JGH Open An open access journal of gastroenterology and hepatology Open Access

JGHF Journal of Gastroenterology and Hepatology Foundation

doi:10.1002/jgh3.12533

ORIGINAL ARTICLE

Effects of Home Care on patients with hepatocellular carcinoma treated with sorafenib

Monika Moser,*,† Iuliana-Pompilia Radu*,† and Jean-François Dufour*,†

*Hepatology, Department of Clinical Research, University of Bern and †University Clinic for Visceral Surgery and Medicine, Inselspital, Bern, Switzerland

Key words
liver cancer, oncology, quality of life, sorafenib, treatment.

Accepted for publication 11 March 2021.

Correspondence
Jean-François Dufour, University Clinic for Visceral Surgery and Medicine, Inselspital, Bern, Switzerland.
Email: jf.dufour@svmed.ch

Declaration of conflict of interest: Jean-François Dufour: Advisory committee for Abbvie, Bayer, BMS, Fallk, Genfit, Genkyotex, Gilead, Heparegenerix, Intercept, Lilly, Merck, Novartis. Monika Moser: None. Iuliana-Pompilia Radu: None.

Abstract

Background and Aim: Treatment with sorafenib causes diverse side effects, which limits adherence. This work assesses whether Home Care, a psychosocial nursing intervention, prolongs the duration of treatment in patients with advanced hepatocellular carcinoma (HCC) and if it influences health-related quality of life (HRQL).

Methods and Results: This is a cohort study using data from patients receiving sorafenib in the prospective Bern HCC Cohort at the University Hospital. Duration of treatment, overall survival, and HRQL using the Functional Assessment of Cancer Therapy-Hepatobiliary questionnaire were compared in the two groups. A total of 173 patients were eligible for the analysis. Among them, 141 were in the Home Care program, and 32 were not. Patients with Home Care had a significantly longer duration of treatment (265 days *vs* 152 days, $P = 0.003$) and a better functional well-being (17.7 *vs* 12.5, $P = 0.015$).

Conclusion: Psychosocial interventions such as Home Care are a valid method in improving adherence to sorafenib and can therefore be recommended.

Introduction

Hepatocellular carcinoma. Hepatocellular carcinoma (HCC) is among the most common types of cancer and the second most common cause of cancer-related death worldwide.[1] The most common risk factors are hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, unhealthy alcohol use, non-alcoholic steatohepatitis (NASH), and metabolic diseases such as hemochromatosis.[2,3]

The management of HCC is complex, but there is a large number of potentially useful therapies.[4] Well-established treatments include surgical resection, liver transplantation, or local ablation, which are potentially curative, and palliative therapies such as chemoembolization and sorafenib, which aim to improve survival. Treatment allocation should be based on the Barcelona Clinic Liver Cancer (BCLC) staging system.[5]

The tyrosine–multikinase inhibitor drug sorafenib was approved as the first systemic treatment of advanced stages of HCC in 2008.[6] The benefit of sorafenib over placebo has been shown in two randomized, double-blind, multicenter phase III trials.[7,8] Since then, sorafenib is recommended for patients with preserved liver function (Child-Pugh-A class) and advanced BCLC stage C.[9]

Although there are many benefits of the treatment with sorafenib, the drug has shown different adverse effects that need to be taken into account. Most of the side effects are considered manageable to a certain degree. Those include diarrhea, fatigue, nausea and vomiting, hand–foot skin reaction, anorexia, and hypertension. Notwithstanding the lack of apparent danger, these tolerable toxicities may influence the quality of life.[10]

Interestingly, the occurrence of certain side effects correlates with response to treatment. The disease control rate and survival in patients with skin toxicity were better compared to those with no skin reactions.[11,12] Similar observations have been made for diarrhea and hypertension.[9,13,14]

Health-related quality of life. Health related quality of life (HRQL) is increasingly becoming an outcome of interest in disease management. Patients with chronic liver disease or HCC report a worse overall HRQL compared to the general population.[15] Several studies in the past have identified HRQL as a valuable prognostic factor in patients with hepatobiliary cancer.[16-20] Recent research has shown that the evaluation of HRQL also increases the accuracy of survival prediction in HCC when added to the Eastern Cooperative Oncology Group Performance Status, which is used in the BCLC staging system.[21]

