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ORIGINAL RESEARCH

Antibiotic Therapy is Associated with Worse Outcome in Patients with Hepatocellular Carcinoma Treated with Sorafenib

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Background: Antibiotic treatment (ABT) affects the outcome of cancer patients treated with immune checkpoint inhibitors (ICIs) and chemotherapy, possibly by altering the gut microbiome. We investigated the impact of ABT on overall survival (OS) and progression-free survival (PFS) in patients with advanced HCC treated with sorafenib.

Methods: HCC patients treated with sorafenib between 05/2006 and 03/2020 at the Medical University of Vienna were retrospectively analyzed. ABT was defined as antibiotic use within 30 days prior to or after sorafenib initiation.

Results: Of 206 patients, the majority was male (n=171, 83%) with a mean age of 66±9.6 years. Half of patients (n=94, 46%) had impaired liver function (Child-Pugh stage B). Median time of follow-up was 10.8 (95% CI: 9.2–12.3) months. ABT was administered in 23 (11%) patients due to different types of proven or clinically suspected bacterial infections (n=17, 74%) and hepatic encephalopathy (n=6, 26%). The median duration of ABT was 14 (IQR: 12–30) days. Penicillin (n=13, 57%), followed by rifaximin (n=6, 26%), fluoroquinolones (n=3, 13%), and cephalosporins (n=1, 4%), was administered in the ABT group. The ABT group had a significantly shorter median OS (4.7 (95% CI: 3.2–6.1) months vs 11.4 (95% CI: 9.9–12.9) months, p=0.012), which was confirmed in multivariable analysis (HR: 1.91 (95% CI: 1.1–3.2), p=0.014). Similarly, PFS trended to be shorter in the ABT group (3.5 (95% CI: 1.6–5.4) months vs 4.8 (95% CI: 3.9–5.7) months, p=0.099). None of the 10 patients with complete or partial response was found in the ABT group.

Conclusion: ABT was independently associated with worse outcomes in sorafenib-treated HCC patients. Prospective studies are needed to elucidate the underlying mechanism.

Keywords: antibiotics, hepatocellular carcinoma, sorafenib, targeted therapy

Introduction

Hepatocellular carcinoma (HCC) accounts for the majority (70–90%) of primary liver cancers and represents the second and sixth most common cause of cancer-related death in men and women, respectively.[1,2] HCC develops predominantly in patients with underlying cirrhosis[3,4] and is often detected in advanced stages where systemic therapy is the only treatment option.[5,6]

For over a decade, the multi-tyrosine kinase inhibitor (TKI) sorafenib remained the standard of care in patients with advanced HCC.[5] Recently, the combination of atezolizumab plus bevacizumab showed superiority over sorafenib regarding both primary endpoints overall survival (OS) and progression-free survival (PFS),[7] and consequently became the new reference standard in first-line systemic treatment.[8,9]

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Nevertheless, sorafenib will continue to play a key role in the treatment algorithm of advanced HCC given that other effective systemic therapies (eg, regorafenib, cabozantinib, ramucirumab) have only been approved for sorafenib-experienced individuals.[5,10–12]

Patients with cancer are susceptible to bacterial infections due to the immunosuppressive milieu caused by the malignancy itself and due to treatment-related immunosuppression.[13] Thus, cancer patients often receive antibiotic treatment (ABT), which modulates the gut microbiome. Gut microbiota regulate tumor-promoting and tumor-suppressing pathways in patients with HCC,[14,15] and may influence response to ICIs in different types of cancers.[16–19] Mice with a favourable composition of the commensal microbiome experienced a greater therapeutic activity from ICI therapy.[19,20] While modulation of the gut microbiome by fecal microbiota transplant promoted response to ICIs in immunotherapy-refractory melanoma patients,[21,22] ABT was associated with shorter survival in patients with different cancer types treated with ICIs[16,23] and TKIs.[17,24] Patients with advanced chronic liver disease (ACLD) commonly suffer from intestinal dysbiosis and bacterial translocation, which may promote immune dysfunction via the gut–liver axis.[25,26] Accordingly, the modulation of the gut microbiome could have even more profound effects in patients with HCC than in other tumors.[14,27]

The impact of ABT on the outcome of cancer patients treated with tyrosine kinase inhibitors (TKIs) is unclear. Thus, we investigated the association between early ABT and survival in patients with advanced HCC treated with sorafenib.

