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International and multicenter real-world study of sorafenib-treated patients with hepatocellular carcinoma under dialysis

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Abbreviations

HCC: hepatocellular carcinoma; BCLC: Barcelona Clínic Liver Cancer; ECOG-PS: Eastern Cooperative Oncology Group–Performance status; CI: confidence interval; CKD: chronic kidney disease; TKI: tyrosine kinase inhibitors; HCV: hepatitis C virus; HBV: hepatitis B virus; AE: adverse event; PT: prothrombin time; INR: international normalized ratio; CTCAE: Common Terminology Criteria for Adverse Events; OS: overall survival; IQR: interquartile range; PTH: parathyroid hormone; TVP: tumoral portal vein thrombosis; M1: metastasis; DM: diabetes mellitus; NAS: nephroangiosclerosis; GMN: glomerulonephritis; SOR: sorafenib; AST: aspartate aminotransferase; ALT: alanine aminotransferase

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Conflicts of interest

Álvaro Díaz-González: Speaker fees and travel grants from Bayer. Travel grants from BTG and GILEAD.

M Sanduzzi-Zamparelli: Speaker fees and travel grants from Bayer. Travel grants from BTG.

L. da Fonseca: Speaker fees and travel grants from Bayer and IPSEN.

GG Di Costanzo: Speaker fee from Abbvie, travel grants from Bayer, Alpha-Sigma, and MSD.

R. Alves: Advisory Board, Bayer.

M. Iavarone: Speaker fees from Bayer, Gilead Science, Janssen, BTG, Abbvie. Consultant in BTG.

C. Leal: Speaker fees and travel grants from Bayer.

AM. Matilla: Speaker: Bayer, BTG and Bristol-Myers. Consultant: Bayer.

G. Aballay Soteras: Advisory and consultation fees Bayer, speaker honoraria Bayer.

MA Wörns: Lecture fees from Abbvie, Bayer, Bristol-Myers Squibb, Celgene, Gilead, Incyte, Ipsen, MSD, Norgine. Consultant/advisory role for Abbvie, Bayer, Bristol-Myers Squibb, Eisai, Gilead, Ipsen, Norgine, Roche.

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M. Ladekarl: Travel expenses by Bayer.

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S. Pascual: Lecture fees from Intercept, Gilead, Abbvie. Consultancy in Abbvie/Bayer.

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M. Vergara: Advisory board from Gilead and lectures for Abbvie, MSD, intercept, Janssen Gylag and Gilead. Lectures: Intercept.

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M Sala: Lectures and travel grants: Bayer.

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Abstract

Background & Aims: Information on safety and efficacy of systemic treatment in patients with hepatocellular carcinoma under dialysis are limited due to patient exclusion from clinical trials. Thus, we aimed to evaluate the rate, prevalence, tolerability, and outcome of sorafenib in this population.

Methods: We report a multicenter study comprising patients from Latin America and Europe. Patients treated with sorafenib were enrolled; demographics, dose modifications, adverse events, treatment duration, and outcome of patients undergoing dialysis were recorded.

Results: As of March 2018, 6156 hepatocellular carcinoma patients were treated in 44 centers and 22 patients were concomitantly under dialysis (0.36%). The median age was 65.5 years, 40.9% had hepatitis C, 75% had Child-Pugh A, and 85% were BCLC-C. The median time to first dose modification, treatment duration, and overall survival rate were 2.4 months (IQR, 0.8–3.8), 10.8 months (IQR, 4.5–16.9), and 17.5 months (95%CI, 7.2–24.5), respectively. Seventeen patients required at least 1 dose modification. The main causes of first dose modification were asthenia/worsening of ECOG-PS and diarrhea. At the time of death or last follow-up, four patients were still on treatment and 18 had discontinued sorafenib: 14 were due to tumor progression, 2 were sorafenib-related, and 2 were non-sorafenib-related AE.

Conclusions: The outcomes observed in this cohort seem comparable to those in the non-dialysis population. Thus, to the best of our knowledge, this is the largest and most informative dataset regarding systemic treatment outcomes in hepatocellular carcinoma patients undergoing dialysis.