Generic and disease-specific measures to assess HRQL have been developed over the past few decades.[22,23] The most widely used tool is the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire.[24] This 27-item score

consists of the following four subscores, where patients rate the accurateness of different statements from 0 to 4: physical well-being (e.g. I am in pain, I lack energy), social well-being (e.g. I am supported by my family, my family has accepted my disease), emotional well-being (e.g. I feel sad, I feel hopeless), and functional well-being (FWB; e.g. I have accepted my disease, I sleep well). The score was later supplemented by the 18-item Hepatobiliary Cancer Subscale (HCS) to form the more specific 45-item instrument for hepatobiliary cancers known as the Functional Assessment of Cancer Therapy-Hepatobiliary questionnaire (FACT-Hep).[25] The HCS consists of additional questions regarding specific issues such as jaundice, itching, fever, and gastrointestinal symptoms. Two further studies support the validity of the FACT-Hep in assessing disease-related symptoms and clinically meaningful disease progression.[26,27]

A limited number of studies has looked into the HRQL assessed by the FACT-Hep in patients with HCC. Overall, patients with HCC show worse HRQL but better social and family well-being.[15] In addition, the FACT-Hep has been used to evaluate the effect of several treatments.[28-31]

The benefit of prescribed medication is often decreased due to lack of adherence of patients due to subjective or objective side effects. Similarly, nonadherence is also spread among sorafenib patients, which is of concern due to increasing use and cost of such oral oncology medications.[32] Interventions such as intensive support, information, and counseling are widely used to enhance the adherence of people who are prescribed self-administered medications. Methods currently used are complex and mildly effective.[33] Furthermore, Steel et al.[34] have shown a clinically significant rise in HRQL due to an individually tailored psychosocial intervention in patients with HCC.

Strategies such as patient education, an open dialog between patients and the health-care team, and reporting of adverse events have been evaluated for sorafenib. Such interventions minimize the necessity of dose reduction or discontinuation of sorafenib.[35]

Similarly, MediService, a mail-order pharmacy of Switzerland, offers so-called Home Care support for their patients treated with sorafenib (Nexavar, Bayer, Austria). Home Care consists of a personal visit after prescription and registration, one phone call per month, the possibility of inbound calls, and further individual approaches. The goal is the management of adverse events in order to attain better adherence and thus maximize treatment duration for as long as the indication is given.

The MediService Home Care Team covers Switzerland and is multilingual. All team members possess an appropriate level of professional nursing education and long-term experience. Home Care is free of charge. It is offered to all patients with a sorafenib prescription.

The aim of this article is to investigate the effect of Home Care support on the treatment duration of sorafenib and overall survival. In addition, the study estimates the HRQL using the FACT-Hep in patients with and without Home Care before and under therapy with sorafenib.

Methods

Design. This study is a retrospective analysis of prospectively acquired data. The data were obtained from the Bern HCC cohort, which is a prospective cohort study that was started on the 1st of August 2010 at the University hospital of Bern. All patients aged at least 18 years with a diagnosis of HCC in the last 12 months are enrolled after signing an informed consent form. A valid diagnosis of HCC must be established by either noninvasive criteria (typical radiological hallmarks) or pathology according to the European Association for the Study of the Liver clinical practice guidelines.[5] A total of 136 different variables (i.e. demographic, clinical, laboratory, radiological, treatment, and HRQL data) are evaluated at inclusion and reevaluated at follow-up every 3 months. The end of data collection for this analysis was the 31st of December 2019. Included were all the patients from the cohort who received sorafenib at inclusion or during the observational time. Using the information from MediService, the patients were sorted into two groups: The first group included patients who were in the Home Care program, and the second group included patients not in the Home Care program. The groups were then compared, and mean sorafenib treatment duration, overall survival, and the FACT-Hep scores evaluated.

