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Capecitabine in advanced hepatocellular carcinoma: A multicenter experience☆

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ABSTRACT

Background: Recent data suggest a potential activity and a good tolerability of capecitabine in advanced hepatocellular carcinoma (HCC).
Aims: To evaluate capecitabine activity and safety in a wide cohort of advanced HCC patients.
Methods: Retrospective analysis of 143 capecitabine-treated patients (January 2010 to December 2017) in three centers of the Veneto Oncology Network.
Results: Capecitabine was administered in second and third line, but also in first line instead of sorafenib in Child-Pugh B patients (70%), compromised clinical conditions (14%) or contraindications to antiangiogenetics (16%). Median overall survival (OS) and time to progression (TTP) were 6.9 and 2.8 months, respectively. There were no differences in OS and TTP between the 32 patients treated with non-metronomic scheme (2000 mg/day for 14 days) and the 111 patients treated with metronomic scheme (1000 mg/day) after correction for prognostic factors at baseline with a propensity score analysis. Capecitabine was more active in patients intolerant to sorafenib than in those progressing during treatment ($p = 0.024$). At least one adverse event (mainly hematological) was experienced by 73% of patients but discontinuation was necessary only in 11 (8%).
Conclusions: Capecitabine can be considered an active and safe option in advanced HCC, especially for patients unfit for other treatments.

1. Introduction

Hepatocellular carcinoma (HCC) is globally the sixth most common cancer and the fourth most frequent cause of cancer-related death, with 854.000 incident cases and 810.000 deaths per year [1]. The incidence of HCC is progressively increasing, especially in western countries [2]. Despite the surveillance in cirrhotics, in many patients (approximately 30%) the diagnosis is achieved when curative treatments are no longer feasible [3–5].

Sorafenib, an oral multi-tyrosine kinase inhibitor, currently represents the standard first-line systemic therapy for advanced HCC (BCLC-C) or tumors progressing after loco-regional therapies, with well preserved liver function (Child-Pugh A) [6]. However, 80–90% of treated patients experience at least one drug-related adverse event (AE), leading to dose reduction in about half cases and to permanent discontinuation in 30–40% of them [7–9]. Moreover, sorafenib fails to control cancer progression in about 30–40% of patients [7,10]. Many drugs have been tested in first line versus sorafenib [11–13] and in second line after sorafenib failure [14–17]. Ten years passed before we had other effective drugs for advanced HCC: lenvatinib [18] demonstrated its non inferiority compared to

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sorafenib in first line, while regorafenib [19] and cabozantinib [20] were able to determine a survival improvement against placebo in second line after sorafenib. The scenario of systemic therapies in advanced HCC is rapidly evolving, and soon also nivolumab [21], ramucirumab [22] and pembrolizumab [23] could be approved in Europe.

Standard chemotherapy has never been proved effective in the treatment of HCC [24], either because of the refractoriness of the tumor or due to the coexistence of cirrhosis, which impairs both drug metabolism and reduces tolerability.

Capecitabine is an orally administered 5-Fluorouracil (5-FU) prodrug absorbed as an intact molecule via the gastrointestinal tract [25–27]. Thymidine phosphorylase, that is more expressed in tumor than in normal surrounding cells, promotes an enzymatic reaction generating 5-FU selectively in tumor tissue [25,27]. Capecitabine has been investigated in the treatment of advanced HCC using either a conventional [28–32] or a metronomic approach [33–38], with no definitive results in term of survival benefit. All those studies however proved the favorable tolerability profile of capecitabine, especially when metronomically administered. The concept of metronomic chemotherapy [39], defined as the chronic administration of chemotherapeutic agents at relatively low, minimally toxic doses, without drug free breaks, has been recently introduced in oncology. The main advantage is toxicity reduction, but metronomic administration seems also to improve antitumoral effect [39–45].

Metronomic chemotherapy is particularly appealing in patients with hepatocellular carcinoma, who are in most instances fragile and present low tolerability to chemotherapeutics. After the first pioneering work of Farrag et al. [33] on metronomic capecitabine in advanced HCC, a series of studies evaluated that treatment in both naïve and sorafenib-treated patients [34,35,37,38], confirming its safety and suggesting a role in providing a survival benefit.

This multicenter study aims to retrospectively evaluate the activity and the safety of capecitabine in a large group of patients with advanced hepatocellular carcinoma treated with different therapeutic schemes.