Materials and Methods

Study Design

We retrospectively included patients treated with sorafenib for advanced HCC between 05/2006 and 03/2020 at the Division of Gastroenterology and Hepatology, Vienna General Hospital/Medical University of Vienna. Diagnosis of HCC was established by histology or dynamic imaging (computed tomography [CT]/magnetic resonance imaging [MRI] scans) according to the European Association for the Study of the Liver (EASL) guidelines.[2] Data analysis was performed in accordance with the Helsinki Declaration and approved by the local ethics committee of the Medical University of Vienna (#1759/2015). A written informed consent was waived by the local ethics committee due to the retrospective design of this study. All individually identifiable patient data were assessed in a confidential manner that prevented unauthorized use and disclosure to any third parties/persons.

Patients and Definitions

Eligible patients were adults (>18 years) diagnosed with HCC and treated with sorafenib. Patients receiving systemic therapy in combination with other treatments (eg, local ablative therapy/chemoembolization/SIRT) and patients with insufficient records were excluded from this study. Furthermore, we excluded patients with Child-Pugh score (CPS) class C and patients who died during ABT or within one week (7 days) after cessation of ABT in order to minimize the potential bias of infection-related mortality. Patient characteristics and information on antibiotic treatment (ABT), laboratory parameters (including AFP levels), tumor characteristics, and Eastern Cooperative Oncology Group performance status (ECOG PS) were collected from the clinical documentation system. ABT was defined as a prescription of any antibiotic substance within 30 days prior to or after the start of sorafenib. CPS was used to assess liver function at baseline. Baseline was defined as the date of sorafenib initiation.

Statistics

Statistical analyses were performed using IBM SPSS Statistics 26 (SPSS Inc., Armonk, New York, USA) R 4.1.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism 9 (GraphPad Software, La Jolla, California, USA). Continuous variables were reported as mean ± standard deviation (SD) or median (interquartile range; IQR), and categorical variables were shown as numbers (n) and proportions (%) of patients. Comparisons of proportions and of continuous variables were performed by Chi-squared test and unpaired Student's *t*-test, respectively. Overall survival (OS) was defined as the time from the start of sorafenib to the date of death or last contact. Progression-free survival (PFS) was defined as the time from the start of sorafenib to the date of radiological progression or date of death/last follow-up, whatever came first. DCR was defined as the proportion of patients with complete response (CR), partial response (PR) or stable disease (SD) as the best objective response. Survival curves were calculated by Kaplan–Meier method and compared by Log rank test. Propensity score matching (1:5) was performed by applying the R "MatchIt" package. Restricted mean survival time (RMST) was calculated as an alternative

measure of "life expectancy" until a given timepoint, if the "proportional hazards" assumption was not met. It is defined as the average time free from an event up to a milestone time point and thus a numeric expression of the area under the Kaplan–Meier survival curve.[28,29] Restricted mean time lost (RMTL) was defined as the survival time lost up to a specific time point, thus representing the area above the Kaplan–Meier survival curve.[30] R "survRM2" package was applied to RMST and RMTL calculations. Multivariable analyses were performed by Cox regression analysis and variables with a p-value <0.1 in univariable analysis and those considered relevant were included. A two-sided p-value <0.05 was considered to be statistically significant.

Results

Patient Characteristics and Outcome

In total, 346 patients with HCC were treated with sorafenib between 05/2006 and 03/2020 at the Division of Gastroenterology and Hepatology, Medical University of Vienna. Of those, patients were excluded from this study due to inadequate documentation (n=49), combination treatment (n=47), Child-Pugh class C (n=42), and death within one week after ABT cessation (n=2) (Figure 1). Consequently, 206 patients were included in this study. Detailed patient characteristics are shown in Table 1. The majority of patients were male (n=171, 83%) with a mean age of 66±9.6 years. One-hundred forty-seven (71%) patients had cirrhosis, predominantly with non-viral etiology (n=147; 71%). Almost half of the patients (n=94, 46%) had an impaired liver function, as defined by CPS B, and the majority of patients (n=188, 91%) had an intermediate-advanced stage HCC (BCLC B-C). Of note, baseline characteristics of patients who did (n=23) and did not receive ABT (n=183) were not significantly different (Table 1). Median time of follow-up was 10.8 (95% CI: 9.2–12.3) months.