Methods. For this analysis, we used the demographic data obtained at inclusion. For the other baseline parameters such as tumor stage and laboratory parameters, the data corresponding to the time when sorafenib was prescribed were used (either at inclusion or at the next follow-up visit).

Treatment duration was defined as the time from the date of beginning of sorafenib therapy (day of first order of sorafenib at MediService) to the time of death, switching to another therapy, or stopping for another reason such as intolerable side effects or progression of disease. Overall survival was defined as the time from the beginning of sorafenib therapy to the time of death, last follow-up evaluation, or the date of data censoring.

To determine HRQL, the FACT-Hep questionnaire was used.[25] It consisted of physical (PWB), social/family (SWB), emotional (EWB), and FWB, and the disease-specific HCS subscores. PWB, SWB, EWB and FWB were added to form the FACT-G score. Adding the HCS to the FACT-G formed the FACT-Hep total score. Furthermore, the Trial Outcome Index (TOI), a summary index of physical/functional outcomes often used in clinical trials testing physical health interventions such as pharmaceutical treatments, was calculated by combining PWB, FWB, and HCS scores. All 45 items used a 5-point scale ranging from "not at all" (0) to "very much" (4). The questionnaires were scored according to the Functional Assessment of Chronic Illness Therapy manual.[36]

HRQL was compared first at inclusion provided a questionnaire was filled out before the start of therapy with sorafenib. Second, the follow-up FACT-Hep after the start of therapy with sorafenib was compared.

A second analysis excluding patients with BCLC stage D and/or Child-Pugh C class was conducted to eliminate a possible large effect size of this small sample of patients with advanced stage of HCC, which is not typically suitable for sorafenib treatment.

Analysis. For comparison of the two groups, means and standard deviations were calculated. The chi square test was used to

calculate *P*-values for categorical variables. For continuous variables, the t-test was applied. Curves for cumulative survival rates were calculated using the Kaplan–Meier method and compared by the log-rank test. A *P*-value of <0.05 was considered statistically significant.

The information was extracted into an encoded Excel file after collection. Missing values were specifically retrieved from the hospital database. All calculations were conducted using SPSS version 26. All data were prospectively collected and retrospectively analyzed.

Ethics. The local ethics committee (Kantonale Ethikkommission Bern, Bern, Switzerland) approved the collection of patient information and the study protocol (2018-00347), which was consistent with the principles of the current version of the Declaration of Helsinki.

Table 1 Baseline characteristics

	Home Care		No Home Care		
	n = 141		*n* = 32		
	n	%	*n*	%	*P* value
Age[†]	66		63		0.082
Gender					0.167
Male	120	85.1	24	75	
Female	21	14.9	8	25	
BMI[†]	27.5		27.5		0.985
Comorbidity					
Alcohol[‡]	21	14.9	5	15.6	0.862
Smoking	39	27.7	6	18.8	0.341
Treatment[§]					
Resection	28	19.9	6	18.8	0.887
TACE	29	20.6	4	12.5	0.294
TAE	17	12.1	3	9.3	0.668
RFA	5	3.5	1	3.1	0.885
MWA	9	6.4	3	9.3	0.548
SIRT	14	9.9	1	3.1	0.217
External radiotherapy	7	5	0	0.0	0.198
Etiology[¶]					
Alcohol	63	44.7	8	25	**0.041**
HBV	23	16.3	6	18.8	0.739
HCV	42	29.8	10	31.3	0.871
NASH	50	35.5	9	28.1	0.429
Haemochromatosis	10	7.1	1	3.1	0.406
BCLC					0.709
0	0	0.0	0	0.0	
A	2	1.4	1	3.1	
B	46	32.6	12	37.5	
C	90	63.8	19	59.4	
D	3	2.1	0	0.0	
Child-Pugh Grade					0.294
A	75	60.3	13	56.3	
B	48	34.8	12	37.5	
C	3	2.1	2	6.3	
MELD[†]	10		11		0.408
Creatinine (μmol/L)[†]	83.2		79.1		0.545
Bilirubin (μmol/L)[†]	26.6		41		0.102
INR[†]	1.14		1.21		0.238
AFP (kU/L)[†]	4930.7		4741.8		0.957

[†]Mean value.

