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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

# Metronomic capecitabine as second-line treatment for hepatocellular carcinoma after sorafenib discontinuation

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## Abstract

**Purpose** Metronomic capecitabine (MC) is a well-tolerated systemic treatment showing promising results in one retrospective study, as second-line therapy after sorafenib failure, in patients with hepatocellular carcinoma (HCC).

**Methods** 117 patients undergoing MC were compared to 112 patients, eligible for this treatment, but undergoing best supportive care (BSC) after sorafenib discontinuation for toxicity or HCC progression. The two groups were compared for demographic and clinical features. A multivariate regression analysis was conducted to detect independent prognostic factors. To balance confounding factors between the two groups, a propensity score model based on independent prognosticators (performance status, neoplastic thrombosis, causes of sorafenib discontinuation and pre-sorafenib treatment) was performed.

**Results** Patients undergoing MC showed better performance status, lower tumor burden, lower prevalence of portal vein thrombosis, and better cancer stage. Median (95% CI) post-sorafenib survival (PSS) was longer in MC than in BSC patients [9.5 (7.5–11.6) vs 5.0 (4.2–5.7) months ($p < 0.001$)]. Neoplastic thrombosis, cause of sorafenib discontinuation, pre-sorafenib treatment and MC were independent prognosticators. The benefit of capecitabine was confirmed in patients after matching with propensity score [PSS: 9.9 (6.8–12.9) vs. 5.8 (4.8–6.8) months, ($p = 0.001$)]. MC lowered the mortality risk by about 40%. MC achieved better results in patients who stopped sorafenib for adverse events than in those who progressed during it [PSS: 17.3 (10.5–24.1) vs. 7.8 (5.2–10.1) months, ($p = 0.035$)]. Treatment toxicity was low and easily manageable with dose modulation.

**Conclusions** MC may be an efficient and safe second-line systemic therapy for HCC patients who discontinued sorafenib for toxicity or tumor progression.

**Keywords** Hepatocellular carcinoma · Metronomic capecitabine · Second-line chemotherapy · Survival · Toxicity

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## Introduction

The oral multi-tyrosine kinase inhibitor sorafenib currently represents the only evidence-based treatment for advanced hepatocellular carcinoma (HCC) in patients with preserved liver function. However, phase 3 trials and field practice surveys have shown that 80–91% of treated patients experience adverse events (AEs), leading to dose reductions in about half cases and a treatment discontinuation in 28–40% of them (Llovet et al. 2008; Iavarone et al. 2011; Lencioni et al. 2014). Moreover, sorafenib fails to control cancer progression in about 30–40% of patients (Llovet et al. 2008; Iavarone et al. 2011). According to data available in the literature, a percentage ranging from 40 to 56% of patients who fails sorafenib is potentially amenable to second-line clinical trials (Llovet et al. 2013; Reig et al. 2013; Shao et al. 2014). So far, several different anticancer agents, such as brivanib, ramucirumab and everolimus have failed to improve survival as second-line treatments in phase 3 randomized controlled trials (RCTs) (Llovet et al. 2013; Finn et al. 2012; Zhu et al. 2014, 2015). The reasons of these failures may be either an inadequate stratification of patients or the intrinsic toxicity of some of these drugs that cause severe AEs, the occurrence of which is facilitated by the co-presence of cirrhosis (Llovet et al. 2015). More recently, this dismal scenario has been partially modified by regorafenib, a potent multikinase inhibitor, that succeeded in improving the survival of patients tolerant to sorafenib but with cancer progression, compared with placebo (Bruix et al. 2017). Indeed, even this new cornerstone of systemic therapy for HCC does not accomplish the need of patients who do not tolerate sorafenib.

Capecitabine, a prodrug of 5-fluorouracil (5-FU) metabolized to the active drug preferentially in liver and tumor tissue by thymidine phosphorylase (Walko and Lindley 2005), has been tested as first- and second-line treatment for HCC by some studies, using either the conventional or metronomic approach (Patt et al. 2004; Lee et al. 2009; Farrag 2012; He et al. 2013; Abdel-Rahman et al. 2013; Brandi et al. 2013; Granito et al. 2015; Murer et al. 2016; Casadei Gardini et al. 2017). The obtained results are sparse and rather conflicting, and only one of these studies compared capecitabine with best supportive care (BSC) in the setting of second-line therapy (Casadei Gardini et al. 2017). However, all the aforementioned investigations proved that capecitabine is well tolerated and, in particular, when the *metronomic* regimen (Kerbel and Kamen 2004; Cramarossa et al. 2014; Pasquier et al. 2010) is utilized. This approach, recently used in oncology, does not deliver high drug dose per unit time, nor is a cyclic maximum-tolerated dose regimen followed by prolonged drug-free breaks. It relies, instead, on continuous administration of low drug doses, which reduce the gastrointestinal and bone marrow toxicity of chemotherapy (Kerbel and Kamen 2004). This is an important feature for the treatment of fragile patients, such as cirrhotic subjects. The potential efficacy of metronomic chemotherapy depends on several mechanisms: (a) inhibition of tumoral angiogenesis due to a curbed production of growth factors by tumor micro-environmental cells; (b) reduction of the therapeutic resistance of the tumor; (c) activation of the adaptive and innate immune response through a reduction of immune-suppressive populations of regulatory T cells, an influence on dendritic and cytotoxic cells, and a recruitment and activation of innate immune cells (Pasquier et al. 2010; Kareva et al. 2015).

The effects of metronomic capecitabine (MC) in patients with advanced HCC was first tested by Farrag, who described a modest anti-tumor efficacy and a low toxicity of this treatment (Farrag 2012). Three pioneering studies have shown that MC is active and well tolerated in both treatment-naïve and sorafenib-experienced patients (Brandi et al. 2013; Granito et al. 2015; Casadei Gardini et al. 2017). However, none of them provided information about the potential influence of the cause of sorafenib discontinuation (toxicity or failure to control cancer) on MC efficacy.

This multicentric study compares MC to BSC in HCC patients who discontinued sorafenib and explores whether causes of sorafenib withdrawal can affect outcomes of patients undergoing this therapy.