Abstract word count: 242

Keywords: Hepatocellular carcinoma, sorafenib, dialysis, adverse events, safety, survival.

Lay summary

- Patients with chronic kidney disease undergoing dialysis are usually excluded from randomized trials that evaluate cancer therapies.
- Sorafenib are levantinib a first-line treatment for advanced hepatocellular carcinoma (HCC), is a safe and effective treatment, but there are no specific data on treatment of HCC patients undergoing dialysis.
- This study shows that sorafenib is safe in patients with HCC and dialysis and their outcome appears similar to patients without dialysis.

Introduction

Currently, systemic treatment for hepatocellular carcinoma (HCC) relies on a sequential approach combining first- and second-line agents. In both settings, more than one option has proven survival benefit. Sorafenib and lenvatinib are first-line treatments, while regorafenib, cabozantinib, and ramucirumab are used as alternatives. However, the strict inclusion criteria of the pivotal trials with these agents did not cover the whole spectrum of clinical situations, which impairs the applicability of their results in some populations. Only one phase I study has considered specific populations as one of their cohorts.[1]

Interest in developing therapeutic strategies in the field of HCC has increased exponentially since the approval of sorafenib in 2008, although many attempts have resulted in discouraging results. The presentation of a positive trial of atezolizumab plus bevacizumab in first-line therapy could change first-line clinical practice, but currently no data from immunotherapy trials include this profile of patients.[2]

The decision to implement systemic treatment for HCC in particular patient subgroups such as those with prior liver transplantation, liver dysfunction, HIV, or chronic comorbidities is hampered by the lack of prospective data. While small cohorts evaluated patients with some of these characteristics, there is currently no data relative to systemic therapy in patients with a history of chronic kidney disease (CKD).[3–5]

The incidence of HCC in patients on dialysis is not well established. Renal replacement therapies or kidney transplantation are required in about 1% of patients with CKD. More than 400,000 people are yearly treated with dialysis in the United States and Europe[6,7] and 250,000 people in Latin America.[8] In Western countries, the prevalence of Hepatitis C Virus (HCV) carriers in patients undergoing hemodialysis ranges between 3 and 20%[9–11] and the incidence of HCC in the CKD population has been estimated to be around 2.03 per 1000 person-years.[12]

CDK is associated with a complex chain of comorbidities such as cardiovascular complications,[13] bone metabolism alterations,[14] anorexia, cachexia, and weight loss,[15] gastrointestinal disorders (directly or indirectly related to phosphate-binder treatments),[16] and thyroidal disorders.[17] Thus, the use of sorafenib in CKD patients remain uncertain, excluding CKD patients from clinical trials.[18,19] Data on the safety of tyrosine kinase inhibitors (TKI) treatment in patients undergoing

dialysis are limited to patients with renal cell carcinoma treated with sunitinib[20] and sorafenib.[21] Only one phase I trial evaluated the safety and pharmacokinetic profile of sorafenib in patients with renal or hepatic dysfunction.[1] This study included 17 HCC patients and of these only 9 patients were under dialysis. However, there is no information regarding the cancer type of these patients and of their liver function status. Thus, it is not possible to properly ascertain data affecting patients with HCC or whether the data would be similar for dialysis patients.

The only possible way to generate real-world data in patients with HCC and CKD under dialysis is through a comprehensive multicenter study. Thus, we designed an international and collaborative network study aimed to evaluate the prevalence of HCC patients receiving dialysis and sorafenib simultaneously. Additionally, we aimed to describe the safety profile and clinical outcomes of patients who received simultaneously sorafenib and dialysis, taking into consideration the risk of mortality in this subset of patients.

Materials and Methods

This is a retrospective cohort focused on HCC patients treated with sorafenib with CKD requiring dialysis (dialysis-sorafenib) between 2009 and April 2018. Centers with expertise in HCC management from Latin America and Europe participated in the study. Data from all centers who accepted to participate in the study were recorded, regardless of whether they had patients undergoing dialysis or not. We considered the total number of patients treated with sorafenib monotherapy at each center as the initial study cohort and the dialysis-sorafenib patients were selected as the target population of the study. Thus, data of individual patients were collected from centers that treated patients with sorafenib and dialysis simultaneously. The study was approved by the institutional review board (HCB/2018/0013) and complied with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki.