Antibiotic Treatment

Antibiotic treatment (ABT) was administered in 23 (11%) patients for the following indications: hepatic encephalopathy (n=6, 26%), urinary tract infection (n=5, 22%), infection of unknown origin (n=4, 17%), and other infections requiring antimicrobial therapy (n=8, 35%) (Table 2). Penicillin (n=13, 57%) was used most frequently, followed by rifaximin (n=6, 26%), fluoroquinolones (n=3, 13%), and cephalosporins (n=1, 4%). Overall, the median duration of antibiotic treatment was 14 (IQR: 12–30) days. In patients with rifaximin, the median duration of ABT was 127 (IQR: 30–528) days, while it was 14 (IQR: 9–14) days in patients receiving other antibiotic treatments. Antibiotics were prescribed within thirty days prior to and after sorafenib start in eleven (48%) patients each, while one (4%) patient was started on the day of sorafenib start.

Antibiotic Treatment and Outcome

Median OS was shorter in patients with ABT vs patients without ABT (4.7 (95% CI: 3.2–6.1) months vs 11.4 (95% CI: 9.9–12.9) months, p=0.012) (Figure 2A, Table 3, Supplemental Table 1). In multivariable Cox regression analysis (Table 3), ABT (HR: 1.91 (95% CI: 1.1–3.2), p=0.014) was significantly associated with

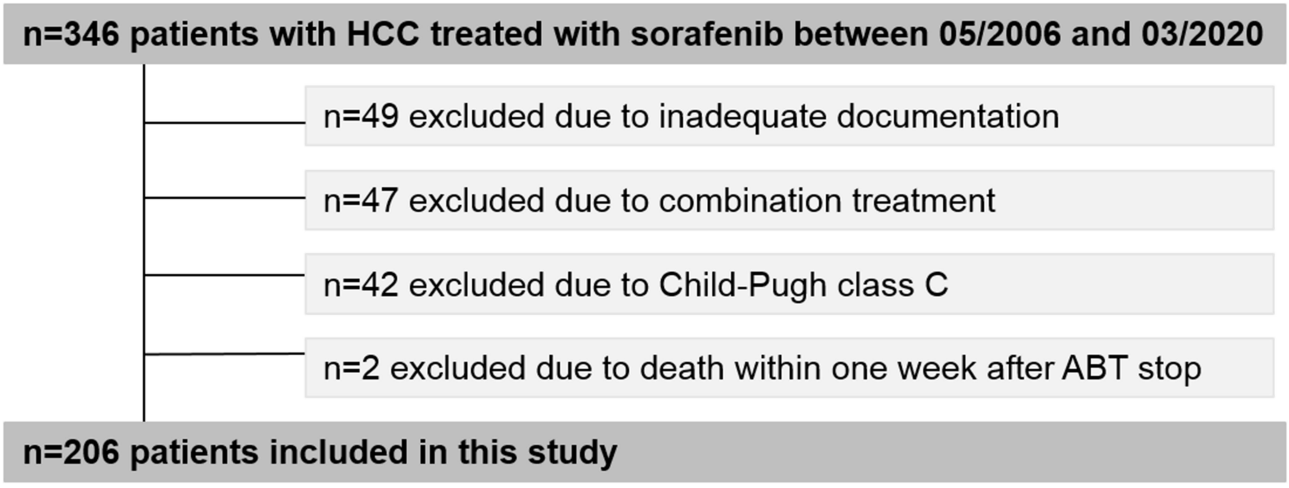

Figure 1 Patient flow chart.