## Materials and methods

We retrospectively analyzed the records of 335 HCC patients who were treated with sorafenib from January 1st 2009 to July 31st 2015 and discontinued treatment for cancer progression or intolerance (severe AEs) in the six centers: S. Orsola-Malpighi hospital, Bologna, University hospital of Pisa, Pisa, Careggi hospital, Florence, Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e Cura dei Tumori (IRST) IRCCS, Meldola, Ospedale per gli Infermi, Faenza, and Cardarelli hospital, Naples.

Sorafenib intolerance was defined as the occurrence of intolerable toxicity despite supportive therapy and/or dose reduction (to a minimum of 400 mg/day), or after 1 week of sorafenib withdrawal, or recurring after its restart. AEs were graded according to the National Cancer Institute, Common Terminology Criteria for Adverse Events classification, version 4 (Common Terminology Criteria for Adverse Events 2009). Radiological tumor progression was defined according to modified RECIST criteria (Lencioni and Llovet 2010).

We excluded 67 (20.0%) patients belonging to Child-Pugh (C–P) class C, or Barcelona Clinical Liver Cancer

(BCLC) stage D or Eastern Cooperative Oncology Group-performance status (PS) > 2 from the study. Among the 268 selected patients, 117 were treated with MC (cases), while 151 received BSC (controls), according to the policy of each center (Fig. 1). In particular, Bologna hospital started shifting patients from sorafenib to MC in case of tumor progression or unacceptable drug-related toxicity since 2009, while Meldola, Faenza, Firenze and Pisa hospitals adopted this strategy in 2011. Conversely, Naples hospital never utilized this practice, and shifted patients to BSC.

The eligibility criteria for MC treatment were: Eastern Cooperative Oncology Group (ECOG) PS ≤ 2, C–P score ≤ 8, bilirubin ≤ 3 mg/dL, PS ≤ 2, platelet count ≥ 50,000/mmc, hemoglobin level > 9 g/dL, white blood cell count > 1500/mmc, transaminases < 5 × the upper normal level, creatinine ≤ 1.5 mg/dL, no ascites or ascites controlled by diuretics, encephalopathy ≤ 1, and no history of coronary disease or heart failure. The same criteria were utilized to select the control subjects among BSC-treated patients. As a result, the population enrolled in the study included 117 MC cases and 112 BSC controls.

Capecitabine was administered orally, at the dose of 500 mg bid. At discretion of the referral treatment provider, this dosage could be increased up to 500 mg tid if the drug was well tolerated and the first radiological control showed signs of tumor progression. MC was continued until the occurrence of radiological *and* symptomatic (ECOG PS ≥ 3, 2 and/or ≥ 2 unit increase of C–P score) progression of HCC or for unacceptable toxicity. Drug-related AEs were managed with supportive therapy, dose reduction or treatment suspension.

Diagnosis of cirrhosis was based on the presence of an irregular liver profile at ultrasound, ultrasonographic/endoscopic signs of portal hypertension and clinical and/or laboratory features.

The liver disease was attributed to:

- hepatitis C virus (HCV), if patients showed serum anti-HCV antibody;
- hepatitis B virus (HBV), if patients were HBV surface antigen carriers (± hepatitis delta virus);
- alcohol, if the daily ethanol intake was > 60 g for women and > 80 g for men, for > 10 years, in the absence of any other cause of liver injury;
- non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis, according to the American Association for the study of the liver practice guidelines;
- multiple causes, for any combination between viral infections, alcohol abuse and NAFLD;
- others, including hemochromatosis, Wilson disease, alpha-1 antitrypsin deficiency, primary biliary cholangitis and sclerosing cholangitis.

HCC histology was available in 57 out of 117 (48.7%) cases and 54 out of 112 (48.2%) controls. In non-biopsied patients, HCC diagnosis was established according to European Association For The Study Of The Liver guidelines (Bruix et al. 2001; European Association For The Study Of The Liver 2012).

HCC was staged at the time of enrolment by multiphase-computed tomography or magnetic resonance imaging according to the BCLC staging system (Bruix et al. 2005).

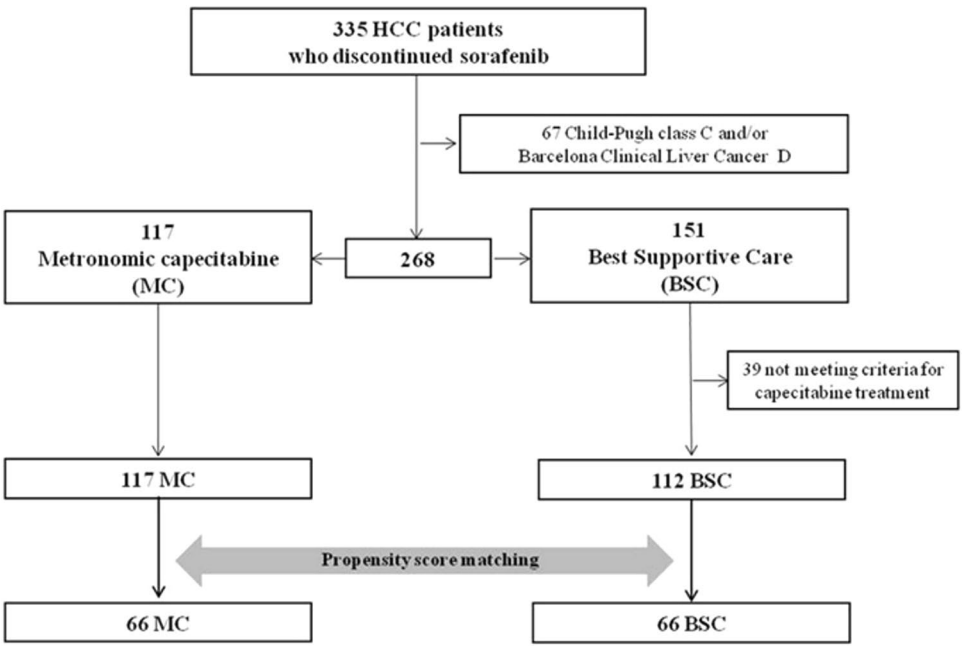


**Fig. 1** CONSORT diagram of the study

Additional investigations were performed when clinically appropriate.

Both MC and BSC patients underwent laboratory and clinical follow-up monthly. Imaging procedures were repeated every 2–3 months in MC patients. Instead, in BSC controls, imaging techniques were performed only when considered clinically necessary and outside the intention of checking tumor progression.

