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Early diarrhoea under sorafenib as a marker to consider the early migration to second-line drugs

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Abstract

Background: Despite atezolizumab and bevacizumab (A + B) is currently the first-line treatment for hepatocellular carcinoma (HCC) patients, some patients will not be adequate for this combination. In the setting of sorafenib some adverse events have been proposed as prognostic factors.

Objective: To characterize the early diarrhoea development as prognostic factor in 344 HCC patients.

Methods: The development of early diarrhoea in sorafenib treatment defined as patients who developed diarrhoea and needed dose modification within the first 60 days of treatment (e-diarrhoea) and 3-grouping variables were analysed: Patients with e-diarrhoea, patients who developed diarrhoea after the first 60 days of treatment (L-diarrhoea) and patients that never developed diarrhoea (never diarrhoea).

Results: The median overall survival in sorafenib treated patients was significantly different across groups (6.8 months for e-diarrhoea, 26.7 months for L-diarrhoea and 13.3 months for never-diarrhoea). The emergence of e-diarrhoea was associated with poor outcomes (hazard ratio [HR] 1.84 [95%CI 1.15–2.95]), while there was no increased/decreased risk of dismal evolution in patients with L-diarrhoea (HR 0.66 [95%CI 0.42–1.03]).

Conclusion: The emergence of e-diarrhoea in HCC patients treated with sorafenib is an early predictor of dismal evolution under this therapy. Thus, prompt identification of these non-responders may be useful for an early switch to second-line therapies.

KEYWORDS

diarrhoea, hepatocellular carcinoma, resistance, sorafenib, survival, tyrosine kinase inhibitor

Álvaro Díaz-González and Víctor Sapena contributed equally.

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Key Summary

Established knowledge on this subject

- Diarrhoea is a frequent adverse event of sorafenib and its emergence has been associated to better outcomes.

What are the significant and/or new findings of this study?

- Early diarrhoea (e-diarrhoea) in hepatocellular carcinoma patients treated with sorafenib is an early predictor of dismal evolution.
- Diarrhoea under sorafenib should not be taken as a predictive parameter of lack of benefit.
- E-diarrhoea could be used as clinical biomarker for switching to second-line therapies.

INTRODUCTION

The combination of atezolizumab with bevacizumab has surpassed the benefits of sorafenib,[1] and lenvatinib has already been shown to be non-inferior to sorafenib.[2] At the same time, regorafenib,[3] cabozantinib[4] and ramucirumab[5] have provided survival benefit upon progression or intolerance to sorafenib, in the case of cabozantinib[4] and ramucirumab.[5] Indeed, cabozantinib has also been proven effective in third-line treatment options. Furthermore, in the United States, the Food and Drug Administration (FDA) has granted accelerated approval or breakthrough designation to agents (nivolumab,[6] pembrolizumab,[7] combination of lenvatinib with pembrolizumab[8] and of durvalumab with tremelimumab[9]) which have shown persuasive results despite an absence of positive phase 3 Trials. The availability of several options will prime the individualization of the treatment selection according to the profile of the patients so that survival benefits are maximized and potential adverse events (AEs) leading to treatment intolerance and interruption minimized. In this sense, despite the superiority of the atezolizumab plus bevacizumab combination, some patients will not be adequate for this combination (i.e., large oesophageal varices, prior transplantation and renal failure) and sorafenib and lenvatinib will still be used in a relevant proportion of patients as first-line or as a default second-line treatment, which will likely move the options into later lines. In such instance, emergence of specific evolutionary events associated to better or worse outcome will influence the physician's ability to identify treatment failure/dismal outcome and try to provide therapeutic benefit by switching to a second option among those known to be effective. A known example of an AE linked to better outcome is the development of dermatologic AEs,[10–12] but in the case of other AEs such as diarrhoea, the association with distinct survival is not well established.[10,13,14]