Table 1 Patient Characteristics of Patients with and without Antibiotic Treatment

		With ABT (n=23)	Without ABT (n=183)	p-value
		Number (%) or mean±SD/median (IQR)		
Age (years)	Mean±SD Range	69±7 56–82	66±10 28–88	0.080
Sex	Male Female	18 (78%) 5 (22%)	153 (84%) 30 (16%)	0.556
Cirrhosis	Yes No	18 (78%) 5 (22%)	129 (71%) 54 (29%)	0.437
Etiology	Viral Non-viral	8 (35%) 15 (65%)	51 (28%) 132 (72%)	0.489
Child-Pugh Classification	A B	9 (39%) 14 (61%)	103 (56%) 80 (44%)	0.120
ECOG PS	0 ≥1	12 (52%) 11 (48%)	114 (62%) 69 (38%)	0.348
Macrovascular invasion	Yes No	13 (56%) 10 (44%)	82 (45%) 101 (55%)	0.375
Extrahepatic metastases	Yes No	9 (39%) 14 (61%)	59 (32%) 124 (68%)	0.491
BCLC stage	A B C	- 4 (17%) 19 (83%)	18 (10%) 41 (22%) 124 (68%)	0.207
AFP (IU/mL)[a]	<200 ≥200	15 (65%) 8 (35%)	92 (59%) 63 (41%)	0.592
CRP (mg/dL)[b]	<1 1–5 ≥5	6 (26%) 9 (39%) 8 (35%)	76 (45%) 64 (38%) 28 (17%)	0.072

Notes: [a]Data available in n=178 patients. [b]Data available in n=191 patients.
Abbreviations: ABT, antibiotic treatment; AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status.

reduced OS, independently of performance status (HR: 1.61 (95% CI: 1.1–2.3), p=0.009), AFP level (AFP ≥ 200IU/mL: HR: 1.56 (95% CI: 1.1–2.2), p=0.012), CRP level (CRP 1–5 mg/dL: HR: 2.54 (95% CI: 1.7–3.8), p<0.001; CRP ≥ 5 mg/dL: HR: 1.97 (95% CI: 1.2–3.2), p=0.007), etiology, CPS, and macrovascular invasion (all not significant). Within Child-Pugh stages, patients with ABT had a significantly shorter median OS compared to patients without ABT when classified as CPS A (3.5 (95% CI: 0–7.6) vs 14.3 (95% CI: 10.8–17.9) months, p=0.003), while only a trend was observed in CPS B (4.7 (95% CI: 1.0–8.4) vs 8.2 (95% CI: 6.2–10.2) months, p=0.598). There was also a trend towards shorter PFS in the ABT group (3.5 (95% CI: 1.6–5.4) months vs 4.8 (95% CI: 3.9–5.7) months, p=0.099) (Figure 2B), which remained statistically nonsignificant in multivariable analysis (Supplemental Table 2).

Evaluation of Best Overall Response

One hundred fifty-two patients (74%) had at least one follow-up imaging and were therefore evaluable for the best radiological response assessment. In the non-ABT (n=136) vs ABT group (n=16), 10 (7%) vs 0 (0%) had complete/partial response, 48 (35%) vs 7 (44%) had stable disease, and 78 (58%) vs 9 (56%) had progressive disease. Even though there was no difference in disease-control rate (ABT vs non-ABT group, 44% vs 43%), none of the patients who received antibiotics had a complete or partial response.

ABT and Outcome (Propensity Score Matched Cohort)

In order to balance prognostic factors between patients with and without ABT, propensity score matching (1:5) using CPS, macrovascular invasion, extrahepatic spread, and ECOG performance status was performed. The propensity score matched cohort included 138 patients, of whom 23 patients belonged to the ABT group and 115 to the non-ABT group. Baseline characteristics were well balanced between the two groups (Supplemental Table 3). There was a clear trend towards shorter OS (4.7 (95% CI: 3.2–6.1) vs 11.3 (95% CI: 9.1–13.4) months, p=0.079) in patients with ABT vs without ABT (Supplemental Figure 1).

