patients from RaPido group began the therapy with lower dose and less often as a second line therapy.

Table 10. Comparison of the two groups of patients

	RaPiDo n=34 (%)	**CHIEF n=40 (%)**	***P value***
Median age (years) [CI 95%]	66.3 [63.4-68.2]	65.6 [60.7-70.6]	0.6
Male Gender	31 (91)	31 (77)	0.1
Tobacco			
- No	12 (35)	6 (18)	
- Former smoker	19 (56)	18 (53)	**0.05**
- Current smoker	3 (9)	10 (29)	
Diabetes	10 (29)	22 (56)	**0.02**
Mean MELD score [CI 95%]	8.3 [7.4-9.2]	10.5 [8.8-12.1]	**0.02**
Main aetiology			
- Alcohol	15 (56)	9 (25)	
- Metabolic	3 (11)	0 (0)	**0.03**
- Alcohol + metabolic	4 (15)	9 (25)	
- Viral	2 (7)	8 (22)	
HCC diagnostic			
- Screening	12 (35)	16 (53)	
- Incidental finding	9 (27)	0 (0)	**0.005**
- Pain	10 (29)	6 (20)	
- Decompensation of cirrhosis	3 (9)	8 (27)	
HCC characteristics			
- Size of the biggest nodule	64 [41-100]	55 [47-71]	0.9
- Median number of nodules	7 [3-10]	5 [2-5]	0.2
- Metastasis	22 (64)	9 (37)	**0.04**
- BCLC B	6 (17)	4 (12)	0.4
- BCLC C	28 (83)	30 (88)	0.4
Management before cabozantinib			
- Ablation	2 (6)	10 (26)	**0.02**
- Surgery	11 (32)	6 (15)	**0.08**
- Liver transplantation	5 (15)	1 (2)	**0.05**
- TACE	12 (35)	16 (41)	0.5
- Sorafenib	34 (100)	33 (82)	**0.01**
Cabozantinib management			
- On label	8 (24)	14 (37)	0.2
- 2nd line therapy	11 (32)	21 (62)	**0.01**
- Median initiation dosage	20 [20-40]	40 [40-60]	**0.001**

Discussion

This real-life observational study is, to our knowledge, the first to describe, using two data sources, the use and sequencing of cabozantinib since it has obtained its label in 2018 in France. The CHIEF cohort has some inclusion criteria while the RaPido group patients are unselected patients from our regional HCC-dedicated multidisciplinary consultation meeting. The 2 groups of patients were significantly different in terms of clinical characteristics (more diabetic patients and smokers in the CHIEF cohort group) and for the circumstances of diagnostic. On the other hand, no significant difference was found for HCC characteristics, and the data from our patients also appeared similar to the CELESTIAL data, with patients having globally advanced disease, metastatic (53%) with macrovascular invasion (38%)(13).

This study highlights the frequent use of cabozantinib off-label, which is often the case after a new anticancer therapy has been made available. Indeed, therapeutic innovations are regularly given with a compassionate use to patients who have failed prior treatment. A meta-analysis published in 2017 highlighted that 13 to 71% of patients with cancer have been treated at least once with a off-label treatment (15). To our knowledge, in France, there is no data about the off-label use of cancer therapy but the update of the social security financing law on this subject in 2021 reflects a current situation (16,17). In spite of these circumstances of use, the mean duration of treatment in our work remained similar to CELESTIAL's (5.1 months versus 5.2 months) as well as the median overall survival (11.5 months versus 10.2 months) whereas cabozantinib use occurred later in the therapeutic history of HCC and the patients were less selected. Indeed, CELESTIAL excluded patients who had received more than 2 lines of treatment (our population included 57%) and patients with liver transplantation for HCC (our population included 6 cases). Therefore, off-label

prescription of cabozantinib, especially in the patients described above, does not seem inappropriate.

Moreover, for radiological tumour response, we observed an objective response rate (CR+PR) similar to that observed in CELESTIAL (5% versus 4%). Among the 74 patients included, 10 out of 11 patients with an objective response were still being treated at the last news. Conversely, the tumour control rate (PR+SD) in our work was significantly lower than that reported in CELESTIAL (22% versus 64%), which can be explained by missing data in still alive patients and the absence of centralized review of the imaging.

We observed that all patients who were previously treated with sorafenib received a mean dosage of 600 mg/d with adequate tolerability (26% withdrawal due to intolerance). A Japanese phase 2 study demonstrated the efficacy of cabozantinib in 2 groups, one sorafenib-naïve and another previously treated (18). The progression-free survival of the previously treated group appeared significantly longer. This result suggested that sorafenib escape may be due to MET overexpression, making HCC secondarily more sensitive to cabozantinib.