Tumor response (TR) to MC was evaluated by modified Response Evaluation Criteria In Solid Tumours (Lencioni and Llovet 2010), as MC also has anti-angiogenic effects.

All patients provided signed informed consent to the study. Patients receiving MC signed a further consent form for the administration of the second-line therapy. The study was approved by the Institutional board of the participating groups.

### Statistical analysis

The primary end points were post-sorafenib survival (PSS) and overall survival from the beginning of sorafenib administration (OS), while secondary end points were MC safety and the best TR to MC. Continuous data were expressed as mean ± standard deviation (SD) or median and intervals, while discrete variables as absolute value and relative frequency. Mann–Whitney *U* test was used to compare continuous data; $\chi^2$ Pearson's test and Fisher's test to compare discrete data. OS was measured from the day of sorafenib discontinuation to death, with values censored at 2015 July 31st (end of the study) or at the last evaluation. Survival was analyzed by a Kaplan–Meier test, and differences were assessed by the log-rank test. Variables associated with survival ($p < 0.10$) at univariate analysis were included in the multivariate regression Cox model.

A propensity score model was developed to control results for baseline variable imbalances between treatment groups. A multivariate logistic regression analysis was applied to calculate the propensity score. This model provided a 1:1 matching without replacement between MC and BSC patients, using the exact matching method (D'Agostino 1998). Survival analysis was repeated in the matched population. Statistical significance was met with 2-tailed $p$ value $< 0.05$. All statistical analyses were performed with SPSS v23.0 (Apache Software Foundation, Chicago, Illinois).

## Results

The main characteristics of the study population are reported in Table 1. Male sex accounted for about 80% of cases in both groups, whereas MC patients were slightly younger than BSC patients. There were no significant differences in etiology of liver disease, hepatic function [C–P class and Model for End Stage Liver Disease (MELD)] and metabolic comorbidities. Instead, the two groups differed for the following features: MC patients showed a more frequently preserved PS (PS 0: 62.9 vs 49.1%, respectively, $p = 0.007$), smaller HCCs (4.7 vs 6.4 cm, $p < 0.001$), a lower prevalence of neoplastic thrombosis (23.1 vs 35.7%, $p = 0.036$) than BSC patients. Therefore, the distribution of BCLC stages was more favorable in MC than in BSC patients ($p = 0.001$). One-hundred and three (88%) MC patients and 65 (58.0%) BSC patients had undergone previous locoregional treatment of HCC ($p < 0.001$).

To minimize the confounding effect of the uneven distribution of baseline characteristics, a propensity score matching was performed. MC and BSC patients were matched for the independent prognosticators (at Cox models) which were: ECOG-PS, neoplastic thrombosis, causes of sorafenib discontinuation and pre-sorafenib treatments. The matching allowed us to select 66 pairs of patients (1:1 case–control matching) homogeneous for all baseline characteristics except the nodule size which was larger in BSC group (Table 2).

Median length of sorafenib treatment was 3.4 months (25th–75th : 1.9–8.2) in MC group and 3.6 months (25th–75th : 2.5–4.1) in BSC group ($p = 0.609$). MC was started after a median of 23 days (25th–75th : 11–44) from sorafenib discontinuation. The dosage of capecitabine was increased from 500 mg bid to 500 mg bid in 11 patients. Median length of MC treatment was 3.6 months (25th–75th: 2.5–7.2). A dose reduction was necessary in six (5.1%) patients because of AEs. No patients required permanent drug withdrawal for this reason.

### Radiological response and survival

Radiological evaluation was available in 95 (81.2%) MC patients and was missing in 22 patients due to an early worsening of health conditions preventing the radiological control or death occurrence. The best TR was: complete response in 1 (1.0%) patient who also showed a dramatic drop of alpha-fetoprotein (from 1909 to 2.6 ng/mL); partial response in 3 (3.2%); stable disease in 34 (35.8%) patients; disease progression in 57 (60.0%).

Median PSS was 9.5 months (95% CI 7.5–11.6) in MC patients and 5.0 months (95% CI 4.2–5.7) in BSC patients ($p < 0.001$) (Fig. 2a). After propensity score matching, the figures of PSS remained fairly similar to those of the original treatment groups, with MC confirming its superiority over BSC [9.9 months (6.8–12.9) vs. 5.8 months (4.8–6.8), $p = 0.001$] (Fig. 2c).

Even OS (time from the start date of sorafenib therapy to death or last visit date) was significantly longer in MC than in BSC patients [16.7 (14.2–19.3) vs. 10.7 (8.4–13.1)