Since there was an obvious difference in median OS within the first 12 months, we calculated RMTL up to this timepoint. Patients in the ABT group had a RMTL of 6.2 (95% CI: 4.6–7.8) months, compared to 3.5 (95% CI: 2.7–4.3) months in patients without ABT, resulting in a difference of −2.7 (95% CI: −4.5-[−0.9], p=0.003) months lost. Similar results were obtained when investigating the RMTL between patients with and without ABT within the first 24 months (16.2 (95% CI: 12.9–19.4) vs 11.7 (95% CI: 10.2–13.3) months), resulting in a difference of −4.4 (95% CI: −8.0-[−0.9]), p=0.015) months lost.

Discussion

While evidence on the impact of ABT on immunotherapy efficacy is increasing, studies evaluating the association between ABT and outcome of cancer patients treated with

Table 2 Antibiotic Treatment 30 Days Prior to or After Sorafenib Initiation

		Number (%) or Mean±SD/Median (Range)
Number of patients with antibiotic treatment		23 (100%)
Type of antibiotic treatment	Penicillin Rifaximin Fluoroquinolone Cephalosporin	13 (54%) 6 (25%) 4 (17%) 1 (4%)
Indication for antibiotic treatment	HE UTI Infection of unknown origin Other	7 (30%) 5 (22%) 4 (18%) 7 (30%)
Median duration of antibiotic treatment (days)	Median (IQR)	14 (12–30)
Initiation of antibiotic treatment	Prior to sorafenib start After sorafenib start At sorafenib start	11 (48%) 11 (48%) 1 (4%)

Abbreviations: HE, hepatic encephalopathy; UTI, urinary tract infection.

TKIs are lacking. In our cohort of 206 patients with HCC treated with sorafenib, antibiotic treatment (30 days prior to or after sorafenib initiation) was independently associated with worse OS. Additionally, none of the patients in the ABT group had a complete or partial response to sorafenib treatment.

Mechanistically, the negative association between ABT and survival may be related to ABT-induced disruption of the gut microbiome. The gut microbiome acts as a key modulator of the immune system by regulating local as well as systemic immunity and by exerting tumor-promoting and tumor-suppressing functions.[14] While some patients are responders to certain anti-cancer therapies, some do not derive any clinical benefit from the same treatments. Besides other patient and tumor factors, this may also be partly related to differences in the composition of the gut microbiome. Preclinical studies highlighted the importance of the gut microbiome in the context of controlling anti-tumor responses to chemotherapy[31,32] and immunotherapy.[33,34]

Recent clinical evidence suggests differences in the diversity and composition of the gut microbiome in patients who respond and do not respond to immunotherapy,[19,20] including HCC patients.[35] Hence, modulation of the gut microbiome emerges as a promising target to improve efficacy of cancer treatment.

Experimental exposition of germ-free mice with fecal material from patients responding to immunotherapy led to improved tumor control, augmented immune responses, and greater efficacy of antitumor therapy.[19,20] In line with this, fecal microbiota transplantation improved the response to reinitiated PD-1-targeted ICIs in immunotherapy-refractory melanoma patients.[21,22] Data suggesting that the gut microbiome affects the outcome of patients with HCC treated with immunotherapy were reported recently.[35]

ABT imposes profound changes on the diversity of the gut microbial system[36] which, in combination with anti-cancer therapies, might impact the outcome of cancer patients. Indeed, recent evidence supports a negative association between ABT and clinical outcomes in cancer patients treated with TKIs,[17,24] chemotherapy[31] and ICI therapy.[13,19,20,23,35] While concomitant therapy with antibiotics and epidermal growth factor receptor (EGFR)-TKIs in patients with advanced non-small cell lung cancer (NSCLC) was associated with shorter PFS, there were no changes in ORR or DCR in another study.[24] In patients with metastatic renal cell carcinoma (mRCC) treated with VEGF-targeting therapies among others, antibiotic users had a shorter PFS and lower ORR compared to antibiotic nonusers, while OS was not negatively impacted by ABT in the group of patients receiving anti-VEGF therapy.[17] Furthermore, initiation and duration of ABT seems to be relevant in this context. Pinato et al reported a time-dependence of antibiotics exposure as a strong determinant of outcome in patients treated with ICIs, as those with initiation of antibiotics prior to ICI therapy had an increased risk of primary progression compared to patients with concurrent ABT.[37] Others suggested that the duration of ABT may