2. Materials and methods

2.1. Study population

We retrospectively analyzed the records of 168 patients with hepatocellular carcinoma treated with capecitabine between January 1st 2010 and December 31st 2017 in three centers part of Veneto Oncology Network: Padova University Hospital (Gastroenterology Unit), Istituto Oncologico Veneto IRCCS (Unit of Medical Oncology I, Padova) and Feltre Hospital (Medical Oncology Unit). One hundred forty-three patients (85.1%) were included in the study, while 25 (14.9%) were excluded for lack of follow-up data or for being treated with combination therapy (capecitabine + sorafenib or gemcitabine).

The baseline recorded characteristics of patients treated with capecitabine were: Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2, Child-Pugh score A or B, total serum bilirubin $\leq$3 mg/dL, platelets count $\geq 50 \times 10^9$/L, haemoglobin level $\geq$9 g/dL, white blood cell count $\geq 1.5 \times 10^9$/L, transaminases $\times$5 the upper normal level, creatinine $\leq$1.5 mg/dL, no ascites or ascites controlled by diuretics, encephalopathy $\leq$1 and no history of coronary disease or hearth failure.

Capecitabine was administered orally with two schemes: metronomic scheme (MS, capecitabine at the dosage of 1000 mg/day, continuously without drug-free breaks) and non-metronomic scheme (NMS, capecitabine at the dosage of 2000 mg/day administered for 14 days followed by 7 days of interval). NMS was used in oncologic setting, where medical oncologists applied conventional capecitabine scheme in patients with HCC who were more likely to tolerate it.

Patients stopped treatment either because of radiological and/or symptomatic progression of HCC (ECOG-PS $\geq$3, $\geq$2 unit increase of Child-Pugh score), or because of the occurrence of unacceptable toxicity. Several patients continued capecitabine despite proved radiological tumor progression because they were still receiving clinical benefit from the treatment. Drug-related adverse events (classified according to the National Cancer Institute Common Terminology Criteria for Adverse events, NCI-CTCAE version 4.03) were properly managed with supportive therapy, dose reduction or drug interruption.

Diagnosis of HCC was obtained according to European guidelines available at the time of diagnosis [46,47].

Before starting capecitabine treatment, HCC was staged by multiphase chest and abdomen CT scan or magnetic resonance according to the BCLC staging system [48]. Additional investigations were performed, when clinically indicated.

Patients underwent clinical follow-up every 2 months; for the first 2 months of treatment, patients were monitored with laboratory tests (blood count) every 15 days to assess the onset of early hematological AEs. Imaging exams (abdomen ultrasound, CT or MRI) were repeated every 2–3 months or more frequently when clinically indicated.

Tumor response was evaluated according to modified Response evaluation Criteria in Solid Tumor (mRECIST) [49]. In patients who had no imaging after capecitabine treatment (25 patients, 18%), the progression was defined according to biochemical (AFP) or clinical parameters.

All patients, at the beginning of treatment, signed a center specific informed consent agreeing to receive treatment and to the anonymized collection of their clinical data. The study was conducted in accordance to the ethical guidelines of the 1975 declaration of Helsinki.

2.2. Statistical analysis

Continuous data were expressed as mean $\pm$ standard deviation (SD) or median and intervals, while discrete variables as absolute value and relative frequency. Student's t test was used to compare continuous data, X^2 Pearson's test and Fisher's test to compare discrete data.

Overall survival (OS) was calculated from the date of the beginning of capecitabine treatment to death, with values censored at 2017 December 31st (end of the study) or at the last evaluation. Time to progression (TTP) was calculated from the date of the beginning of capecitabine treatment to the first evidence of cancer progression. OS and TTP were expressed in months as median values with 95% confidence interval (CI). Survival curves were estimated using Kaplan–Meier method and were compared with the Log-rank test.