[‡]Defined as ongoing consumption of >30 g/day.

[§]Some patients have undergone multiple treatments before sorafenib.

[¶]Patients can have multiple etiologies.

P values marked in bold denote statistical significance at the p < 0.05 level.

AFP, alpha 1 fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C Virus; INR, International normalized ratio; MELD, Model For End-Stage Liver Disease; MWA, microwave ablation; NASH, non-alcoholic steatohepatitis;; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolization.

Results

Baseline characteristics of the entire group. Adding the data of MediService to the Bern HCC Cohort resulted in the identification of a total of 197 eligible patients treated with sorafenib. After the exclusion of 24 patients (insufficient data: 16 cases, liver transplantation: 8 cases), 173 patients remained for the evaluation. The Home Care group consisted of 141 patients overall, whereas the No Home Care group included 32 patients.

The demographic and tumor characteristics, as well as the treatments before sorafenib, of these two groups are summarized in Table 1. This population was composed of 83% males, with a mean age of 66 years. Most patients (n = 89, 51.4%) had previously received another treatment for HCC. Resection was the most common treatment (19.7%) followed by transarterial chemoembolization (19.1%) and transarterial embolization (11.6%). Sorafenib was use as the first line therapy in 48.6% patients The most frequent etiology was alcohol-induced liver disease (41.0%), followed by NASH (34.1%), HCV (30.1%), HBV (16.8%), and hemochromatosis (6.4%). On sorafenib initiation, 88 (50.9%), 60 (34.7%), and 5 (2.9%) were classified as Child-Pugh classes A, B, and C, respectively. According to the BCLC staging system, 3 (1.7%), 58 (33.5%), 109 (63%), and 3 (1.7%) patients were assigned to stage A, B, C, or D.[5]

Both groups were comparable for most of the parameters, except liver disease etiology: 44.7% had alcohol-induced liver disease in the Home Care group *versus* 25% in the No Home Care group.

A separate analysis excluding the six patients with BCLC stage D and/or Child-Pugh class C showed comparable results with the same difference in etiology.

Duration of treatment and overall survival. The main analysis of this study was the comparison of the mean duration of treatment. Table 2 displays the mean duration of treatment for the two groups with a significantly higher value in the Home Care group (265 compared to 152 days, P = 0.003).

In addition, the overall survival of the two groups was compared. Figure 1 shows the Kaplan–Meier analysis for overall survival. In accordance with the prolonged treatment duration in the Home Care group, overall survival is longer in this cohort (391 *vs* 288 days). However, this result is not significant according to the log-rank test.

Comparing the groups without the six patients with advanced stages showed similar results.

Health-related quality of life. Table 3 shows the FACT-Hep questionnaire with the total scores and subscores at inclusion and after start of therapy. In both groups, a large number of scores could not be calculated because of missing data due to different reasons such as incomplete questionnaires or completely missing questionnaires due to lacking language knowledge or different or unknown reasons. In the Home Care group, the number of missing values ranged from 51 to 53 at inclusion and from 86 to 89 at follow-up. In the No Home Care group, there were 17 missing values for each score at inclusion and follow-up.

At inclusion, the means were 100.5 for the TOI score, 83.3 for the FACT-G, and 142.8 for the FACT-Hep with no significant difference between the two groups and likewise for the subscores. At follow-up, the mean TOI, FACT-G, and FACT-Hep values were lower (87.9, 77.3, and 130.0, respectively). The analysis of the two groups at follow-up showed a TOI score of 89.0 in the Home Care group compared to 84.0 in the No Home Care group, a FACT-G of 78.3 in the Home Care group and 73.8 for the No Home Care group, and FACT-Hep of 131.4 in the Home Care group and 124.9 for the No Home Care group. These were not significantly different (P = 0.311, 0.249, and 0.304). However, the FWB was significantly lower in the No Home Care group (12.5 *vs* 17.7 with P = 0.015).

In the same way as for baseline characteristics, treatment duration, and overall survival, the results for HRQL were interchangeable when excluding patients with BCLC stage D and Child-Pugh class C.