**Table 1** Baseline characteristics of enrolled patients

| Baseline characteristics | Capecitabine group | BSC group | *p* values |
|---|---|---|---|
| Patients, *n* (%) | 117 (51.1) | 112 (48.9) | |
| Age, years | 68.0 ± 9.9 | 70.4 ± 10.7 | 0.016 |
| Male, *n* (%) | 92 (78.6) | 88 (78.6) | 1.000 |
| Etiology (*n* 221), *n* (%) | | | |
| HCV | 71 (64.0) | 69 (62.7) | 0.213 |
| HBV | 15 (13.5) | 10 (9.1) | |
| Alcohol | 7 (6.3) | 17 (15.5) | |
| NAFLD/cryptogenic | 10 (9.0) | 8 (7.3) | |
| Multiaetiology | 8 (7.2) | 5 (4.5) | |
| Others | 0 (0) | 1 (0.9) | |
| Child–Pugh class (*n* 142) *n* (%) | | | 0.858 |
| *A* | 91 (77.8) | 86 (76.8) | |
| *B* | 26 (22.2) | 26 (23.2) | |
| MELD score | 9.1 ± 2.6 | 9.4 ± 2.3 | 0.080 |
| Hypertension, *n* (%) | 43 (36.8) | 51 (45.5) | 0.177 |
| Diabetes, *n* (%) | 29 (24.8) | 36 (32.1) | 0.256 |
| Ascites (*n* 142), *n* (%) | 32 (27.6) | 42 (38.9) | 0.088 |
| ECOG-PS (*n* 142) *n* (%) | | | 0.007 |
| 0 | 73 (62.9) | 54 (49.1) | |
| 1 | 40 (34.5) | 45 (40.9) | |
| 2 | 3 (2.6) | 11 (10.0) | |
| Portal vein thrombosis (*n* 143), *n* (%) | 34 (29.3) | 41 (36.9) | 0.217 |
| Portal branch | 20 (60.6) | 30 (73.2) | |
| Segmental | 7 (21.2) | 6 (14.6) | |
| Both | 6 (18.2) | 5 (12.2) | |
| Neoplastic thromobosis, *n* (%) | 27 (23.1) | 40 (35.7) | 0.036 |
| Metastasis (*n* 227), *n* (%) | 74 (63.2) | 84 (76.4) | 0.043 |
| Max. nodule size (mm) | 47.3 ± 25.8 | 64.2 ± 34.1 | < 0.001 |
| Tumor spread (*n* 221), *n* (%) | | | 0.869 |
| Unilobar | 22 (20.0) | 24 (21.6) | |
| Bilobar | 88 (80.0) | 87 (78.4) | |
| BCLC, *n* (%) | | | 0.001 |
| *B* | 14 (12.0) | 1 (0.9) | |
| *C* | 103 (88.0) | 111 (99.1) | |
| Pre-sorafenib treatment, n (%) | 103 (88.0) | 65 (58.0) | < 0.001 |
| Sorafenib treatment duration, median (range) | 3.4 months (1.9–8.2) | 3.6 months (2.5–4.1) | 0.609 |
| Causes of sorafenib discontinuation (*n* 226), *n* (%) | | | 0.139 |
| Progression | 85 (72.6) | 68 (62.4) | |
| Adverse events | 31 (26.5) | 37 (33.9) | |
| Liver failure | 1 (0.9) | 4 (3.7) | |
| Clinical Biochemistry | | | |
| INR | 1.2 ± 0.2 | 1.2 ± 0.1 | 0.291 |
| Bilirubin (mg/dL) | 1.1 ± 0.6 | 1.2 ± 0.6 | 0.063 |
| Albumin (g/dL) | 3.6 ± 0.5 | 3.5 ± 0.5 | 0.154 |
| Creatinine (mg/dL) | 0.9 ± 0.3 | 0.9 ± 0.3 | 0.701 |
| Hb (g/dL) | 12.2 ± 2.4 | 12.1 ± 2.2 | 0.385 |
| PLT ($\times 10^3$/mmc) | 166.2 ± 102.6 | 153.8 ± 83.5 | 0.801 |
| AFP (ng/mL) | 5326 ± 15,410 | 4,442.2 ± 10,225 | 0.873 |

Continuous variables are expressed as mean ± standard deviation (SD)

*BMI* body mass index; *HCV* hepatitis C virus; *HBV* hepatitis B virus; *NAFLD* non-alcoholic fatty liver disease; *MELD* model of end-stage liver disease; *ECOG-PS* eastern cooperative oncology group-performance status; *CLIP*, Cancer of the Liver Italian Program; *BCLC* Barcelona Clinic Liver Cancer; *INR* International Normalized Ratio; *Hb* hemoglobin; *PLT* platelet; *GPT* glutamic pyruvic transaminase; *GOT* glutamic oxaloacetic transaminase; *AFP* alpha-fetoprotein

**Table 2** Baseline characteristics of patients after matching with the propensity score analysis for independent prognostic factors (ECOG-PS, neoplastic thrombosis, causes of sorafenib discontinuation and pre-sorafenib treatments)

| Baseline characteristics | Capecitabine group | BSC group | *p* values |
|---|---|---|---|
| Patients, *n* (%) | 66 (56.4) | 66 (58.9) | |
| Age (years) | 68.7 ± 9.3 | 69.3 ± 10.7 | 0.466 |
| Male, *n* (%) | 54 (81.8) | 48 (72.7) | 0.213 |
| Etiology, *n* (%) | | | 0.671 |
| HCV | 40 (64.5) | 44 (67.7) | |
| HBV | 10 (16.1) | 6 (9.2) | |
| Alcohol | 3 (4.8) | 6 (9.2) | |
| NAFLD/cryptogenic | 5 (8.1) | 6 (9.2) | |
| Multiaetiology | 4 (6.5) | 3 (4.6) | |
| Child–Pugh class, *n* (%) | | | 0.145 |
| A | 47 (71.2) | 55 (83.3) | |
| B | 19 (28.8) | 11 (16.7) | |
| MELD score | 8.9 ± 2.4 | 9.2 ± 2.3 | 0.395 |
| Hypertension, *n* (%) | 25 (37.9) | 28 (42.4) | 0.594 |
| Diabetes, *n* (%) | 18 (27.3) | 23 (34.8) | 0.347 |
| Ascites, *n* (%) | 24 (36.4) | 23 (35.9) | 0.960 |
| ECOG-PS, *n* (%) | | | 1.000 |
| 0 | 40 (60.6) | 40 (60.6) | |
| 1 | 26 (39.4) | 26 (39.4) | |
| 2 | 0 (0.0) | 0 (0.0) | |
| Portal vein thrombosis, *n* (%) | 22 (33.3) | 17 (25.8) | 0.516 |
| Portal branch | 15 (68.2) | 13 (76.5) | |
| Segmental | 3 (13.6) | 3 (17.6) | |
| Both | 4 (18.2) | 1 (5.9) | |
| Neoplastic thromobosis, *n* (%) | 19 (28.8) | 19 (28.8) | 1.000 |
| Metastasis, *n* (%) | 45 (68.2) | 54 (81.8) | 0.107 |
| Max. nodule size (mm) | 43.8 ± 27.8 | 59.9 ± 31.2 | 0.001 |
| Tumor spread, *n* (%) | | | 0. 806 |
| Unilobar | 11 (18.3) | 11 (16.7) | |
| Bilobar | 49 (81.7) | 55 (83.3) | |
| BCLC, *n* (%) | | | 0.115 |
| *B* | 6 (9.1) | 1 (1.5) | |
| *C* | 60 (90.9) | 65 (98.5) | |
| Pre-sorafenib treatment, *n* (%) | 52 (78.8) | 52 (78.8) | 1.000 |
| Sorafenib treatment duration, median (25th–75th) | 3.7 months (1.8–8.7) | 3.8 months (1.9–8.5) | 0.998 |
| Causes of sorafenib discontinuation, *n* (%) | | | 1.000 |
| Progression | 51 (77.3) | 51 (77.3) | |
| Adverse events | 15 (22.7) | 15 (22.7) | |
| Liver failure | 0 (0.0) | 0 (0.0) | |
| Other | 0 (0.0) | 0 (0.0) | |
| Clinical Biochemistry | | | |
| INR | 1.2 ± 0.2 | 1.1 ± 0.1 | 0.626 |
| Bilirubin (mg/dL) | 1.1 ± 0.5 | 1.2 ± 0.6 | 0.436 |
| Albumin (g/dL) | 3.5 ± 0.5 | 3.5 ± 0.5 | 0.865 |
| Creatinine (mg/dL) | 0.8 ± 0.2 | 0.9 ± 0.3 | 0.757 |
| Hb (g/dL) | 12.6 ± 1.6 | 11.8 ± 2.3 | 0.028 |
| PLT ($\times 10^3$/mmc) | 154.4 ± 91.7 | 146.7 ± 80.9 | 0.942 |
| AFP (ng/mL) | 6153.8 ± 18,081.8 | 4394.7 ± 9476.5 | 0.834 |