To compare MS and NMS groups minimizing the confounding effects of the different distribution of baseline characteristics, a propensity score matching with the method of inverse probability weighting (IPWT) was performed. MS and NMS patients were matched for: presence of cirrhosis, etiology of liver disease, Child-Pugh score, ECOG-performance status, number of liver lesions, diameter of the largest liver lesion, presence of macrovascular invasion, presence of metastases, BCLC stage and line of capecitabine therapy. For variable balance assessment the standardized difference between the two groups and the variance ratio were used. For a proper balance in the variables, an absolute standardized difference $\leq$0.25 and a variance ratio between 0.5 and 2 were considered [50]. Kaplan–Meier method and log-rank tests were used to esti-

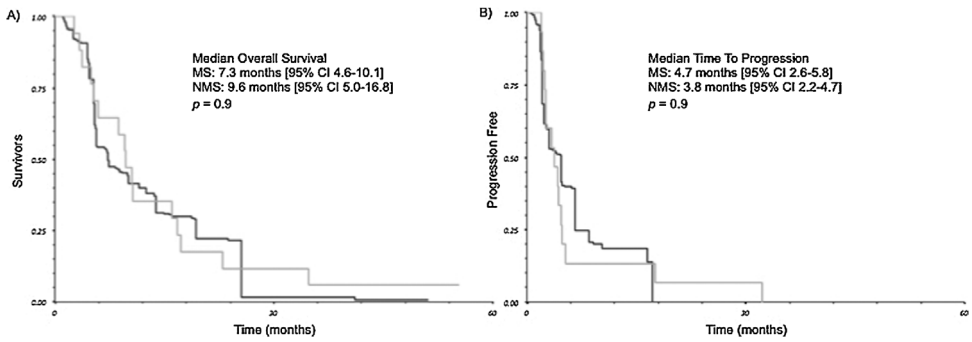

Fig. 1. (A) Overall survival of patients treated with metronomic scheme (black line) and non-metronomic scheme (grey line) after propensity score matching. (B) Time to Progression of patients treated with metronomic scheme (black line) and non-metronomic scheme (grey line) after propensity score matching (MS = metronomic scheme; NMS = non-metronomic scheme).

mate and compare the curves using the weights obtained with the IPWT method.

Variables associated with survival at the univariate analysis were included in the Cox multivariate regression model to establish the independent prognostic predictors.

Statistical significance was met with a 2-tailed p value < 0.05. All statistical analysis were performed using StatsDirect ver. 3.1.14-2017 (StastDirect Ltd, Cheshire, UK) and SAS/STAT® ver.14.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

The 143 patients were treated with capecitabine in first (30%), second (52%) and third line (18%). Capecitabine was administered instead of sorafenib in first line because of Child-Pugh B (30 pts, 70%), compromised clinical conditions (6 pts, 14%) and other contraindications to antiangiogenetics (7 pts, 16%). Among patients treated with capecitabine in second and third line, 21 (28%) and 3 (12%) were Child-Pugh B, respectively (Table 1).

Patients' biological, clinical and tumor characteristics are reported in Table 2. Of our cohort, 111 patients (78%) were treated with MS and 32 (22%) with NMS. Male sex accounted for approximately 80% in both groups while MS patients were slightly older than NMS. MS patients had more frequently HCC on a cirrhotic liver ($p = 0.0017$) and had more often a viral etiology of the underling liver disease ($p = 0.0026$). NMS patients had a better Child-Pugh score ($p = 0.02$), better ECOG-PS ($p < 0.0001$) and less advanced tumors, with smaller lesions ($p = 0.0002$) and less frequent macrovascular invasion ($p < 0.0001$). Lastly, NMS-treated patients had a better cancer stage according to the BCLC stage ($p = 0.0009$).

3.1. Survival analysis and response to treatment

Mean length of capecitabine treatment was 5.7 months [95% CI 4.1–7.3]. Patients treated with NMS received treatment for a significantly longer period of time (10.2 [95% CI 3.9–16.5] vs. 4.3 months [95% CI 3.4–5.2]; $p = 0.002$).

Considering the entire cohort, the median overall survival (OS) was 6.9 months [95% CI 5.7–8.1] and the median time to progression (TTP) was 2.8 months [95% CI 2.0–3.6]. The OS of patients treated in third line was 10.5 months [95% CI 5.3–15.6] vs. 5.4 [95% CI 3.0–7.8] and 6.8 months [95% CI 5.1–8.4] of those treated in first and second line, respectively ($p = 0.01$).

NMS-treated patients achieved a better OS, with a 10.5 [95% CI 7.2–13.7] versus 5.7 months [95% CI 4.0–7.3] survival ($p = 0.0005$). Patients subsequently treated with additional chemotherapy (i.e. gemcitabine or oxaliplatin) after capecitabine discontinuation had a median OS of 13.8 [95% CI 7.0–20.7] versus 4.7 months [95% CI 3.6–5.7] of patients undergoing BSC ($p < 0.0001$). Censoring the OS of these patients at the time of the new treatment, the survivals achieved for the NMS and MS treated patients were 6.0 months [95% CI 1.3–10.6] and 4.9 months [95% CI 3.8–5.9], respectively ($p = 0.03$).