Data collected for the analysis

Data were anonymized and collected from medical records by each local investigator and were centrally compiled and analyzed. The following variables were registered: the first date a patient

started sorafenib, the number of patients treated with sorafenib, management policy, radiological criteria, and the follow-up schedule after starting sorafenib in each center.

Additionally, from the dialysis–sorafenib patients, we collected the following baseline characteristics: Barcelona Clinic Liver Cancer (BCLC) stage, level of functionality according to the Eastern Cooperative Oncology Group–Performance Status (ECOG-PS) scale, etiology of CKD, and sorafenib starting dose. The evolutionary events occurring during sorafenib treatment and details of the dialysis in these patients, such as time on dialysis, number and causes of adverse events (AEs), sorafenib-dose modifications, pattern of radiological tumor progression, and reason for sorafenib discontinuation, were also collected. Liver function was evaluated using albumin, bilirubin, and prothrombin time (PT). For centers that sent INR instead of PT, we calculated PT from the INR value. Additionally, we registered whether patients had received post-sorafenib therapy and the survival status at the database lock.

AEs were not classified using the Common Terminology Criteria for AEs (CTCAE) classification because of the retrospective nature of the study. In addition, this classification has changed over the years. All these factors may lead to over- or under-reporting.

Outcomes and assessments

Treatment duration was defined as the time from sorafenib initiation to treatment discontinuation. Overall survival (OS) was defined as the time from sorafenib initiation to death from any cause or last follow-up visit and the post-sorafenib survival was calculated from the date of sorafenib discontinuation to death or last-follow-up.

Statistical analysis

Categorical variables are described as frequencies and percentages and continuous variables as median and interquartile ranges (IQR). Comparisons between two groups for quantitative or ordinal variables were assessed by Mann–Whitney U test. Fisher's exact test was used to compare categorical variables. Survival rates and curves were determined using the Kaplan-Meier method. The last update was August 2018. Analysis was done censoring survivals at the time of last follow-up or death. Wilcoxon signed-rank test was used to compare paired

continuous variables. All calculations were performed with STATA version 14.2 (StataCorp Inc., TX).

RESULTS

Seventy centers were contacted and 57 centers initially agreed to participate. Finally 44 centers provided the requested information. Between 2009 and April 2018, a total of 6,156 patients were treated with sorafenib in centers from Spain, Italy, Brazil, Argentina, Germany, France, Austria, Colombia, Mexico, Uruguay, and Denmark. Eleven of these centers had at least one patient treated with sorafenib and dialysis simultaneously, for a total of 22 patients (Figure 1). Of these 6,156, 22 patients represented 0.36% of the initial cohort and were further characterized. We did not calculate the incidence of patients under dialysis who were candidates to sorafenib treatment because for most of them, the renal replacement therapy and HCC treatment were performed in different centers.

Management of sorafenib and radiological evaluation

Sorafenib management

Two of 44 centers considered concomitant dialysis a contraindication for sorafenib, while for 42 centers dialysis was not considered a limiting factor. The same treatment protocol was applied to all patients regardless of whether they were under dialysis or not in 39 out of the 42 centers. However, 2 centers started sorafenib at a reduced dose in the case of dialysis patients and one center routinely shared the patient management with a nephrologist consultant.

Briefly, 20 centers examined the patients twice during the first month and the schedule of visits varied in the other 22 centers (Supplementary Figure 1a). Thirty-one of the 42 centers examined these patients monthly after the first month and the remaining centers had a variable schedule of visits, which ranged from biweekly to every 3 months (Supplementary Figure 1b).