In this study, we evaluated, through time-dependent statistical analysis, the association of the development of diarrhoea and the timing of its onset with patient survival in order to determine whether such an AE may help to predict prognosis while on treatment. In this sense, in a prior study in a subgroup of this cohort, we observed that those patients who presented diarrhoea early during follow-up had lower systemic levels of sorafenib and its metabolite. While such findings could be linked to a specific MRP2*3972 polymorphism, it could also reflect a suboptimal treatment regime leading to early treatment failure.[15]

MATERIALS AND METHODS

Patients

This is a retrospective analysis of a prospective database of all patients treated with sorafenib in our unit from 2008 to 2019 (whole cohort).

The following inclusion/exclusion criteria were used in our unit to start sorafenib: (1) Hepatocellular carcinoma (HCC) diagnosed according to EASL guidelines; (2) adequate liver function (albumin >2.8 g/dl; total bilirubin <3 mg/dl; and alanine and aspartate aminotransferases <5 times the upper limit of the normal range), and Child-Pugh score 6–7 points; (3) performance status (PS) 0–1; (4) controlled arterial hypertension and stable peripheral vascular disease; (5) adequate haematologic profile (haemoglobin >8.5 g/dl; and prothrombin time >50%); and (6) adequate renal function (serum creatinine <1.5 times the upper limit of the normal range). Exclusion criteria: (1) myocardial infarction in the past year or active ischaemic heart disease; (2) acute variceal bleeding in the last month; (3) severe peripheral arterial disease; (4) cardiac arrhythmia under treatment with drugs other than beta-blockers or digoxin; (5) uncontrolled ascites; (6) encephalopathy; and (7) unfeasibility to fulfil the follow-up schedule. The institutional review board approved the study (and HCB/2017/1016).

Treatment and follow up

Sorafenib was initiated at full dose (800 mg/day) and adjusted according to the manufacturer's recommendations in most of the patients included in the cohort. Specific details about dose initiation are described in Table S1. Clinical and biochemical assessments took place every 4 weeks. Imaging assessment (RECIST 1.1 plus BCLC amendments) took place at 4 weeks and every 8 weeks thereafter.[16,17] Patients ineligible for regorafenib were enrolled in second-line clinical trials when appropriate (Table S2).

Adverse events

We recorded all AEs of grade ≥ II occurring between treatment initiation and 30 days after the last dose. AEs were classified according to the Common Terminology Criteria for Adverse Events version 4.03.[18]

Statistical analysis

Quantitative variables were expressed as median and interquartile range (IQR 25th–75th percentiles). Categorical variables were described as absolute frequencies and percentages (%). Time to event variables were described with the Kaplan–Meier method, reporting median and confidence intervals (95% CI), and the observed survival functions was compared with the log-rank test.

Univariate and multivariate time-dependent survival Cox models were used to estimate the hazard ratios (HR) and their 95% CI. For the multivariate models, we included the clinically relevant variables: baseline BCLC status, baseline ECOG-PS and DAE60 as time-dependent covariables. Two principal categorical time-dependent variables were analysed, the first was the development of early diarrhoea (Yes/No) defined as patients who developed diarrhoea and needed dose modification within the first 60 days of treatment (e-diarrhoea). The second was a three-grouping variable: Patients with e-diarrhoea, patients who developed diarrhoea after the first 60 days of treatment (L-diarrhoea) and the third group included the patients that never developed diarrhoea (never diarrhoea). For all these analyses, only grade ≥ II AEs were considered.

The figures for the visualization of the risk between the groups of the time-dependent variables were created using the survival function, estimated with the survival Cox models.

The level of significance was set at the two-sided 5% level, and all calculations were performed with SAS 9.4 software (SAS Institute).

RESULTS

Patients

From January 2008 to August 2019, 344 patients were treated with sorafenib in our Unit. At the time of database lock (August 2019), the median follow-up was 12.3 months (IQR 5.7–22.5), the median treatment time 5.6 months (IQR 2–12.8) and overall survival (OS) 13.6 months (95%CI 12–15.1) and 52 patients presented grade ≥ II diarrhoea.