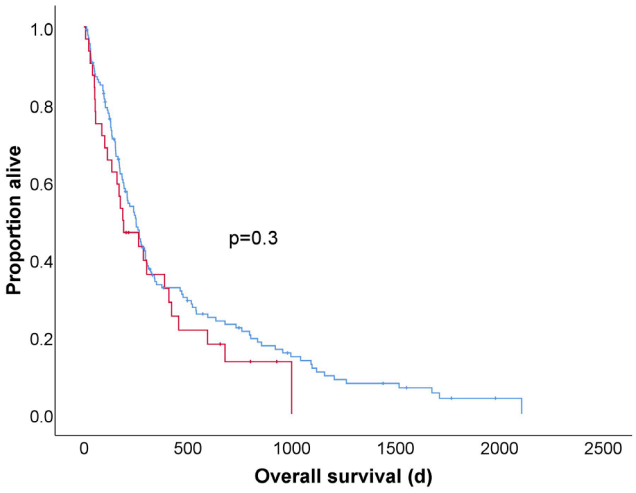

Figure 1 Kaplan–Meier analysis for overall survival. Compares patients with Home Care to patients without Home Care. Log-rank test: P = 0.300. Whole cohort: ⌐¬, Home Care; ⌐¬, no Home Care; ⊢⊣, Home Care censored; ⊢⊣, no Home Care censored.

Table 2 Mean duration of treatment

	Home Care n = 141	No Home Care n = 32	P value
Duration of treatment (day)	265	152	**0.003**

P values marked in bold denote statistical significance at the p < 0.05 level.

Table 3 Health-related quality of life (HRQL)

	Home Care			No Home Care			
	n = 141			*n* = 32			
	n[†]	Missing values[‡]	Score[§]	*n*[†]	Missing values[‡]	Score[§]	*P* value
Baseline HRQL							
PWB	89	52	21.8	15	17	23.1	0.341
SWB	89	52	24.3	15	17	23.4	0.572
EWB	89	52	18.1	15	17	18.7	0.585
FWB	90	51	18.9	15	17	19.3	0.795
HCS	89	52	59.9	15	17	58.3	0.510
TOI total	88	53	100.5	15	17	100.7	0.961
FACT-G total	89	52	83.1	15	17	84.5	0.738
FACT-Hep total	88	53	142.8	15	17	142.8	0.992
Follow-up HRQL							
PWB	53	88	17.9	15	17	20.3	0.111
SWB	54	87	24.5	15	17	23.9	0.693
EWB	55	86	17.7	15	17	17.0	0.530
FWB	55	86	17.7	15	17	12.5	**0.015**
HCS	54	87	53.4	15	17	51.1	0.422
Trial Outcome Index total	53	88	89.0	15	17	84.0	0.311
FACT-G total	53	88	78.3	15	17	73.8	0.249
FACT-Hep total	52	89	131.4	15	17	124.9	0.304

[†]Number of patients with complete scores.

[‡]Number of patients with missing scores.

[§]Mean value.

P values marked in bold denote statistical significance at the $p < 0.05$ level.

EWB, emotional well-being; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-Hep, Functional Assessment of Cancer Therapy-Hepatobiliary; FWB, functional well-being; HCS, Hepatobiliary Cancer Subscale; PWB, physical well-being; SWB, social well-being.

Discussion

The aim of this study was to evaluate the efficacy of Home Care support in patients treated with sorafenib. The Home Care and No Home Care groups were compared in terms of treatment duration, overall survival, and HRQL. The results showed a significantly longer treatment duration and a better survival rate in the Home care group but without statistical significance. Concerning the HRQL, only the subscore FWB was significantly lower in the No Home Care group.