Radiological evaluation

The schedule of radiological assessments differed across the centers but none modified their usual radiological follow-up because of dialysis. Briefly, 28 centers performed radiological evaluation every 3 months, 10 every two months and evaluations in the remaining centers ranged from every 3–6 months (See details in Supplementary Figure 1c). Both CKD and HCC diseases were treated at the same center in only 54.6% of the cases. Thus, this precluded the estimation of the time to progression and progression-free survival for this study.

Supplementary table 1 shows the number of patients treated simultaneously in the same center, when, and where the patients under dialysis were treated.

Baseline characteristics of dialysis-sorafenib patients

Baseline characteristics of the 22 dialysis-sorafenib patients are summarized in Table 1. Most patients were male (19/22) with a median age of 65.5 years (IQR 54–68) and diagnosed with liver cirrhosis (20/22). The most common cause of liver cirrhosis was Hepatitis C virus (HCV; 9/22), followed by Hepatitis B virus (4/22), a combination of HCV and alcohol (4/22), alcohol (3/22), and other causes (2/22). Two patients were non-cirrhotic (1 had chronic hepatitis C and the other was a liver transplant recipient); almost all cirrhotic patients were Child-Pugh A (15/20) and 5 were Child-Pugh B. All patients were BCLC B or C (18 BCLC-C and 4 BCLC-B) and had ECOG-PS of 0 or 1 (10 PS-0 and 12 PS-1). The most frequent causes of CKD were diabetic nephropathy, nephroangioesclerosis, or a combination of both in 14/22 cases. Other CKD etiologies were membranoproliferative glomerulonephritis, IgA nephropathy, polycystic nephropathy, and previous nephrectomy. None of the patients was under peritoneal dialysis and the median time on hemodialysis prior to sorafenib treatment initiation was 18 months (IQR 13–24).

Clinical outcome and treatment duration of sorafenib-dialysis patients

Three centers started treatment with a half-dose of sorafenib. The median follow-up and sorafenib treatment duration were 14.7 months (IQR, 7.2–23.9) and 10.8 months (IQR, 4.5–16.9), respectively. The rate and most frequent cause of sorafenib dose modification were 77.3% and clinical deterioration or diarrhea, respectively. The main reasons motivating definite discontinuation were tumor progression (77.8%), followed by sorafenib-related AEs (11.1%) and non-sorafenib-related AEs (11.1%) (Figure 3). Table 2 describes the percentage of Severe AE

(SAE) according to the type of AE. Seven patients (31.8%) presented SAE grade 3 or above. Five patients (22.7%) presented any AE leading to hospitalization due to acute arterial thrombosis, pulmonary edema, septic arthritis, cardiac output reduction, and seizures; 4 of 7 were considered sorafenib-related according to their physicians. Sorafenib-related SAE in these 4 patients were caused by acute arterial thrombosis, asthenia, arterial hypertension (AHT), and cardiac output reduction).

Among patients who presented radiological tumor progression, 71.4% presented concomitant symptomatic progression and 28.6% had extra-hepatic spread. Four patients (18.2%) were on sorafenib treatment at the last update and none received second-line treatment. Eighteen patients discontinued sorafenib, all but 4 discontinued due to tumor progression. Other reasons for discontinuation were sorafenib-related AEs in 2 patients (diarrhea in one patient and arterial thrombosis in the other). The remaining 2 patients discontinued due to liver failure and acute pulmonary edema, which were not considered to be sorafenib-related.

Phosphocalcic metabolism

Phosphocalcic metabolism and PTH values were available for 11 and 6 patients included in the study, respectively. At baseline, median calcium, phosphorus, and PTH values were 8.7 mg/dL (IQR, 8–9.3), 4.7 mg/dL (IQR, 4–6.6) and 118.2 pg/mL (IQR, 8–312), respectively. There was no difference between baseline values, at sorafenib reduction or at definitive discontinuation ($p = 0.18$ for calcium and $p = 0.36$ for phosphorus).

Adverse events profile

Seventeen of 22 patients presented at least one sorafenib dose modification because of AEs. The median time from sorafenib initiation to the first dose modification was 2.4 months (IQR, 0.8–3.8). Reasons for dose modifications are summarized in Table 2. The median number of dose adjustments was 1, regardless of the starting dose. Nevertheless, the time to first dose modification differed between patients who started at full dose and half-dose (2.4 months [IQR, 0.8–4.6] vs. 2 months [IQR, 0.7–3.2], respectively).