Baseline characteristics

Table 1 summarizes the baseline characteristics of the 344 patients included in the whole cohort (83.7% Child-Pugh A, 54.1% BCLC-C, 90.1% ECOG-PS 0, 41.9% arterial hypertension, and 28.2% diabetes mellitus). None of the patients with e-diarrhoea or L-diarrhoea were treated with laxatives prior or at the moment of diarrhoea emergence.

Adverse events

Baseline characteristics of patients stratified by the time of appearance of diarrhoea as defined above are summarized in Table 2. Median time to first diarrhoea onset was 84 days (IQR 26–158). Twenty-two patients (6.4%) developed e-diarrhoea and 30 (8.4%) L-diarrhoea. Finally, 292 patients never presented diarrhoea during follow-up. Only two patients who developed e-diarrhoea and eight patients who presented L-diarrhoea had DAE60 (Table S1).

Diarrhoea as a predictor of OS

We found no differences between patients who developed e-diarrhoea or L-diarrhoea according to baseline characteristics or initial dose of sorafenib. However, the rate of discontinuation in the first 60 days was higher in the e-diarrhoea group, and as expected, the OS was longer in the L-diarrhoea group of patients. Evolutionary events are summarized in Table S1.

The multivariate analysis consistently identified baseline ECOG-PS and BCLC stage as well as the emergence of early dermatologic AE60 (DAE60) as independent predictors of OS, while Child-Pugh did not have independent predictive power in this study.

OS was significantly different according to the presence of e-diarrhoea, L-diarrhoea and never diarrhoea ($p < 0.0001$). Median OS was 6.8 months (95%CI 3.3–11.2), 26.7 months (95%CI 17.5–37.9) and 13.3 months (95%CI 11.7–14.7), respectively. To avoid the flaw due to the fact that late diarrhoea always includes long-term survivors we performed a time-dependent cox regression analysis. This model identified that the development of e-diarrhoea was associated with worse outcome as compared against those who never developed diarrhoea, with HR values of 1.84 (95%CI 1.15–2.95) and against those who presented L-diarrhoea, with HR 0.66 (95%CI 0.42–1.03). Predicted survival function is represented in Figure 1 and multivariate analysis in Table 3.

Diarrhoea and radiological progression

Fourteen out of the 22 patients who presented e-diarrhoea did not present radiological progression of the tumour at the time of diarrhoea emergence. The pattern of progression of those eight patients who presented radiological progression was growth of preexisting intrahepatic lesions (IHG), growth of preexisting extrahepatic lesions (EHG), new intrahepatic lesions (NIH) and new extrahepatic lesions (NEH), with two patients for each pattern. The median OS of patients who had radiological progression at the time of developing diarrhoea