The label of cabozantinib indicates a dosage of 60 mg/d but this dosage seems difficult to maintain over the long term because of side effects, and in our study as in the CELESTIAL study, the mean dosage was 40 mg/d. Forty percent of patients have withdrawn cabozantinib because of adverse events. Among the main side effects identified in our work, we found the decompensation of cirrhosis (27% of patients), mainly with ascites, but also with hepatic encephalopathy or digestive bleeding. It should be noted that decompensation of cirrhosis was not mentioned as such in the CELESTIAL trial, except for ascites in 12% of patients. This difference can be explained by the fact that in our study, the main aetiologies of cirrhosis were excessive

alcohol consumption or both metabolic and alcohol consumption corresponding respectively to 38 and 21% of patients. Whereas in CELESTIAL, the main aetiology was viral (64%) and excessive alcohol consumption concerned only 16 to 24% of patients, implying a different patient profile in terms of tolerance, especially since in our study, 13 patients (18%) were not weaned.

The strength of our study is that it reports a unique experience of using cabozantinib in clinical practice with unselected patients. It also provides information on treatment sequencing and patient history. Weaknesses include a certain number of missing data, especially regarding the latest news, and the small number of patients compared to the 700 in CELESTIAL.

In conclusion, this study allowed us to describe the modalities of use of cabozantinib in routine practice, in a "natural" environment and not constrained by a protocol. This study, which included unselected Caucasian patients with alcohol-related cirrhosis treated with cabozantinib mainly off-label (Child B, OMS 2, beyond second line), obtained results that were perfectly comparable in terms of survival, treatment duration and tolerance to those obtained in the CELESTIAL registration study. Real-life studies are still rare, but although they have limited power, they are essential in the phase IV trials. Thus, they can be used to homogenize practices in order to optimize management by comparing practices. For example, according to the results of our study, we could propose increased monitoring of the occurrence of side effects in diabetic patients or patients who have had side effects with sorafenib. In 2017, the Ministry of Health commissioned a report on this subject to provide an overview of the situation in France (19). It emerges that many works of this type are carried out, but unfortunately, with no resource pooling between the different institutions, the results are not disclosed in the most optimum manner.

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Date de soutenance : 09/04/2021
Titre de la thèse : Données inter-régionales sur le séquençage et l'utilisation en pratique clinique du cabozantinib dans la prise en charge du carcinome hépatocellulaire à partir de la base RaPiDo et de la cohorte CHIEF.

Thèse - Médecine - Lille 2021
Cadre de classement : hépatologie, oncologie
DES + spécialité : DES hépato-gastro-entérologie - FST cancérologie
Mots-clés : Carcinome hépato-cellulaire, cabozantinib, thérapie ciblée

Résumé :
Contexte : Le cabozantinib, nouvel inhibiteur de tyrosines kinases, a obtenu une extension d'AMM pour le traitement du CHC en 2nd ligne après sorafenib en 2018 après la communication des résultats de l'étude de phase 3 CELESTIAL. A ce jour, peu de données d'utilisation et de séquençage des différents traitements médicaux du CHC en pratique clinique quotidienne sont disponibles. Dans notre étude, nous avons décrit le profil des patients de la "vraie vie" recevant du cabozantinib, dans le but d'évaluer le séquençage et l'usage en pratique clinique du cabozantinib et de comparer nos résultats à ceux de CELESTIAL.
Patients et méthodes : Nous avons mené une étude observationnelle rétrospective incluant des patients du CHRU de Lille via une extraction de la base RaPiDo et des patients de la cohorte nationale CHIEF entre Juin 2018 et Janvier 2021. Les données complémentaires de suivi cliniques, biologiques et morphologiques ont été saisies de manière prospective.
Résultats : Soixante-quatorze patients ont été inclus. Il s'agissait principalement d'hommes (84%) avec un antécédent de cirrhose (38% liée à une consommation excessive en alcool et 21% d'origine alcoolique et métabolique). Le CHC était classé BCLC C dans 85% des cas. On retrouvait une différence entre les 2 groupes (RaPiDo et CHIEF) au niveau des caractéristiques des patients mais les caractéristiques des CHC étaient similaires. Le cabozantinib était prescrit dans le cadre de l'AMM dans 31 % des cas. La durée moyenne de traitement était de 5,1 mois. Le taux de réponse objective était de 4% et le taux de contrôle de la maladie de 22%. Quarante % des patients ont arrêté le traitement pour intolérance. Les effets secondaires mis en évidence étaient l'asthénie, la diarrhée et la décompensation de cirrhose. Le diabète et l'antécédent d'effets secondaires sous sorafenib étaient des facteurs de risques associés à la survenue de grade ¾.
Conclusion : Cette étude observationnelle est, à notre connaissance, l'unique à décrire l'utilisation et le séquençage du cabozantinib depuis l'obtention de l'AMM en 2018 en France. Nous avons mis en évidence une utilisation fréquente du cabozantinib en dehors de son AMM mais avec des taux de réponse objective et une médiane de survie globale similaires aux données de l'étude d'enregistrement CELESTIAL.

Composition du Jury :
Président : Professeur Philippe MATHURIN
Assesseurs : Professeur Nicolas PENEL, Professeur Éric NGUYEN-KHAC, Docteur Massih NINGARHARI
Directeur de thèse : Professeur Sébastien DHARANCY