The baseline characteristics (i.e. gender, median age) of the studied population were in line with previously published data.[2,3,37] Most patients were classified as BCLC stage C when therapy with sorafenib was started, which is not surprising because the BCLC guidelines suggest systemic treatment with sorafenib at that stage.[9] Strikingly, the etiology of alcoholic steatohepatitis was found more frequently in the Home Care group. One possible explanation is that this risk factor might predispose to a certain insecurity, leading to a more help-seeking behavior and thus participation in the Home Care program. Previous studies have shown that psychosocial treatment is recommended in patients with alcoholic liver disease as it is successful in educating and motivating patients.[38]

Despite the higher prevalence of the alcoholic etiology, known to be predisposed to noncompliance, we found that the Home care group had a longer duration of therapy compared to the No Home Care group.[39]

Home Care intervention offers close accompaniment and frequent contact with the patients, which allows a better understanding of their general physical conditions and the disease itself. During the initial visits, the patients are informed about possible medication side events, drug reactions, and the importance of adherence to treatment. In addition, patients received follow-up phone calls every month, and further individual approaches were taken. All these measurements allow a deeper understanding of the therapy goals and the side effects and translate into a longer duration of therapy. Although there is a paucity of research evidence on the effectiveness of patient educational interventions, such methods may enhance adherence and, consequently, maximize health outcomes and quality of life.[40]

In addition to treatment efficacy, the patients' quality of life has to be taken into consideration. In line with previous reports, we observed that the mean values of the whole cohort before and under therapy shows a decline in every section except for SWB for both groups. This might be explained as being a result of support by family and friends, from which patients with HCC benefit.[15,22]

Another interesting finding was that the No Home Care group had a lower FWB score under therapy compared to the Home Care group. During Home Care visits and phone calls, some of the issues included in this score are addressed directly. For instance, the ability to sleep, disease acceptance, and the ability to enjoy free time are thus improved.

Side effect management is a major part of Home Care, which may improve several items of different subscores of the

FACT-Hep (e.g. pain, diarrhea). Apart from FWB, the subscores were nonsignificantly higher in the Home Care group at follow-up, except for physical well-being. Although the impact in numbers seems modest, we believe that even a small improvement of HRQL is clinically significant and, for each individual, relevant. Unfortunately, there is no additional data available regarding side effect management and patient satisfaction.

The group with Home Care also shows longer overall survival, without reaching statistical significance. This supports the thesis that sorafenib is an effective therapy and that treatment adherence is crucial for a beneficial outcome. The difference of overall survival was around 100 days, which is in accordance with the modest net benefit of sorafenib shown in previous studies.[41]

Study limitations. Despite the prospectively acquired data and although the study represents the management of HCC in a tertiary university center in Switzerland, there are certain limitations. In the current study, a relatively small number of patients, particularly in the group without Home Care, was analyzed. Moreover, for HRQL, there were only limited data available. This might strongly limit the power of the analysis. Furthermore, the study was neither randomized nor blinded, which could potentially lead to selection bias. It must, however, be said that, although randomization would be desirable, blinding seems inherently difficult in this context. Nevertheless, this study offers insight into the benefits of the Supplementary health-care act of Home Care.

As for our clinic, we will continue to recommend Home Care for patients treated with sorafenib. A complex and severe disease such as HCC demands versatile and intense care. Therefore, the patients usually benefit from closer attendance and praise the program. Home Care does, of course, not replace any visit at the hospital but is an advantageous addition. The uptake in other centers is desirable, although the organization and training of staff may be limiting. Fortunately, MediService has started to implement Home Care support in other centers, as well as for some other drugs.

Conclusion

In conclusion, this preliminary study shows that Home Care prolongs treatment duration with sorafenib and improves FWB. The effect on overall survival remains elusive. Based on our findings, we believe that Home Care intervention should be recommended for patients treated with sorafenib and possibly other systemic therapy.

Acknowledgments

We thank MediService for having placed the data at our disposal and for the unobstructed cooperation. We are indebted to the Swiss Foundation against Liver Cancer for funding this research.