TABLE 1 Baseline characteristics of the whole cohort

Characteristics	*n*
Patients, *n*	344
Gender (male/Female), *n* (%)	296 (86)/48 (14)
Age (Years), median [IQR]	63.8 [55.9–71.1]
Aetiology	
HCV	135 (39.2)
Alcohol	83 (24.1)
HCV + alcohol	42 (12.2)
HBV	22 (6.4)
Cryptogenic	7 (2)
No cirrhosis	10 (2.9)
Others	45 (13.2)
Child-pugh (A/B/No cirrhosis), *n* (%)	288 (83.7)/46 (13.4)/10 (2.9)
BCLC (A/B/C), *n* (%)	2 (0.6)/156 (45.3)/186 (54.1)
Diabetes mellitus (yes), *n* (%)	97 (28.2)
Arterial hypertension (yes), *n* (%)	144 (41.9)
Vascular invasion (yes), *n* (%)	120 (34.9)
Extrahepatic spread (yes), *n* (%)	89 (25.9)
ECOG-performance status (0/1/2), *n* (%)	310 (90.1)/33 (9.6)/1 (0.3)
Haemoglobin (g/L), median [IQR]	13.5 [12.1–14.8]
Leukocytes (count 10^9), median [IQR]	5.3 [4.1–6.7]
Platelets (count 10^9), median [IQR]	131 [87–186]
AST (UI/L), median [IQR]	64 [40–104]
ALT (IU/L), median [IQR]	54 [33–95]
Alkaline phosphatase (IU/L), median [IQR]	232 [155–348]
GGT (IU/L), median [IQR]	143 [82–274]
Total bilirubin (mg/dl), median [IQR]	1 [0.7–1.6]
Conjugated bilirubin (mg/dl), median [IQR]	0.5 [0.3–0.8]
Albumin (g/L), median [IQR]	39 [35–43]
Prothrombin time (%), median [IQR]	81 [68–91]
Alpha-fetoprotein (ng/dl), median [IQR]	27 [8–391]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; GGT, gamma-glutamyl transferase; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; IU, International Units.

was 3.7 months (IC95% 2.7–9.3), while the median OS of those who developed diarrhoea without radiological progression was 8.1 months (IC95% 3.3–17.2).

DISCUSSION

According to the results of our study, the development of early diarrhoea after starting sorafenib is associated to reduced survival if compared to patients who do not develop such AE. It is important to stress that the prognostic value involves the development of such an event early during follow-up, while the registration of diarrhoea at any time point during the clinical evolution of the patients is surely flawed. Patients who survive longer and thus enjoy the maximal benefits of sorafenib, have longer time exposure under treatment and, by default, this is closely related with higher rate of AEs. Prior studies[13,14,19] suggested a better survival in patients who developed diarrhoea among other toxicities, but no control for the time of appearance was done in those investigations and this potential flaw is shared by most studies in the oncology realm. Time-dependent assessment of the AEs