Also the NMS time to progression (TTP) was significantly higher than that of MS: 3.9 months [95% CI 2.2–5.5] versus 2.5 months [95% CI 1.9–3.1] ($p = 0.03$).

In order to correctly compare the efficacy of MS and NMS, a propensity score analysis with the IPWT method was used to minimize the important differences between the two groups at baseline. After the balancing for the different prognostic characteristics of patients, the OS of MS and NMS patients were comparable (7.3 months [95% CI 4.6–10.1] vs. 9.6 months [95% CI 5.0–16.8], $p = 0.9$). Also the TTP was not significantly different between the two groups: 4.7 [95% CI 2.6–5.8] for MS and 3.8 months [95% CI 2.2–4.7] for NMS (p = 0.9) (Fig. 1).

The response to treatment was assessable in 138 patients (96.5%), because 5 (3.5%) had an early discontinuation due to AEs. The best response to treatment was: complete response (CR) in 2 patients (1.5%), partial response (PR) in 8 patients (5.8%) and stable disease (SD) in 30 patients (21.7%); the other 98 patients (71.0%) progressed during capecitabine treatment. The disease control rate (CR + PR + SD) was 29.0%. NMS guaranteed a better disease control rate than MS (38.8% vs. 26.2%; $p = 0.04$). The response to capecitabine, regardless of the scheme of treatment, correlated with survival: the OS was 5.4 months for progressive disease (PD) [95% CI 4.0–6.8], 9.2 months for SD [95% CI 3.9–14.5], 18.7 months for PR + CR [95% CI 1.9–39.4] ($p = 0.0002$).

Of the 90 patients previously treated with sorafenib, 57 (63%) discontinued sorafenib for PD and 33 (37%) for intolerance. A larger survival benefit occurred in those forced to suspend sorafenib due to intolerance compared to those with cancer progression (8.4 months [95% CI 6.0–10.8] vs. 5.0 months [95% CI 3.6–6.3], $p = 0.024$) (Fig. 2).

At univariate analysis variables associated with OS were Child-Pugh score, ECOG performance status, number of hepatic lesions and diameter of the largest one, presence of macrovascular invasion, BCLC stage, scheme of capecitabine treatment, response to treatment and additional therapy after capecitabine discontinuation. A multivariate analysis with the Cox model (log rank test) identified only number of hepatic lesions (<3; 3–5; >5) ($p = 0.002$) and therapy after capecitabine ($p = 0.03$) as independent prognostic factors.

A recent study by Giannini et al. [51] describes the "natural history" of patients with advanced hepatocellular carcinoma (BCLC C) undergoing BSC included in the ITA.LI.CA. database. The patients are subgrouped according to the clinical features determining their allocation (ECOG performance status [PS], macrovascular invasion [MVI], extrahepatic spread [EHS]). In our study we lack a control

Table 1
Systemic therapy and line of treatment with capecitabine; Child-Pugh class and ECOG-PS are shown in the lower part of the table according to the line of capecitabine treatment.

Systemic therapy					
		All patients	First-line	Second-line	Third-line
Sorafenib		90	87	3	0
Chemotherapy + RCTs[a]/experimental therapies		31	13	22[c]	0
Capecitabine		143	43	75	25
Child-Pugh class and ECOG-PS according to line of capecitabine treatment					
		First-line (43 pts)	Second-line (75 pts)	Third-line (25 pts)	
Child-Pugh	A	13 (30%)	54 (72%)	22 (88%)	
	B	30 (70%)	21 (28%)	3 (12%)	
ECOG-PS[b]	0	14 (33%)	32 (43%)	16 (64%)	
	1	23 (53%)	33 (44%)	9 (36%)	
	2	6 (14%)	10 (13%)	/	

[a] RCTs: Randomized clinical trials.
[b] ECOG-PS: Eastern cooperative oncology group – performance status.
[c] 4 patients underwent chemotherapy in first and second line.

Table 2
Patients' clinical, biological and tumoral characteristics, also according to their treatment schedule.