References

1 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J. Clin.* 2015; **65**: 87–108.
2 Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology*. 2004; **127**: 35–50.
3 Gomaa AI, Khan SA, Toledano MB, Waked I, Taylor-Robinson SD. Hepatocellular carcinoma: epidemiology, risk factors and pathogenesis. *World J Gastroenterol*. 2008; **14**: 4300–8.
4 Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet*. 2012; **379**: 1245–55.
5 European Association for the Study of the Liver. European Organisation for Research and Treatment of Cancer, "EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma". *J. Hepatol.* 2012; **56**: 908–43.
6 Reig M, da Fonseca LG, Faivre S. New trials and results in systemic treatment of HCC. *J. Hepatol.* 2018; **69**: 525–33.
7 Llovet JM, Ricci S, Mazzaferro V *et al*. Sorafenib in advanced hepatocellular carcinoma. *N. Engl. J. Med.* 2008; **358**: 378–90.
8 Cheng AL, Kang YK, Chen Z *et al*. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet*. 2009; **10**: 25–34.
9 Marisi G, Cucchetti A, Ulivi P *et al*. Ten years of sorafenib in hepatocellular carcinoma: are there any predictive and/or prognostic markers? *World J. Gastroenterol.* 2018; **24**: 4152–63.
10 Li Y, Gao ZH, Qu XJ. The adverse effects of sorafenib in patients with advanced cancers. *Basic Clin. Pharmacol. Toxicol.* 2015; **116**: 216–21.
11 Vincenzi B, Santini D, Russo A *et al*. Early skin toxicity as a predictive factor for tumor control in hepatocellular carcinoma patients treated with sorafenib. *Oncologist*. 2010; **15**: 85–92.
12 Wang P, Tan G, Zhu M, Li W, Zhai B, Sun X. Hand-foot skin reaction is a beneficial indicator of sorafenib therapy for patients with hepatocellular carcinoma: a systematic review and meta-analysis. *Expert Rev. Gastroenterol. Hepatol.* 2018; **12**: 1–8.
13 Koschny R, Gotthardt D, Koehler C, Jaeger D, Stremmel W, Ganten TM. Diarrhea is a positive outcome predictor for sorafenib treatment of advanced hepatocellular carcinoma. *Oncology*. 2013; **84**: 6–13.
14 Maitland ML, Kasza KE, Karrison T *et al*. Ambulatory monitoring detects sorafenib-induced blood pressure elevation on the first day of treatment. *Clin. Cancer Res.* 2009; **15**: 6250–7.
15 Steel JL, Chopra K, Olek MC, Carr BI. Health-related quality of life: hepatocellular carcinoma, chronic liver disease, and the general population. *Qual Life Res*. 2007; **16**: 203–15.
16 Steel JL, Geller DA, Robinson TL *et al*. Health-related quality of life as a prognostic factor in patients with advanced cancer. *Cancer*. 2014; **120**: 3717–21.
17 Diouf M, Filleron T, Barbare JC *et al*. The added value of quality of life (QoL) for prognosis of overall survival in patients with palliative hepatocellular carcinoma. *J. Hepatol.* 2013; **58**: 509–21.
18 Yeo W, Mo FK, Koh J *et al*. Quality of life is predictive of survival in patients with unresectable hepatocellular carcinoma. *Ann. Oncol.* 2006; **17**: 1083–9.
19 Bonnetain F, Paoletti X, Collette S *et al*. Quality of life as a prognostic factor of overall survival in patients with advanced hepatocellular carcinoma: results from two French clinical trials. *Qual. Life Res.* 2008; **17**: 831–43.
20 Tohme S, Sanin GD, Patel V *et al*. Health-related quality of lIfe as a prognostic factor in patients after resection of hepatic malignancies. *J. Surg. Res.* 2020; **245**: 257–64.
21 Gmür A, Kolly P, Knöpfli M, Dufour JF. FACT-Hep increases the accuracy of survival prediction in HCC patients when added to ECOG performance status. *Liver Int.* 2018; **38**: 1468–74.
22 Fan SY, Eiser C, Ho MC. Health-related quality of life in patients with hepatocellular carcinoma: a systematic review. *Clin. Gastroenterol. Hepatol.* 2010; **8**: 559–64.