TABLE 2 Baseline characteristics of patients attending to diarrhoea presentation

	E-diarrhoea	L-diarrhoea	Never diarrhoea	*p*-value
Patients, *n*	22	30	292	
Male/Female (*n*, %)	22 (100)/0 (0)	28 (93.3)/2 (6.7)	246 (84.3)/46 (15.7)	0.0528
Age (median, IQR)	61.9 [57.8–70.8]	62.6 [57.4–67.9]	64.1 [55.8–71.4]	0.8892
Aetiology, *n* (%)				0.8309
HCV	7 (31.8)	11 (36.7)	117 (40.1)	
Alcohol	7 (31.8)	9 (30)	67 (22.9)	
HCV + alcohol	4 (18.2)	5 (16.7)	33 (11.3)	
HBV	3 (13.6)	1 (3.3)	18 (6.2)	
Cryptogenic	0	2 (6.7)	5 (1.7)	
No cirrhosis	0	0	10 (3.4)	
Others	1 (4.5)	2 (6.7)	42 (14.4)	
Child-Pugh (A/B/No cirrhosis)	18 (81.6)/4 (18.2)/0 (0)	27 (90)/3 (10)/0 (0)	243 (83.2)/39 (13.4)/10 (3.4)	0.6691
BCLC (A/B/C)	0 (0)/10 (45.4)/12 (55.6)	0 (0)/15 (50)/15 (50)	2 (0.7)/131 (44.9)/159 (54.4)	0.9004
Diabetes mellitus, *n*	8 (36.4)	9 (30)	80 (27.4)	0.6272
Arterial Hypertension, *n*	9 (40.9)	8 (26.7)	127 (43.4)	0.2057
Vascular invasion, *n*	10 (45.4)	9 (30)	101 (34.5)	0.5011
Extrahepatic spread, *n*	5 (22.7)	8 (26.7)	76 (26)	>0.999
ECOG-performance status (0/1/2)	18 (81.8)/4 (18.2)/0 (0)	29 (96.7)/1 (3.3)/0 (0)	261 (89.4)/30 (10.3)/1 (0.3)	0.6021
Haemoglobin in g/L, median (IQR)	12.9 (11.8–14.4)	13.5 (12.4–14.8)	13.5 (12.1–14.85)	0.2762
Leukocytes in 10^9, median (IQR)	4.43 [3.4 to 6]	5.6 [3.5 to 6.8]	5.3 [4.1 to 6.7]	0.2287
Platelets in 10^9, median (IQR)	107 [86 to 181]	132.5 [89 to 205]	134.5 [87 to 186]	0.8036
AST in UI/L, median (IQR)	66.5 (37–143)	69.5 (33–97)	64 (41–101)	0.6560
ALT in IU/L, median (IQR)	50.5 (31–96)	64.5 (26–102)	54 (34–95)	0.9278
Alkaline phosphatase in IU/L, median (IQR)	232 (182–311)	198.5 (99–320)	232 (158–356)	0.3839
GGT in IU/L, median (IQR)	189 (123–289)	129 (67–248)	142 (82–269)	0.2939
Total bilirubin in mg/dl, median (IQR)	1.25 (0.9–1.9)	1.2 (0.7–1.6)	1 (0.7–1.6)	0.2035
Conjugated bilirubin in mg/dl, median (IQR)	0.5 (0.4–0.9)	0.6 (0.3–0.8)	0.5 (0.3–0.8)	0.5225
Albumin in g/L, median (IQR)	36.5 (34–40)	39.5 (37–44)	39 (35.5–42.5)	0.0960
Prothrombin time in %, median (IQR)	80.05 (68–89)	80 (66–91)	81.5 (69–91)	0.6978
Alpha-fetoprotein in ng/dl (median, IQR)	26 (6–3052)	43 (6–402)	26 (8–366)	0.9954

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; e-diarrhoea, early diarrhoea, in the first 60 days; GGT, gamma-glutamyl transferase; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; IU, International Units; L-diarrhoea: late diarrhoea, after the first 60 days.

of any drug is missing in the conventional evaluation of toxicity and tolerance usually applied in all oncology trials.

In our study the incidence of diarrhoea during the first week of sorafenib administration was low (1.2%), while the number increased at 60 days (6.4%) if we consider the whole time lapse the patients have been under treatment.

The most relevant message of our study is that those patients who develop early diarrhoea present a poorer prognosis even if we control for baseline tumour stage, concomitant tumour progression, and the presence of cancer-related symptoms at treatment initiation. Diarrhoea under sorafenib should not be taken as a predictive parameter of lack of benefit. The reported association with outcome may be due to any non-identified parameter linked to poor patient prognosis irrespective of the fact that sorafenib would increase life expectancy according to the known reduction of the risk of death along time.

The mechanism for diarrhoea may very likely not be the same in all patients and several factors could be involved including patient

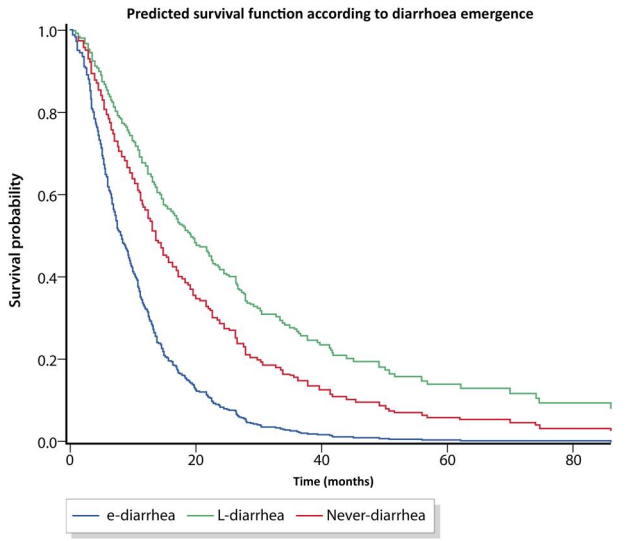

FIGURE 1 Predicted survival function. Patients presenting early diarrhoea are at higher risk of death