		All patients 143 (100%)	MS[a] 111 (78%)	NMS[b] 32 (22%)	*p*
Sex	M	113 (79)	87 (78)	26 (81)	0.5993
	F	30 (21)	24 (22)	6 (19)	
Age (mean ± SD)		65.8 ± 10.9	66.7 ± 10.0	62.6 ± 13.0	0.0546
Cirrhosis	Yes	112 (78)	92 (83)	20 (61)	0.0017
	No	13 (9)	9 (8)	4 (13)	
	HCC post-LT[c]	18 (13)	10 (9)	8 (26)	
Etiology	Alcohol	36 (25)	23 (21)	13 (41)	0.0026
	HBV	12 (8)	8 (7)	4 (12)	
	HCV	57 (40)	48 (43)	9 (28)	
	Other causes	14 (10)	13 (12)	1 (3)	
	Multiple causes	24 (17)	19 (17)	5 (16)	
Child-Pugh score	A	89 (62)	65 (59)	24 (75)	0.02
	B	54 (38)	46 (41)	8 (25)	
ECOG[d] Performance Status	0	65 (46)	37 (33)	28 (86)	<0.0001
	1	62 (43)	59 (53)	3 (10)	
	2	16 (11)	15 (14)	1 (4)	
Number of hepatic lesions	<3	46 (32)	33 (30)	13 (40)	0.1827
	3–5	15 (10)	11 (10)	4 (13)	
	>5	82 (58)	67 (60)	15 (47)	
Diameter of the largest hepatic lesion (cm)	< 3	44 (31)	28 (25)	16 (50)	0.0002
	3–5	35 (24)	27 (24)	8 (25)	
	>5	64 (45)	56 (51)	8 (25)	
Macrovascular invasion	Yes	56 (39)	50 (45)	6 (18)	<0.0001
	No	87 (61)	61 (55)	26 (82)	
Extrahepatic spread	Yes	74 (52)	54 (49)	20 (63)	0.046
	No	69 (48)	57 (51)	12 (37)	
BCLC[e] stage	B	12 (8.5)	5 (4.5)	7 (22)	0.0009
	C	130 (91)	105 (94.5)	25 (78)	
	D	1 (0.5)	1 (1)	0 (0)	

[a] MS: Metronomic scheme.
[b] NMS: Non metronomic scheme.
[c] LT: liver transplant.
[d] ECOG: Eastern oncology cooperative group.
[e] BCLC: Barcelona clinic liver cancer.

group of BSC patients, and we therefore compared the survival of our patients with those reported in the paper by Giannini et al. and depicted in Table 3. Albeit obviously lacking a statistical comparison, the table shows slightly higher survival for capecitabine treated patients. The comparison of the PS1 and PS2 patients is lacking given the limited number of patients belonging to these subgroups.

3.2. Safety

Table 4 reports the adverse events emerged during capecitabine treatment, categorized according to the NCI-CTCAE v 4.03. Overall, 105 patients (73%) experienced at least one AEs of any grade during treatment: 57% had a grade 1–2 AE while 16% a grade 3–4 AE. Main drug-related AEs were thrombocytopenia (38%), anemia (34%), fatigue (22%), leucopenia (18%). Abdominal pain, dyspnea, hand-foot skin reaction, nausea/vomiting, diarrhea and mucositis were reported. Drug-related AEs were in most cases mild and were properly managed. In 11 patients (8%) an AE led to treatment discontinuation, in particular: 3 patients for anemia, 3 for intolerable fatigue, 2 for thrombocytopenia and 1 patient each for acute kidney injury, cholangitis and pulmonary embolism. No treatment-related deaths were recorded.

AEs were slightly, but not significantly, more frequent in NMS group: 26 NMS patients (81%) developed AEs versus 80 MS patients

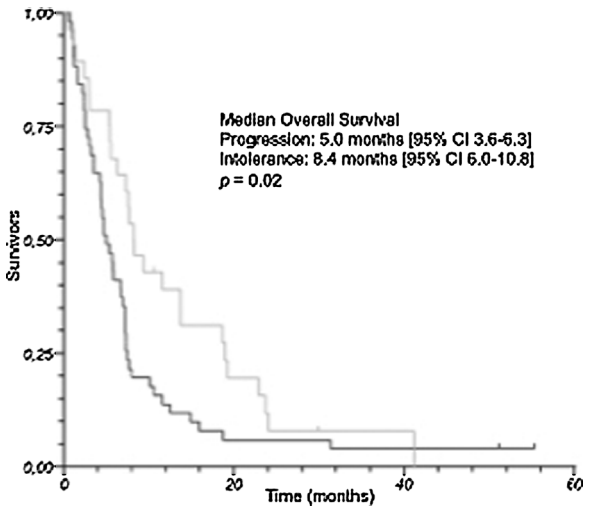

Fig. 2. Overall survival of capecitabine treated patients according to causes of sorafenib discontinuation, disease progression (black line) or intolerance (grey line).