Continuous variables are expressed as mean ± standard deviation (SD) if not otherwise specified

*BMI* body mass index; *HCV* hepatitis C virus; *HBV* hepatitis B virus; *NAFLD* non-alcoholic fatty liver disease; *MELD* model of end-stage liver disease; *ECOG-PS* eastern cooperative oncology group-performance status; *CLIP* Cancer of the Liver Italian Program; *BCLC* Barcelona Clinic Liver Cancer; *INR* International Normalized Ratio; *Hb* hemoglobin; *PLT* platelet; *GPT* glutamic pyruvic transaminase, *GOT* glutamic oxaloacetic transaminase; *AFP* alpha-fetoprotein

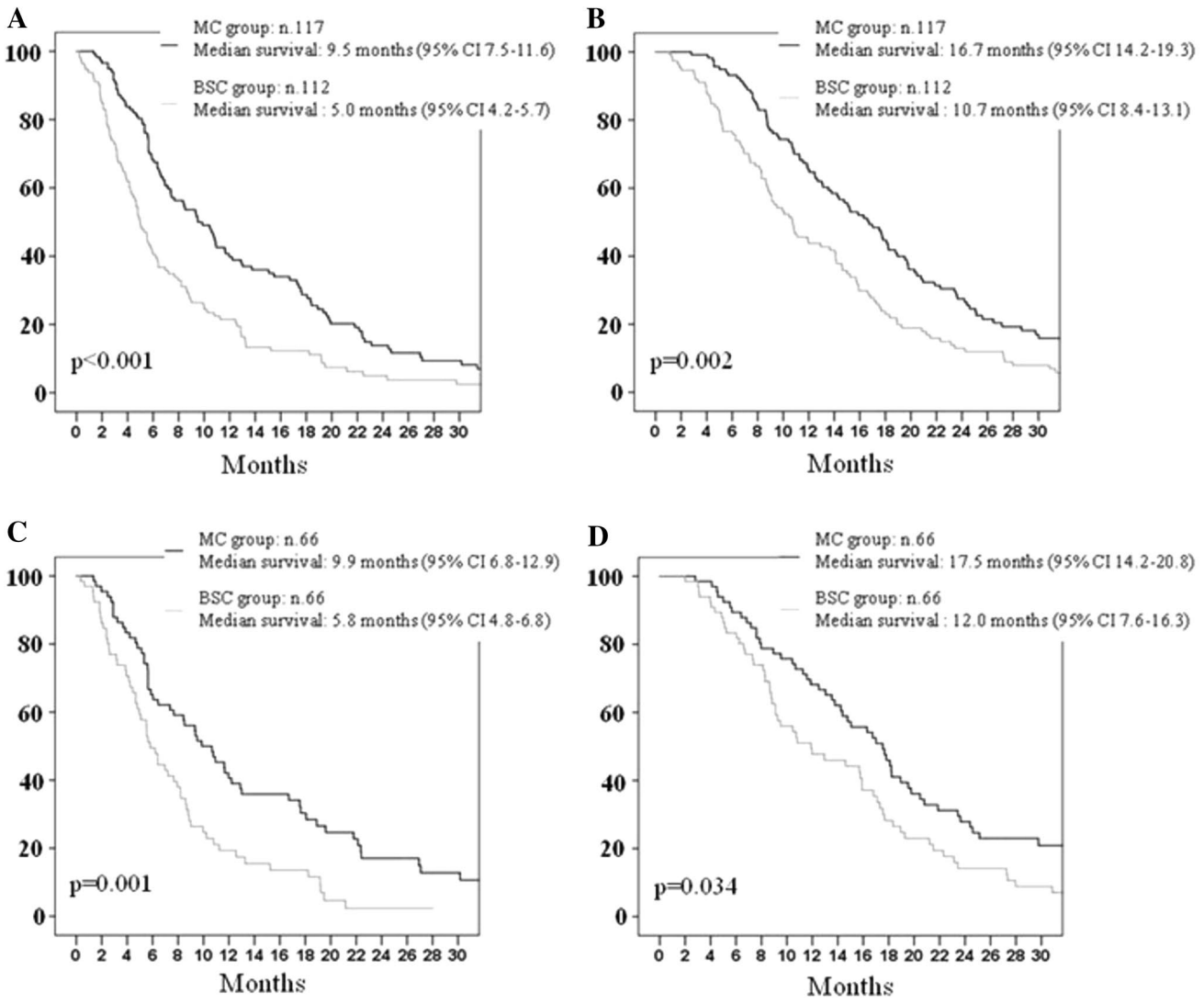


**Fig. 2** Overall survival of patients from the date of sorafenib discontinuation to death before (**a**) and after (**c**) propensity score matching and survival of patients from the start date of sorafenib therapy to death before (**b**) and after (**d**) propensity score matching

months; ($p = 0.002$)] (Fig. 2b). This difference was confirmed after propensity score matching [17.5 (14.2–20.8) vs. 12.0 (7.6–16.3) months; ($p = 0.034$)] (Fig. 2d).