23 Pallis AG, Mouzas IA. Instruments for quality of life assessment in patients with gastrointestinal cancer. *Anticancer Res*. 2004; **24**: 2117–22.
24 Cella BDF, Tulsky DS, Gray G *et al*. The Functional Assessment of Cancer Therapy Scale: development and validation of the general measure. *J Clin Oncol*. 1993; **11**: 570–9.
25 Heffernan N, Cella D, Webster K *et al*. Measuring health-related quality of life in patients with hepatobiliary cancers: the functional assessment of cancer therapy-hepatobiliary questionnaire. *J. Clin. Oncol.* 2002; **9**: 2229–39.
26 Cella D, Butt Z, Kindler HL *et al*. Validty of the FACT Hepatobiliary (FACT-Hep) questionnarie for assessing disease-related symptoms and health-related quality of life in patients with metastatic pancreatic cancer. *Qual Life Res*. 2013; **22**: 1105–12.
27 Steel JL, Eton DT, Cella D, Olek MC, Carr BI. Clinically meaningful changes in health-related quality of life in patients diagnosed with hepatobiliary carcinoma. *Ann. Oncol.* 2006; **17**: 304–12.
28 Wang YB, Chen MH, Yan K, Yang W, Dai Y, Yin SS. Quality of life after radiofrequency ablation combined with transcatheter arterial chemoembolization for hepatocellular carcinoma: comparison with transcatheter arterial chemoembolizaion alone. *Qual. Life Res.* 2007; **16**: 389–97.
29 Salem R, Gilbertsen M, Butt Z *et al*. Increased quality of life among hepatocellular carcinoma patients treated with radioembolization, compared with chemoembolization. *Clin Gastroenterol Hepatol*. 2013; **11**: 1358–65.
30 Steel J, Baum A, Carr B. Quality of life in patients diagnosed with primary hepatocellular cacrinoma: hepatic arterial infusion of Cisplatin versus 90-Yttrium microspheres (Therasphere). *Psychooncology*. 2004; **13**: 73–9.
31 Poon RT, Fan ST, Yu WC, Lam BK, Chan FY, Wong J. A prospective longituindal study of quality of life after resection of hepatocellular carcinoma. *Arch. Surg*. 2001; **136**: 693–9.
32 Mallick R, Cai J, Wogen J. Predictors of non-adherence to systemic oral therapy for advanced hepatocellular carcinoma. *Curr Med Res Opin*. 2013; **29**: 1701–8.
33 Nieuwlaat R, Wilczynski N, Navarro T *et al*. Interventions for enhancing medication adherence. *Cochrane Libr*. 2014; **11**: CD000011.
34 Steel JL, Nadeau K, Olek M, Carr BI. Preliminary results of an individually tailored psychosocial intervention for patients with advanced hepatobiliary carcinoma. *J. Psychosoc. Oncol*. 2007; **25**: 19–42.
35 Walko CM, Grande C. Management of common adverse events in patients treated with sorafenib: nurse and pharmacist perspective. *Semin. Oncol.* 2014; **41**: 17–28.
36 Webster K, Cella D, Yost K. The functional assessment of chronic illness therapy (FACIT) measurement system: properties, applications and interpretation. *Health Qual Life Outcomes*. 2003; **16**: 1–79.
37 Bosetti C, Turati F, La Cecchia C. Hepatocellular carcinoma epidemiology. *Gastroenterology*. 2014; **28**: 753–70.
38 Leggio L, Lee MR. Treatment of alcohol use disorder in patients with alcoholic liver disease. *Am. J. Med.* 2017; **130**: 124–34.
39 Steiner JF, Ho PM, Beaty BL *et al*. Socio-demographic and clinical characteristics are not clinically useful predictors of refill adherence in patients with hypertension. *Circ. Cardiovasc. Qual. Outcomes*. 2009; **2**: 451–7.
40 Arthurs G, Simpson J, Brown A, Kyaw O, Shyrier S, Concert CM. The effectiveness of therapeutic patient education on adherence to oral anti-cancer medicines in adult cancer patients in ambulatory care settings: a systematic review. *JBI Database Syst Rev Implement Rep*. 2015; **13**: 244–92.
41 Llovet JM, Montal R, Sia D, Finn RS. Molecular therapies and precision medicine for hepatocellular carcinoma. *Nat. Rev. Clin. Oncol.* 2018; **15**: 599–617.