The leading causes of first modification were either clinical deterioration or diarrhea. Ten patients required a second-dose modification mainly due to diarrhea, hand–foot skin reaction

(HFSR), and liver decompensation. Finally, 3 patients required a third dose adjustment and 1 patient a fourth.

The leading causes of dose modification in the first three months were diarrhea, HFSR, AHT, asthenia, and ECOG-PS worsening (23.5%, 17.6%, 11.7%, and 11.7%, respectively). Between the third and sixth months, the main causes were ECOG-PS worsening, diarrhea, and folliculitis accounting for 25%, 12.5%, and 12.5% of dose modifications, respectively. Finally, AEs appearing beyond 6 months were the following: liver decompensation not related to sorafenib, polyarthralgia, peripheral vasculopathy, heart decompensation, diarrhea, and asthenia.

Overall survival

Median overall survival of the sorafenib-dialysis cohort was 17.5 months (95% CI, 7.2–24.5) (Figure 2). Five patients were still alive when the study was concluded and all 5 patients were BCLC-C and 3 were Child-Pugh A before starting sorafenib. The median follow-up of these patients was 15.4 months (IQR, 12.5–17.5). Finally, 4 of 5 patients are still on treatment and their median treatment duration is 15.4 months (IQR, 12.6–17.6).

The median OS of patients who discontinued sorafenib due to tumor progression was 11.7 months (95% CI, 3.4–17.5; Supplementary Figure 2). The other 4 patients discontinued sorafenib due to liver failure, pulmonary edema, arterial thrombosis, and diarrhea; their survival rates were 11.2, 24, 26.5 and 38.6 months, respectively.

DISCUSSION

This is the first multicenter international collaborative real-world study that provides evidence supporting the use of sorafenib in HCC patients undergoing dialysis. The prevalence of patients under dialysis was 0.36% in a large initial cohort of 6,156 HCC patients treated with sorafenib. This prevalence could be considered low compared to other orphan populations. The median OS in the cohort was 17.5 months (95%CI, 7.2–24.5) and the main cause of sorafenib discontinuation was tumor progression. In this cohort, the 22 included patients were treated and their life expectancy likely improved owing to sorafenib activity. The median OS was higher than that reported in non-dialysis population. However, the longer overall survival observed in these

patients could be biased due to the small sample size of our study, but it also may reflect a better selection of patients due to the preventive concerns of physicians related to the potential risk of developing cardiovascular AE.

The limitations of running a randomized clinical trial (RCT) involving specific populations underlines the importance of collaborative studies and the ability of academic centers to address unanswered topics to assist physician decision-making in challenging clinical situations. Indeed, the rate of patients that could benefit from systemic treatment would be larger than the 0.36% observed in this cohort. The lack of data from RCTs and the safety concerns deriving from the potential overlap of clinical manifestations of CKD and sorafenib AEs, such as (ischemic heart disease,[22] congestive heart failure or cardiac arrhythmia,[23] peripheral arterial disease,[24,25] cerebrovascular disease, and stroke[26,27]) related to the main causes of CKD such as AHT and diabetes mellitus (DM), suggest caution in sorafenib use in these patients.

Expanding upon what was reported by two participating centers, it is reasonable to speculate that a significant number of groups worldwide also contraindicate sorafenib for HCC patients under dialysis. Although our data can support the use of sorafenib in this population, a comprehensive clinical evaluation should be performed regarding the increased risk of cardiovascular events and worsening of previous conditions such as arterial hypertension and DM.

The fact that none of the patients received any post-sorafenib therapy indicates that patients were treated with sorafenib until symptomatic progression. The broad OS 95%CI (7.2–24.5) could be related to the small sample size and the heterogeneity regarding prognostic factors such as the baseline BCLC stage, pattern of progression, and profile of AEs under sorafenib. However, as the majority of the cohort was staged as BCLC-C, we consider that our results reflect the outcomes expected for patients with advanced HCC.