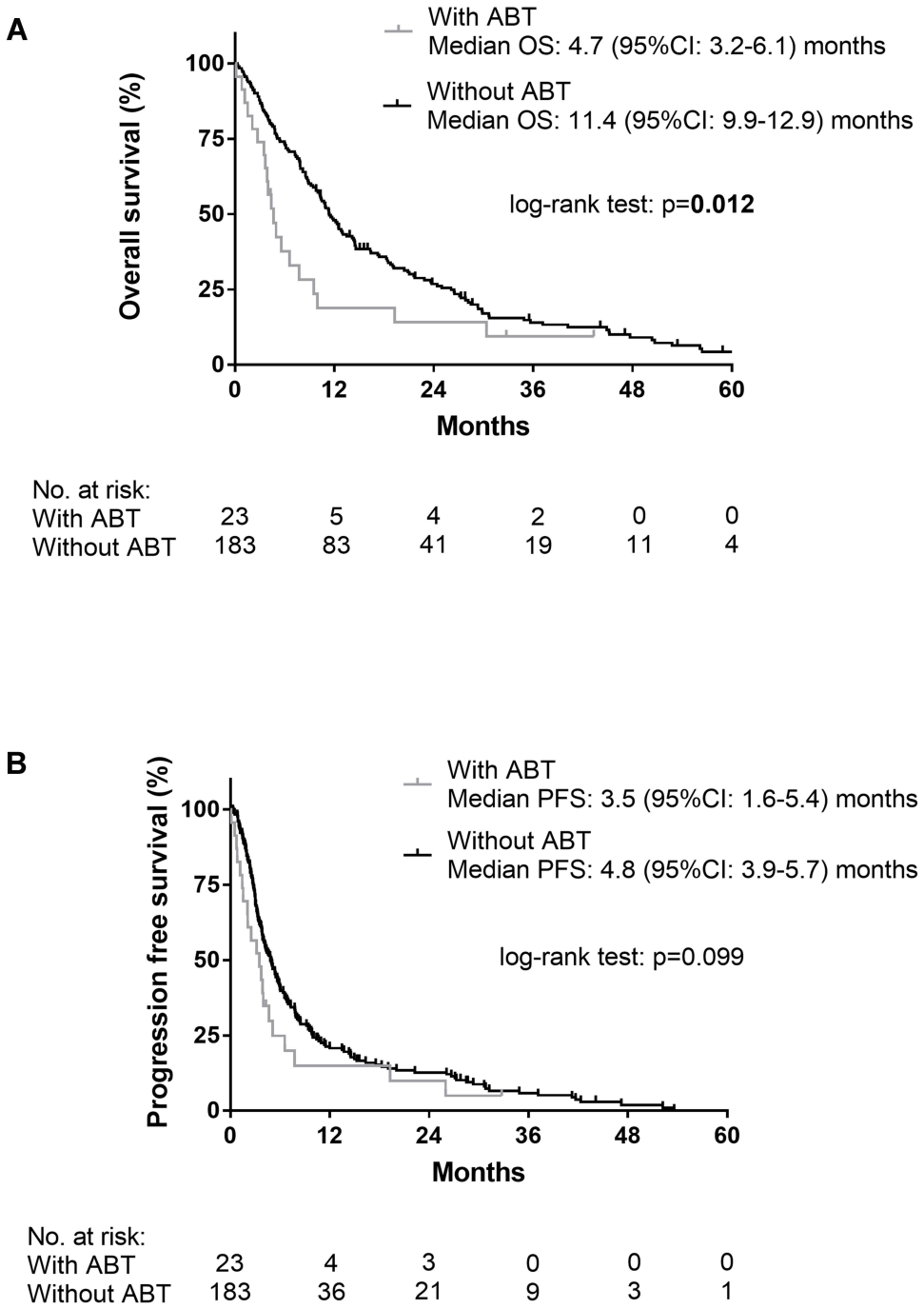

Figure 2 Survival curves of patients with and without antibiotic treatment 30 days prior to or after sorafenib initiation. (**A**) Overall survival and (**B**) progression-free survival. Kaplan-Meier survival curves of patients with and without ABT were compared by Log rank test.