TABLE 3 Survival prediction in the cohort using multivariate time-dependent cox model

	HR	HR CI95%	*p*-value
Performance status	1.88	1.27–2.80	<0.01
Child-Pugh	1.21	0.85–1.73	0.3
BCLC stage	1.44	1.11–1.86	<0.01
DAE60	0.62	0.47–0.82	<0.001
E-diarrhoea[a]	1.84	1.15–2.95	0.01
L-diarrhoea[a]	0.66	0.42–1.03	0.07

Abbreviations: BCLC. Barcelona Clinic Liver Cancer; DAE60, early dermatologic adverse events in the first 60 days; e-diarrhoea, early diarrhoea, in the first 60 days; L-diarrhoea, late diarrhoea, after the first 60 days.

[a]Reference category: Never diarrhoea.

profile at treatment initiation, direct and acute drug-related toxicity and toxicity at long-term in other organs such as the pancreas.[20,21]

We reported that some patients under sorafenib developed intestinal malabsorption and that this was due to pancreatic atrophy that could be compensated by pancreatic enzyme supplementation.[21] In that study, we did not identify a single conventional parameter related to patients' profile, liver function or tumour burden that could be associated to an increased risk of diarrhoea. In addition, despite the inconclusive results of the pharmacokinetics and pharmacogenomics of relationship between drug metabolization, genomic profile and development of AEs and improved efficacy[15] it was a trend towards lower systemic availability of the drug related to a polymorphism of genes such as MRP2*3972. These allelic differences were associated to a higher incidence of diarrhoea and prompted us to hypothesize that such genomic profiles would induce a reduced absorption of the drug and/or prime an impairment of the permeability of the intestinal wall leading to diarrhoea.

In summary, we identified early diarrhoea within the first 60 days of sorafenib treatment as a predictor of worse outcomes. Identification of the predictors for developing diarrhoea would allow to select the optimal therapy in a proportion of patients diagnosed with HCC while avoiding an intervention that may not provide a significant real-world survival benefit.

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CONFLICT OF INTEREST

Álvaro Díaz-González: Speaker fees from Bayer and Intercept. Meeting expenses from BTG, Bayer, Intercept and GILEAD. Víctor Sapena: Travel funding from Bayer. Loreto Boix: Travel funding from Bayer. Neus Llarch: Travel funding and consultancy for Bayer and consultancy for AstraZeneca. Gemma Iserte: None. Marco Sanduzzi-Zamparelli: Speaker fees and travel funding from Bayer. Travel grant from BTG and Eisai. Sergio Muñoz-Martínez: Speaker fees and travel funding from Bayer. Alejandro Forner: Conference fees and travel funding from Bayer; Lecture fees from Gilead and MSD; consultancy fees from Bayer, Guerbert and AstraZeneca. Jordi Bruix: Consultancy fees from Arqule, Bayer, Novartis, BMS, BTG- Biocompatibles, Eisai, Kowa, Terumo, Gilead, Bio-Alliance/Onxeo, Roche, AbbVie, Merck, Sirtex, Ipsen, Astra-Medimmune, Incyte, Quirem, Adaptimmune, Lilly, Basilea, Nerviano. Research grants from Bayer and BTG. Educational grants from Bayer and BTG. Lecture fees from Bayer, BTG- Biocompatibles, Eisai, Terumo, Sirtex, Ipsen. María Reig: Consultancy fees from Bayer, BMS, Roche, Ipsen, AstraZeneca and Lilly. Lecture fees from Roche, Bayer, BMS, Gilead, and Lilly. Research grants from Bayer and Ipsen.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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