The rate of sorafenib discontinuation due to sorafenib-related AEs was similar to that reported in the sorafenib arm of the SHARP and REFLECT trials (11% and 10%, respectively).[18,28] Notably, almost all RCTs and prospective cohorts that have evaluated sorafenib to date mention the rate of AEs but not the median time until the first dose modification, which could be considered an indicator of safety. In our cohort, the median time of the first-dose modification due to AEs was 2.4 months, which was similar to the 2 months mentioned in a previous prospective cohort study

of sorafenib-treated patients.[29] However, the most frequent causes for first dose modification were asthenia and diarrhea, in accordance with previous data[21] in patients with kidney cancer treated with sunitinib or sorafenib. In addition, the safety profile and OS are similar ~~or better~~ than that reported in patients without dialysis.[4,18,19,28,30–32] As expected, the main severe sorafenib-related AEs were related to cardiovascular issues but only 11.1% of patients discontinued treatment.

Comprehensively considering the survival and safety results, in our cohort, sorafenib was feasible as a first-line treatment in patients under dialysis. Since this study did not detect a major safety concern at the full dose, starting at full dose in this population does not seem to be a cause for safety concern. Furthermore, this study also supports the recommendation of reducing the dose due to AEs as is done in non-dialysis populations.

The results of this study should not be extrapolated to other TKIs because the profile of AEs does not overlap. Thus, the rate of grade ≥3 AHT, asthenia and diarrhea in sorafenib were 2, 3, and 8% according to the SHARP trial[18]; 14, 4, and 4% according to the REFLECT trial; and 23, 4, and 4% in the lenvatinib arm of the REFLECT trial.[28]

In conclusion, the design of this study did not allow us to grade AEs according to the same criteria used in clinical trials to calculate the time to progression or progression-free survival, but this is the only large international collaborative study, which has reported the real-world data to support sorafenib treatment in an orphan population The prevalence of patients who received sorafenib and dialysis simultaneously was 0.36% and the rate of sorafenib discontinuation was similar to that reported in the general population of HCC patients under sorafenib.

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Table 1. Baseline characteristics of dialysis–sorafenib patients.

Baseline characteristics	**N = 22**
Female/Male (%)	13.6/83.4
Age (Median, IQR)	65.5 (54–68)
Liver Cirrhosis (Yes %)	90.9
HCV/HBV/HCV+Alc/Alc/others (%)	40.9/18.2/18.2/13.6/9.1
Clinical Ascites (No, %)	81.8
Child-Pugh (A/B/No liver cirrhosis, %)	68.2/22.7/9.1
Previous treatment (%, Yes/No)	50/50
None (n)	11
Surgery (n)	1
Liver transplantation (n)	1
Ablation (n)	2
TACE (n)	6
Surgery + TACE (n)	1
BCLC (B/C, %)	18.2/81.8
ECOG-PS (0/1, %)	45.4/54.6
Vascular invasion (%, Yes/No)	63.6/36.4
Extrahepatic spread (%, Yes/No)	47.6/52.4
TVP and/or M1 (%, Yes/No)	81.8/18.2
Liver tumor burden (%, ≤50%/>50%)	54.6/45.4
Alpha-fetoprotein (ng/mL, median, IQR)	1583.5 (158–6373)
Cause of CKD (DM/NAS/NAS+DM/GMN/Others)	27.7/22.7/13.6/27.3/8.7
Sorafenib starting dose (800/400, %)	68.2/31.8
AST (UI/L, median, IQR)	44 (37–56)
ALT (UI/L, median, IQR)	37 (22–60)
Albumin (mg/dL, median, IQR)	3.58 (3.3–4)
Prothrombin time (%, median, IQR)	83 (70–85)
Total Bilirubin (mg/dL, median, IQR)	0.95 (0.6–1.2)
Creatinine (mg/dL, median, IQR)	5 (3.85–7.07)
Calcium (md/dL, median, IQR)	8.7 (8–9.3)
Phosphorus (mg/dL, median, IQR)	4.7 (4–6.6)
PTH (pg/mL, median, IQR)	118.2 (8–312)