At univariate analysis, ECOG-PS, C–P class, ascites, nodule size, neoplastic thrombosis, BCLC stage, reasons for sorafenib discontinuation, pre-sorafenib treatment, reason for sorafenib discontinuation and MC therapy were associated with PSS (Table 3). To test all these variables in a multivariate model without incurring the bias of multicollinearity, three models were constructed: *Model 1* included MC therapy, C–P class,, BCLC stage, pre-sorafenib treatment and reason for sorafenib discontinuation; *Model 2* comprises MC therapy, ECOG-PS, C–P class, neoplastic thrombosis, metastases, nodule size, pre-sorafenib treatment and reason for sorafenib discontinuation; *Model 3* included MC therapy, ECOG-PS, neoplastic thrombosis, metastases, nodule size, ascites, pre-sorafenib treatment and reason for sorafenib discontinuation (Table 3). These models showed that MC therapy, pre-sorafenib treatment of HCC, neoplastic thrombosis and liver decompensation during sorafenib administration were independently associated with PSS. In every model, MC therapy significantly reduced the mortality risk (reduction rate ranging from 34 to 40%) compared with BSC.

Finally, a sensitivity analysis was performed to test MC effect according to the causes of sorafenib discontinuation. Interestingly, the greatest PSS benefit of MC with respect to BSC occurred in patients intolerant to sorafenib ($p < 0.001$), although a significant benefit was also detectable in those who experienced tumor progression ($p = 0.005$) (Fig. 3).

**Table 3** Univariate and multivariate cox analysis of factors associated with mortality

| Predictors | Univariate | | Multivariate | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Model 1 | | Model 2 | | Model 3 | |
| | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *p* |
| Age, years (continue) | 0.99 (0.98–1.00) | 0.209 | | | | | | |
| Gender (male vs. female) | 1.19 (0.86–1.65) | 0.293 | | | | | | |
| Etiology (HCV vs other) | 0.97 (0.73–1.28) | 0.816 | | | | | | |
| Capecitabine (yes/no) | 0.57 (0.43–0.74) | **< 0.001** | **0.66 (0.50–0.89)** | **0.006** | **0.60 (0.41–0.87)** | **0.007** | **0.63 (0.45–0.88)** | **0.007** |
| ECOG PS | | | | | | | | |
| 0 (reference category) | 1 | | | | 1 | | 1 | |
| 1 | 1.32 (0.99–1.75) | 0.060 | | | **1.51 (1.07–2.13)** | **0.018** | 1.36 (0.99–1.86) | 0.061 |
| 2 | **2.06 (1.18–3.60)** | **0.011** | | | 1.82 (0.94–3.52) | 0.074 | 1.63 (0.83–3.20) | 0.160 |
| Child–Pugh class | | | | | | | | |
| A (reference category) | 1 | | 1 | | 1 | | | |
| B | **1.40 (1.01–1.93)** | **0.044** | 1.27 (0.90–1.78) | 0.175 | 1.24 (0.83–1.85) | 0.300 | | |
| Neoplastic thrombosis (yes/no) | **1.52 (1.12–2.08)** | **0.008** | | | **1.55 (1.09–2.20)** | **0.015** | **1.81 (1.28–2.56)** | **0.001** |
| Metastases (yes/no) | **1.38 (1.02–1.86)** | **0.037** | | | 1.14 (0.78–1.66) | 0.488 | 1.37 (0.96–1.97) | 0.082 |
| Max. nodule size, mm (continue) | **1.01 (1.00–1.01)** | **0.004** | | | 1.00 (1.00–1.01) | 0.537 | 1.00 (1.00–1.01) | 0.358 |
| Pre-sorafenib treatment (yes/no) | **0.62 (0.46–0.84)** | **0.002** | **0.70 (0.51–0.97)** | **0.031** | **0.65 (0.45–0.92)** | **0.017** | **0.71 (0.50–1.00)** | **0.052** |
| Sorafenib treatment duration, days (continue) | 1.00 (0.98–1.02) | 0.621 | | | | | | |
| Reason for sorafenib discontinuation | | | | | | | | |
| Adverse event (reference category) | 1 | | 1 | | 1 | | | |
| Tumor progression | 1.30 (0.96–1.76) | 0.093 | 1.26 (0.93–1.72) | 0.135 | **1.54 (1.05–2.26)** | **0.027** | 1.22 (0.86–1.73) | 0.270 |
| Liver decompensation | **3.41 (1.36–8.54)** | **0.009** | 2.41 (0.92–6.32) | 0.074 | **11.53 (3.76–35.35)** | **< 0.001** | **9.43 (2.68–33.17)** | **< 0.001** |
| Ascites (yes/no) | **1.42 (1.06–1.89)** | **0.018** | | | | | 1.19 (0.86–1.65) | 0.294 |
| BCLC (C vs B) | **2.18 (1.25–3.82)** | **0.006** | 1.55 (0.86–2.79) | 0.143 | | | | |
| Bilirubin, mg/dL (continue) | 1.16 (0.93–1.44) | 0.204 | | | | | | |
| Albumin, g/dL (continue) | 0.83 (0.62–1.10) | 0.184 | | | | | | |
| INR, (continue) | 0.93 (0.49–1.78) | 0.834 | | | | | | |

Significant values are in bold

*HCV* hepatitis C virus; *ECOG-PS* eastern cooperative oncology group-performance status; *AFP* alpha-fetoprotein; *BCLC* Barcelona Clinic Liver Cancer; *INR* International Normalized Ratio; *HR* hazard ratio; *CI* confidence interval

## Safety

Table 4 reports the AEs observed during MC therapy. Overall, 84 patients (71.8%) experienced at least one (any grade) AE. Main drug-related AEs were fatigue (40.2%), thrombocytopenia (12.8%) hand–foot skin reaction (10.3%) followed by diarrhea, rush and nausea/vomiting (7.7% respectively). Most of them were mild, and none directly caused death or drug discontinuation. In seven (6.0%) patients, AEs required a dose adjustment.