Table 3
Comparison between BCLC-C patients treated with best supportive care (Giannini et al. [51]) and our group of BCLC-C patients treated with capecitabine.

BCLC[a] C patients	Survival (months) in BCLC C patients of *Giannini et al.*	Survival (months) in our BCLC C group of capecitabine treated patients (130)
PS[b] 1	13.2	/
PS 2	11.2	/
MVI[c]	4.0	7.0
EHS[d]	5.2	7.2
MVI + EHS	2.0	3.5

[a] BCLC: Barcelona clinic liver cancer.
[b] PS: Performance status.
[c] MVI: Macrovascular invasion.
[d] EHS: Extrahepatic spread.

(72%) ($p = 0.133$). Grade 3–4 AEs more often occurred in MS patients (14% vs. 6%; $p = 0.059$).

4. Discussion

Treatment of advanced HCC still represents a difficult issue, mainly due to lack of therapeutic alternatives, given that, at least in Europe, we have only few approved systemic drugs: sorafenib in first line, regorafenib and cabozantinib in second line [10,19,20]. Regorafenib has been approved very recently for patients with tumor progression but tolerant to sorafenib. However, a relatively large share of patients (30–40%) is intolerant to sorafenib [7–9] and in these patients only cabozantinib could be an option. Beyond these drugs, other therapeutic alternatives are approaching the market: (lenvatinib [18], nivolumab [21], ramucirumab [22], pembrolizumab [23]), but they have still to be approved.

A large number of studies evaluated capecitabine treatment in advanced HCC [28–38]. All these studies demonstrated the tolerability of capecitabine, even in patients with slightly impaired hepatic function and the potential activity of the drug in prolonging HCC patients' survival.

In our study, we retrospectively analyzed the largest series of patients treated with capecitabine: the median OS was 6.9 months and the median TTP was 2.8 months. These results are in line with those previously reported by our group in a smaller series [36], with a shorter survival compared to the literature [34,35,37,38]. The explanation for the shorter median survival lies in the more advanced liver disease of our group of patients (38% of patients had a Child-Pugh score of B, 54% had an ECOG-PS 1–2, 68% had $\geq$3 hepatic lesions, 39% had MVI and 52% EHS).

To the best of our knowledge, the conventional and the metronomic scheme have never been compared, even retrospectively. NMS and MS patients in our cohort not only differed markedly in the sample size, but also in their baseline characteristics: patients treated with the NMS had better liver functional reserve, better clinical conditions and less advanced tumors. Without correction, NMS seems to achieve better results in terms of survival, but after balancing the two groups for the different prognostic characteristics with a IPWT propensity score analysis, no differences in term of efficacy were found between the two groups (median OS of 7.3 vs. 9.6 months ($p = 0.9$); median TTP of 4.7 vs. 3.8 months ($p = 0.9$)).

Post-capecitabine treatments could influence overall survival. Patients treated with additional systemic chemotherapy after capecitabine discontinuation had a better survival than BSC patients (13.8 vs. 4.7 months; $p < 0.0001$). These patients, mostly belonging to the NMS subgroup (53% versus 15% for MS), were apparently fit enough to be treated with additional therapies that prolonged their survival. The impact of the additional therapies was evaluated censoring the OS of patients treated after capecitabine at the time of the new treatment; in this way the median OS was 6.0 months for NMS group vs. 4.9 months for MS group ($p = 0.03$).

A correlation between response to treatment and survival was observed: patients with complete or partial response had a better survival than patients with stable or progressive disease (18.7 months for PR + CR vs. 9.2 months for SD vs. 5.4 months for PD; $p = 0.0002$).

In our study, we confirmed the findings of the paper by Trevisani et al. [38]: in patients previously treated with sorafenib, the

Table 4
Adverse events of capecitabine treatment categorized according to the National Cancer Institute, Common Terminology Criteria for Adverse Events classification version 4.03.