negatively impact the outcome of patients receiving immunotherapy rather than the use of antibiotics per se.[38]

Recently, the combination of atezolizumab plus bevacizumab has become the new systemic front-line treatment for patients with HCC.[7–9] Since most patients with HCC have an underlying liver cirrhosis, a condition typically associated with intestinal dysbiosis,[39] this patient group may particularly benefit from microbiome modulation in order to prevent immunotherapy failure. In addition, the impaired gastrointestinal barrier and systemic inflammation in cirrhosis are also impacted by portal hypertension and beta blocker therapy.[26,40] However, sorafenib itself may influence portal pressure[41] and thus, modulate

Table 3 Uni- and Multivariable Cox Regression Analysis of Prognostic Factors for Overall Survival

		Univariable			Multivariable		
		HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Antibiotic treatment	No Yes	1 1.81	1.13–2.89	**0.014***	1 1.91	1.14–3.21	**0.014***
Etiology	Viral Non-viral	1 1.39	0.99–1.94	0.059	1 1.19	0.80–1.76	0.388
Child-Pugh Classification	A B	1 1.59	1.18–2.13	**0.002**	1 1.22	0.87–1.71	0.256
ECOG PS	0 ≥1	1 2.04	1.50–2.77	**<0.001**	1 1.61	1.13–2.29	**0.009**
Macrovascular invasion	No Yes	1 1.43	1.06–1.92	**0.020**	1 1.13	0.81–1.60	0.471
Extrahepatic spread	No Yes	1 1.08	0.79–1.49	0.620	-	-	-
AFP (IU/mL)	< 200 ≥ 200	1 1.68	1.21–2.32	**0.002**	1 1.56	1.10–2.20	**0.012**
CRP (mg/dL)	< 1 1–5 ≥ 5	1 2.93. 3.06	2.05–4.30 1.99–4.69	**<0.001** **<0.001**	1 2.54 1.97	1.70–3.77 1.20–3.24	**<0.001** **0.007**

Note: *Significant values were marked bold.
Abbreviations: AFP, α-fetoprotein; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status.

the mucosal barrier and molecular signaling through the gut–liver axis.[25]

We acknowledge some limitations of this study. Due to the retrospective design, some information on patient characteristics might not have been documented in full detail. Furthermore, even though our observations are consistent with previously reported data about possible negative effects of antibiotics, use of antibiotics might identify patients with poorer prognosis due to the indication for antibiotic treatment at treatment initiation (ie, bacterial infection in the majority of patients) or an increased susceptibility for infections during follow-up, which increase mortality in patients with cirrhosis.[42] In order to correct for this potential bias, we excluded patients who died within 7 days after cessation of ABT (even though this may not fully reflect the increased risk of infection-related mortality) and CPS C patients, who are particularly prone to infections. Moreover, we can only speculate about a link between ABT and gut microbiome, as we were not able to analyze microbial composition in this retrospective study.

In conclusion, ABT was associated with worse OS in patients with advanced HCC treated with sorafenib. Moreover, there was a trend towards shorter PFS, and none of the patients in the ABT group had a complete or partial response. Changes in the composition of the gut microbiome due to ABT may affect the response to systemic anticancer therapies, including TKIs. Future prospective studies are needed to validate ABT-mediated changes in the gut microbiome as a potential mechanism for failure of TKI therapy.

List of Abbreviations

ABT, antibiotic treatment; AFP, α-fetoprotein; BCLC, Barcelona clinic liver cancer; CI, confidence interval; CPS, Child-Pugh score; CRP, C-reactive protein; CT, computed tomography; ECOG-PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICI, immune checkpoint inhibitor; MRI, magnetic resonance imaging; MWA, microwave ablation; OS, overall survival; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor.

Author Contributions

All authors contributed to data collection or analysis, drafting or revising the article, gave final approval for the version to be published, agreed to the submitted journal, and agreed to be accountable for all aspects of the work.

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Disclosure

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