## Discussion

Several trials testing the efficacy of second-line systemic therapies for patients with advanced HCC have failed (Llovet et al. 2013; Finn et al. 2012; Zhu et al. 2014, 2015; Bruix et al. 2017). The failure likely depended, for some agents, on an inadequate selection of patients owing to the lack of biomarkers able to predict the response to therapy (diluting bias) and, for other agents, on their toxicity in a "fragile"

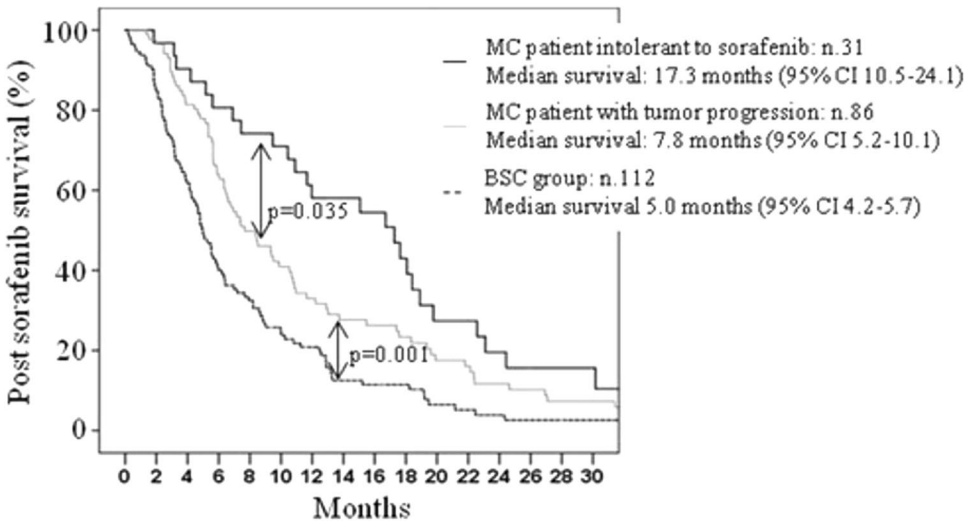


**Fig. 3** Overall survival of metronomic capecitabine and best supportive care patients according to causes of sorafenib discontinuation

**Table 4** Adverse events of metronomic capecitabine categorized according to the National Cancer Institute, Common Terminology Criteria for Adverse Events classification, version 4 (Marinelli et al. 2013)

| | Any grade Number (%) | Grade 1–2 Number (%) | Grade 3–4 Number (%) |
|---|---|---|---|
| Drug related | | | |
| Fatigue | 47 (40.2) | 43 (36.8) | 4 (3.4) |
| Diarrhea | 9 (7.7) | 8 (6.8) | 1 (0.9) |
| Hand–foot skin reaction | 12 (10.3) | 11 (9.4) | 1 (0.9) |
| Rash | 9 (7.7) | 7 (6.0) | 2 (1.7) |
| Nausea/vomiting | 9 (7.7) | 9 (7.7) | |
| Leucopenia | 7 (6.0) | 6 (5.1) | 1 (0.9) |
| Thrombocytopenia | 15 (12.8) | 14 (11.9) | 1 (0.9) |
| Anemia | 4 (3.4) | 4 (3.4) | |
| Cardio toxicity | 2 (1.7) | 2 (1.7) | |
| Not certainly drug related | | | |
| Itch | 7 (6.0) | 6 (5.1) | 1 (0.9) |
| Insomnia | 3 (2.6) | 3 (2.6) | |
| Bleeding | 3 (2.6) | 2 (1.7) | 1 (0.9) |
| Hyperbilirubinemia | 32 (27.4) | 28 (24.0) | 4 (3.4) |
| Ascites | 36 (30.8) | 29 (24.8) | 7 (6.0) |
| Encephalopathy | 5 (4.3) | 5 (4.3) | |
| Anorexia | 2 (1.7) | 2 (1.7) | |
| Edema | 3 (2.6) | 3 (2.6) | |
| Gastritis | 1 (0.9) | 1 (0.9) | |

setting, such as liver cirrhosis, which is the background of most HCCs. A low toxicity of (or a predictable good tolerance to) the agent would represent, therefore, a key factor for the success in this clinical setting. Moreover, the stringent criteria for entering into RCTs could have selected long natural history cases in placebo arms, owing to a *selection bias* of less-aggressive tumors (Llovet et al. 2015).

More recently, an RCT has proven that regorafenib, a potent multikinase inhibitor, increases survival compared with placebo (HR 0.46; 95% CI 0.37–0.56) in patients who stopped sorafenib (Bruix et al. 2017). However, due to the expected overlap toxicity between the two drugs, this trial only included patients who had tumor progression but were tolerant to sorafenib, to curb the risk of regorafenib discontinuation for AEs. Therefore, this advancement in the management of advanced HCC does not represent a suitable option for the 28–40% of patients forced to stop sorafenib owing to its toxicity (Llovet et al. 2008; Iavarone et el. 2011). Moreover, a press release has announced that in phase 3 Celestial RCT cabozantinib has been proven to be an effective second-line treatment in patients with advanced HCC, regardless of the cause of sorafenib discontinuation. (http://www.businesswire.com/news/home/20171016005563/en/Ipsen-Announces-Phase-3-CELESTIAL-Trial-Cabozantinib).

Previous cohort studies, addressing the role of *conventional* therapy with capecitabine (alone or in combination regimens), as first- or second-line systemic therapy for advanced HCC, have demonstrated a certain anti-tumor efficacy and low toxicity (Patt et al. 2004; Lee et al. 2009; He et al. 2013). A phase 2 trial, randomly assigning patients to sorafenib or capecitabine, showed a longer overall and progression-free survival of sorafenib patients but an imbalance of C–P class distribution and extrahepatic tumor spread between groups affect the reliability of results (Abdel-Rahman et al. 2013).

The adjuvant role of conventional capecitabine after curative HCC resection was evaluated in an RCT including 60 patients (Xia et al. 2010). The treatment reduced the risk of

late tumor recurrence as compared to the supportive care and, once more, showed a good tolerability.

One study challenged the effectiveness of MC against BSC, using historical controls (Brandi et al. 2013). In this investigation, 90 patients with advanced HCC treated with MC (59 naïve and 31 post-sorafenib cases) showed a median OS of 14.5 and 9.8 months, respectively. In naïve patients, MC compared favorably with untreated patients matched for demographic and oncologic features (median OS: 15.6 vs. 8.0 months), providing the proof-of-concept of its efficacy as first-line treatment. In another study, the median survival of 26 sorafenib-experienced patients undergoing MC was 8.0 months (Granito et al. 2015). Lastly, a recent study showed that survival of patients sequentially treated with sorafenib and MC was significantly better than that of patients shifted to BSC at the time of sorafenib discontinuation (median OS: 12.0 vs. 9.0 months, respectively), with a 46% reduction of death risk in MC cases (Casadei Gardini et al. 2017). Another indication of MC efficacy is provided by the long-lasting objective TR reported in three patients with an unresectable HCC (Brandi et al. 2010; Marinelli et al. 2013). On the other hand, a brief report by Murer et al. reported a short survival (mean: 6.3 months) in 25 HCC patients undergoing MC as both first- and second-line chemotherapy, with no significant differences between the two groups (Murer et al. 2016). This poorer survival compared with that of our and previous studies (Brandi et al. 2013; Granito et al. 2015) could depend on the worse liver function and performance status of Murer's patients.