IQR: interquartile range, 25–75%; HCV: hepatitis C virus; HBV: hepatitis B virus; Alc: alcohol; TACE: transarterial chemoembolization; TVP: tumoral portal vein thrombosis; M1: metastasis; BCLC: Barcelona Clínic Liver Cancer; ECOG-PS: Eastern Cooperative Oncology Group–Performance Status; CKD: chronic kidney disease; DM: diabetes mellitus; NAS: Nephroangiosclerosis; GMN: glomerulonephritis; SOR: sorafenib; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Table 2. Adverse events leading to sorafenib-dose modifications.

First modification	n (%) [SAE-yes/no]	Second modification	n (%) [SAE-yes/no]	Third modification	n (%) [SAE-yes/no]	Fourth modification	n (%) [SAE-yes/no]
Asthenia	3 (17.7) [1/2]	Diarrhea	2 (20) [0/2]	Polyarthralgia	1 (33.3) [0/1]	Asthenia	1 (100) [0/1]
Diarrhea	3 (17.7) [0/3]	HFSR	2 (20) [0/2]	Folliculitis	1 (33.3) [0/1]		
ECOG-PS Worsening	3 (17.7) [0/3]	Liver decompensation	2 (20) [1/1]	Ascites	1 (33.3) [0/1]		
AHT	2 (11.8) [1/1]	Peripheral vasculopathy	1 (10) [1/0]				
HFSR	2 (11.8) [0/2]	Heart Failure	1 (10) [0/1]				
Liver Failure	1 (5.9) [0/1]	Other GI symptoms	2 (20) [0/2]				
Heart Failure	1 (5.9) [1/0]						
Septic arthritis	1 (5.9) [1/0]						
Pulmonary edema	1 (5.9) [1/0]						

ECOG-PS: Eastern Cooperative Oncology Group–Performance Status; AHT: arterial hypertension; HFSR: hand-foot-skin reaction; Others: septic arthritis, hemorrhoidal bleeding; GI: gastrointestinal.

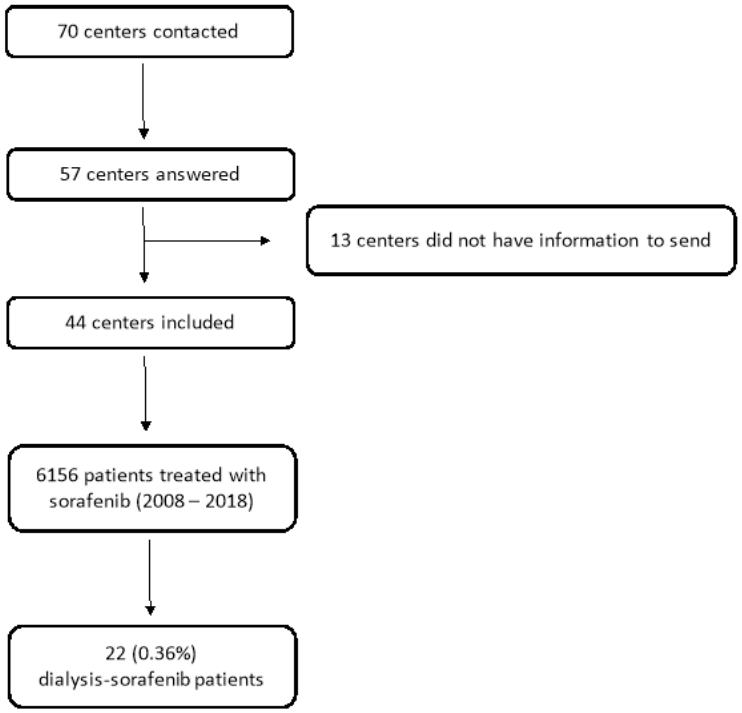
Figure Legends.

Figure 1. Flowchart of centers included in the study.

Figure 2. Overall survival of the cohort. The median overall survival of dialysis–sorafenib patients was 17.5 months. This overall survival (OS) is comparable to OS rates in patients not receiving dialysis and treated with sorafenib.