Adverse events	Any grade [Number (%)]	Grade 1–2 [Number (%)]	Grade 3–4 [Number (%)]
Overall	105 (73)	82 (57)	23 (16)
Leucopenia	26 (18)	25 (16.3)	1 (0.7)
Thrombocytopenia	54 (38)	50 (35)	4 (3)
Anemia	48 (34)	40 (28)	8 (6)
Fatigue	32 (22)	26 (18)	6 (4)
HFS	5 (3)	5 (3)	/
Nausea/vomiting	5 (3)	5 (3)	/
Abdominal pain	9 (6)	9 (6)	/
Dyspnea	7 (5)	7 (5)	/
Diarrhea	3 (2)	3 (2)	/
Mucositis	3 (2)	3 (2)	/
Pulmonary embolism	1 (0.7)	/	1 (0.7)
Acute kidney injury	1 (0.7)	/	1 (0.7)
Cholangitis	1 (0.7)	/	1 (0.7)
Hypoglycemia	1 (0.7)	/	1 (0.7)

greater survival benefit was observed in intolerant patients compared to those with tumor progression (8.4 months vs. 5.0 months; $p = 0.024$). This finding is more relevant if we consider that the only option for patients intolerant to sorafenib is cabozantinib.

Our population of patients has been treated with capecitabine in second-line after sorafenib, in third-line after sorafenib and other chemotherapeutic or experimental drugs (RCTs) and even in first-line for patients that could not be alternatively treated. The longer survival of patients treated in third-line could be again potentially explained by the fact that patients previously treated with sorafenib and included in RCTs, had probably better liver function or slow tumor progression. The higher survival of these patients could be due to the intrinsic characteristics of liver tumor and of cirrhosis, rather than the activity of capecitabine itself.

Capecitabine proved to be a safe option in every study investigating its role in advanced HCC [28,34,35,37,38], even in patients with moderately impaired liver function. Having a therapeutic option for these patients is extremely important because no systemic treatment is currently or will be soon available for advanced HCC patients with impaired liver function (Child-Pugh B). Recently, a paper by De Lorenzo et al. [52] evaluated activity and safety of metronomic capecitabine in a cohort of Child-Pugh B patients, also concluding in favour of the safety and efficacy of the drug.

Despite a higher rate of adverse events compared to other studies [35,37] (73% of patients experienced at least one AEs), these were mainly mild (grade 1–2 in 56% and grade 3–4 in only 16%) and easily manageable. No treatment-related death was observed and only in 11 patients (8%) the treatment was discontinued for AEs. The higher rate of grade 3–4 adverse events in MS group (MS 14% vs. NMS 6%) can be due to the worse liver function and/or clinical condition of these patients. Nature of adverse events recorded in our study was comparable to that reported in literature [35,37,38], even though with a higher rate of haematological problems. The mean length of treatment in our cohort (5.7 months) confirms once more the tolerability of capecitabine.

Lastly, it should not be forgotten that capecitabine is an inexpensive treatment and represent an alternative for advanced HCC easily sustainable by most National Health Systems.

Our study has several limitations, the first of which is its retrospective nature that may have introduced unintentional biases in the analysis. The study population, although the largest in literature at present, is very heterogeneous and this obviously may affect the results interpretation. Despite this, our population offers a "real-world" image of the management of patients with advanced HCC, covering most of the clinical situations we are facing in everyday clinical practice.

Another limit of our study is the lack of a control group of patients treated with BSC. The indirect comparison of survivals in our series with that of patients with advanced HCC undergoing BSC belonging to the ITA.LI.CA database [51], seems to suggest that capecitabine could potentially represent an active treatment.

In conclusion, the results obtained in our large retrospective study are in line with what previously reported in literature regarding efficacy and safety of capecitabine in advanced hepatocellular carcinoma. Metronomic and non-metronomic schemes seem to be equally effective in treatment of advanced HCC. The indirect comparison with the BSC treated ITA.LI.CA patients confirms that capecitabine could be a reasonable option in patients who are not candidate for other treatments. Patients stopping sorafenib for intolerance is the group in whom capecitabine is more active. Capecitabine confirmed to be a well tolerated and a safe treatment in patients with advanced HCC, also in those with impaired liver function. These results need to be confirmed through adequately planned trials, in order to establish the precise role of capecitabine in the therapeutic management of patients with advanced HCC in relation to sorafenib and other emerging systemic targeted therapies.

Conflict of interest

None declared.

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