In our study, median PSS was twofold higher in MC than in BSC patients, leading to a reduction of the death risk of about 35–40%. This result, confirming the previous one observed in a smaller group of sorafenib-experienced patients (Brandi et al. 2013), was corroborated by those obtained after adjustment for confounders in three different multivariate models, and in a nested case–control study.

Furthermore, in line with the result of a previous multicentric Italian study (Casadei Gardini et al. 2017), the superiority of MC over BSC was confirmed once survival was calculated from the beginning of sorafenib chemotherapy. This indicates that the sequential use of sorafenib and MC improves prognosis of HCC patients compared with the shift to BSC after withdrawal of the first-line therapy. The reliability of this assumption is strengthened by the fact that OS of our control group receiving only sorafenib (10.7 months for unselected cases, and 12.0 months for matched cases; Fig. 2b, d) is well comparable with the figures reported by both the SHARP trial (Llovet et al. 2008) and a large field-practice study (Iavarone et al. 2011).

Our results, however, should also be scrutinized in the light of PSS of our BSC patients (5.0 months), which was similar (4.6 months) to that reported by a large field-practice study (Lee et al. 2015) but shorter than that observed in placebo arms of the second-line RCTs (ranging from 7.3 to 8.2 months) (Llovet et al. 2013; Finn et al. 2012; Zhu et al. 2014, 2015; Bruix et al. 2017). This discrepancy may rely on the already mentioned *selection bias* favoring the inclusion in RCTs of patients with well-preserved general conditions and less-aggressive tumors (Llovet et al. 2015). Pertinently, 23% of our patients belonged to C–P class B (which was an exclusion criterion for RCTs), about one-third had ascites, 36% showed vascular invasion, and 76.4% had a metastatic disease. The worse clinical profile may also justify the fairly lower PSS of our MC patients (9.5 months) compared with patients undergoing regorafenib (10.6 months) (Bruix et al. 2017).

Since the cause of sorafenib discontinuation has been claimed to be an important determinant of PSS (Iavarone et al. 2011), we also tested the effect of MC therapy. The treatment demonstrates its superiority over BSC either in patients intolerant to sorafenib or in those who had experienced tumor progression, but the greatest benefit was observed in those who did not tolerate sorafenib (Fig. 3). Therefore, MC appears to be useful regardless of the reason of sorafenib withdrawal, but particularly in the patient population in which regorafenib has not been tested due to an expected risk of overlap toxicity between the two drugs. The benefit due to MC was likely assisted by a lower tumor aggressiveness and a more favorable natural history of the tumor in patients who discontinued first-line treatment for AEs (Iavarone et al. 2011).

Another result that needs a comment is the favorable prognostic meaning of locoregional treatments performed before sorafenib therapy. This unexpected finding may be tentatively explained assuming a lower biological aggressiveness of the tumor, which allowed to manage patients with sequential treatment before reaching an advanced stage.

In all mentioned studies, MC was well tolerated since no drug-related death occurred, AEs were generally mild and easily managed with dose reduction or brief periods of drug discontinuation. A permanent interruption of the therapy was seldom required. Our study confirmed that MC is a safe treatment for cirrhotic patients belonging to C–P class A or B (up to a score $\leq 8$). Most of the AEs we observed (such as ascites, hyperbilirubinemia, edema, itching) cannot be certainly attributed to the drug, as they can be more likely ascribed to the liver disease. Indeed, drug-related AEs were generally mild or moderate, easily manageable with dose adjustment and/or symptomatic therapy, and they were never responsible for permanent drug withdrawal or patient death.

Lastly, it cannot be disregarded that MC is an inexpensive treatment (in Italy its cost is about 100 €/month), representing an approach to advanced HCC easily affordable by most National Health Systems.

Our study has several limitations. The principal one relies on its retrospective nature that may have introduced

unintended biases and precluded a pre-defined regimented follow-up with regard to clinical monitoring of HCC. Nevertheless, it captured "real-world" observational data on MC efficacy and, hence, the shortcomings of the study design should be weighed against the pioneering nature of this multicenter investigation that included university and community institutions.

Second, patient enrollment was affected by a "monolaterality bias", since not all the participating centers offered patients the two therapeutic options we compared. This shortcoming may, in turn, have caused a selection bias, as the lack of a second-line option could have compelled both physicians and patients toward a "stubborn" use of sorafenib (i.e., despite a documented progression) with respect to centers where MC was used as a rescue treatment. Although the similar exposure time to sorafenib in MC and BSC patients stands against this hypothesis, a certain impact of the monolaterality bias cannot be fully excluded since BSC patients had poorer clinical status and greater tumor burden than MC cases. Hence, we tried to override this limitation assessing the effect of MC therapy on the survival adjusted for many confounders and after patient matching with the propensity score. After matching, BSC still had a larger tumor size, but this residual unbalance does not seem to be critical, since such a variable was not an independent prognosticator.

In conclusion, this study provides a proof-of-concept of the efficacy of MC and confirms its safety and efficacy as second-line treatment for patients with HCC and liver cirrhosis (C–P score $\leq 8$) who either did not tolerate sorafenib or progressed during this therapy. It also indicates that the best results of MC can be expected in the former group of patients, representing an oncologic population still awaiting for an effective and safe second-line treatment.

These promising results require confirmation through adequately sized RCTs comparing MC vs. regorafenib (for those experiencing sorafenib failure) or cabozantinib to exactly define the role of this safe and inexpensive therapy in the management of advanced HCC.

## Compliance with ethical standards

**Financial support** Annual Grant from the Italian Ministry of Instruction, University and Research (MIUR).

**Conflict of interest** The authors declare that they have no conflicts of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Human and animal rights statement** This article does not contain any studies with animals performed by any of the authors.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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