Figure 3. Reasons for sorafenib discontinuation. The most frequent reason for sorafenib discontinuation was tumor progression, followed by adverse events. Causes and rates of definite suspension are similar to those real-life cohorts in non-dialysis–sorafenib patients.

Figure 1. Flowchart of centers included in the study.



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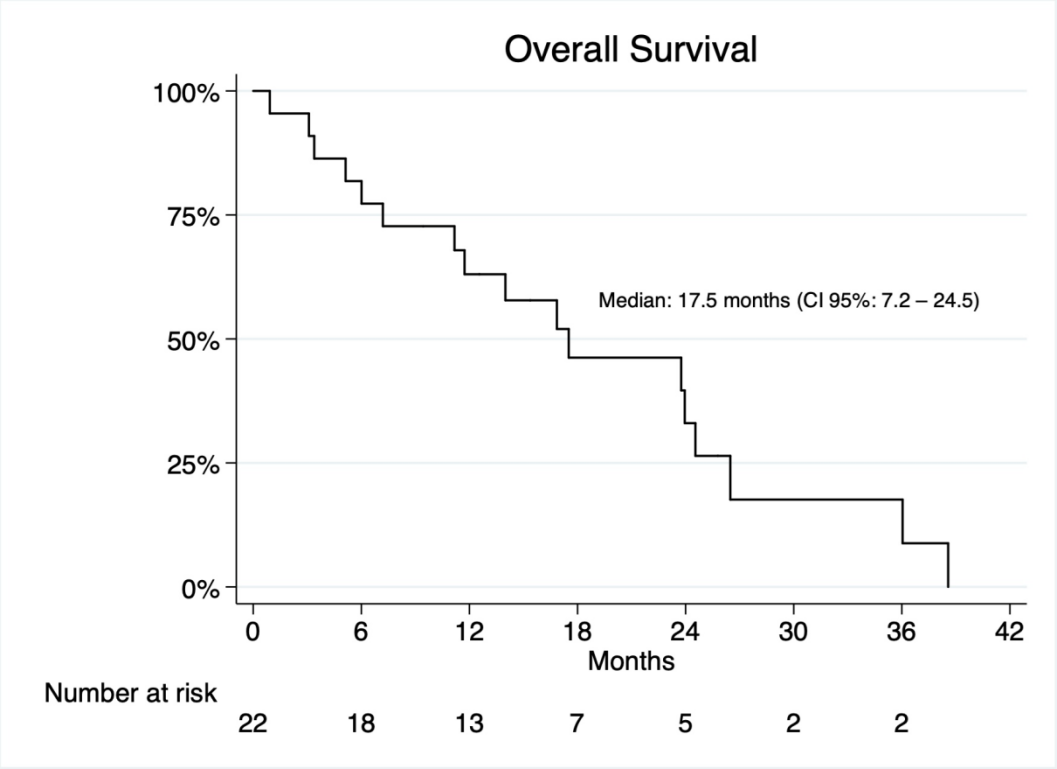

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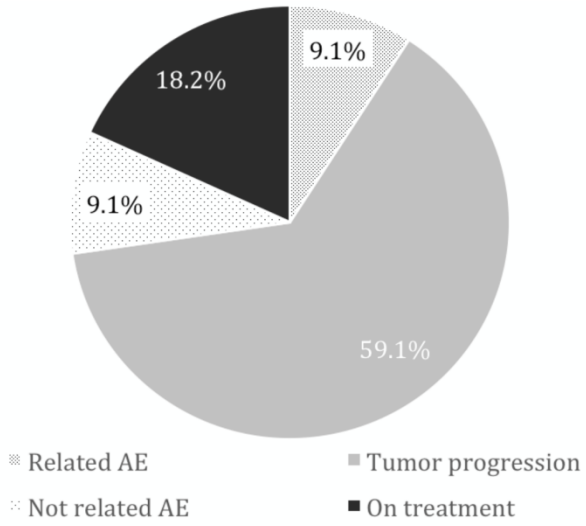

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