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Metronomic capecitabine as maintenance in treatment of hepatocellular carcinoma after localized intervention

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Background
Hepatocellular carcinoma (HCC) accounts for between 85 and 90% of primary liver cancer. Surgery is considered curative treatment; however, local ablative technique has a high rate of recurrence. Different attempts are being tried to decrease time of recurrence with less side effects and toxicities. Metronomic chemotherapy is an emerging method of treatment with less side effects and good tolerability.

Objectives
The aim of the study was to evaluate the effect and toxicity of metronomic capecitabine in HCC patients after localized intervention.

Material and methods
This study included 30 patients with HCC who have been treated with locoregional interference (tranarterial chemoembolization, radiofrequency, or both) and have got complete response (CR) or partial response (PR). The patients were selected from the clinical oncology department, faculty of medicine, Menoufyia University; they received capecitabine 1000 mg/day continuously. Patient characteristics, disease-free survival, time to progression, effect of primary localized intervention on the outcome, and toxicity were evaluated using univariate and multivariable analysis.

Results
Most patients were men with mean age of 54 years and hepatitis C virus positive (73%). Median disease-free survival was 8 months for patients who had CR after localized interference. Median time to progression was 8 and 4.4 months for CR and PR patients, respectively, which was statistically significant ($P = 0.001$). No grade IV toxicity was found. Grade III toxicity was hepatic toxicity (hyperbilirubinemia) and was found in three patients (10%); renal toxicity (elevated creatinine and urea) was found in one patient (3.3%); and one patient stopped due to deterioration of general condition. The most common hematological toxicity was thrombocytopenia grade I (50%) of the studied group. Four patients stopped treatment due to persistent grade III toxicity and one stopped it due to deteriorated performance. Effect of the initial response to localized treatment or the type of this localized intervention on the end outcome was insignificant.

Conclusion
Metronomic capecitabine has a modest antitumor efficacy on HCC patients in CR or PR after localized intervention. However, because of its low toxicity profile, it deserves further attention as a convenient, outpatient-based chemotherapy regimen. We recommend more randomized controlled trials and phase III trials with comparative arm in larger populations.

Keywords:
capecitabine, hepatocellular carcinoma, metronomic

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Introduction

Hepatocellular carcinoma (HCC) is one area of oncology warranting further investigation. Although liver cancer is the fourth most common neoplasm worldwide, its very poor prognosis makes it the third leading cause of cancer-related mortality, responsible for ~600 000 deaths annually [1].

High-incidence regions (>15 cases/100 000 populations/year) include sub-Saharan Africa, the People's Republic of China, Hong Kong, and Taiwan. The incidence is 24.2/100 000 in parts of Africa and 35.5/100 000 in Eastern Asia. Over 40% of all cases of HCC occur in the People's Republic of China, which has an annual incidence of 137 000 cases. Japan has had one of the highest incidence rates of HCC associated with chronic hepatitis C virus (HCV) infection; however, the incidence appears to be decreasing in recent years [2].

Incidence of HCC in Egypt is currently increasing, which may be the result of a shift in the relative importance of HBV and HCV as primary risk factors. HCC is the second most frequent cause of cancer incidence and mortality among men in Egypt. Hospital-based studies

from Egypt have reported an increase in the relative frequency of all liver-related cancers (>95% as HCC), from ~4.0% in 1993 to 7.3% in 2003. To explain this trend, it is necessary to understand the dynamics of HBV and HCV in Egypt [3].

Radical treatments include surgery, local destruction techniques (radiofrequency ablation or percutaneous ethanol injection), and liver transplantation. There are no randomized trials comparing the efficacy of these three approaches, and all evidence is based on cure rates in patient series. The results of these local ablative techniques are also hampered by disease recurrence, varying between 4 and 60% depending on the size of the tumor and the approach used (higher risk in percutaneous than laparoscopic series) [4].

Despite extensive efforts by many investigators, systemic chemotherapy for HCC has been quite ineffective, as evidenced by low response rates and no demonstrated survival benefit. Although many molecular changes have been identified in HCC, we are just beginning to identify the key molecular pathways involved in hepatocarcinogenesis and to assess the relevance of these as potential therapeutic targets [5].

Many studies were conducted exploring the role of capecitabine in treatment of different types of cancer including HCC. Capecitabine was found to be safe for treatment of patients with HCC, including those with compensated cirrhosis. However, the objective response rate was limited [6].

Metronomic chemotherapy was then defined as the chronic administration of chemotherapeutic agents at relatively low, minimally toxic doses, and with no prolonged drug-free breaks. It is thought that this type of chemotherapy inhibits tumor growth primarily through antiangiogenic mechanisms while significantly reducing undesirable toxic side effects [7].

Material and methods

The present study enrolled 30 patients during the period between October 2011 and October 2013 in Menoufyia department of clinical oncology and nuclear medicine. They were radiologically diagnosed HCC and underwent localized intervention [RF, Tnf A Converting Enzyme (TACE), or both] and had partial response (PR) or complete response (CR). They were chosen according to the eligibility criteria included: patients aged 18–70 years, Child-Pugh class A and B, acceptable renal function and hematological parameters, no prior chemotherapy was given, Eastern Cooperative Oncology Group performance status 2 or less, and written consent. They were allowed to continue on continuous low-dose oral capecitabine (1000 mg/m^2) daily until toxicity that prevents treatment or progression. The primary end point of the study was disease-free survival (DFS) (time from CR until progression), and the secondary end point was time to progression (TTP) (time from response to initial localized treatment until disease progression) safety profile. Effect of initial localized intervention on the outcome and effect of the type of localized intervention were also studied. All patients were assessed every month by performing live enzymes tests, serum albumin, serum bilirubin, INR, kidney function, and complete blood picture. Computed tomography was performed every 2 months to assess the patients. Toxicity was assessed by Eastern Cooperative Oncology Group common toxicity criteria toxicity criteria version 2.

Statistical analysis

Data were analyzed using statistical Package for social science program for windows version 20 (IBM Corporation, Armonk, New York, United States). Two types of statistics were performed: descriptive and analytic. The χ^2-test and Fisher's exact test were performed. Progression-free survival and TTP were analyzed using the Kaplan–Meier curve. *P*-value of less than 0.05 was considered statistically significant.

Results

The mean age of the studied patients was 54 years ranging between 45 and 61 years with male predominance representing (26 patients) 86.67% of patients.

The presence of comorbid conditions was studied. Most of the studied patients were HCV positive 73.33% (22 patients). Diabetes mellitus was found in 26.69% of the cases (eight patients) (Table 1).

All patients received a minimum of 2 months of treatment and a maximum of 10 months, with median duration of 5 months. DFS was estimated for patients who had CR to initial intervention with median 8 months (Fig. 1, Kaplan–Meier curve).

Time to disease progression or recurrence was estimated for patient with CR, PR to initial intervention with median time for CR patient 8 months, and for PR patients 4.4 months, which was statistically significant ($P = 0.001$) (Table 2) (Fig. 2, Kaplan–Meier curve).

Analysis of the effect of initial response to localized treatment whether CR or PR and outcome of the study at the end of follow-up period were not statistically significant ($P = 0.473$) (Table 3, Fig. 3).

Analysis of the effect of the initial localized treatment (RF alone or TACE alone or combination of both) with respect to the outcome at the end of the study was performed using Fisher's exact test. It was not significant (Tables 4–6 and Figs. 4–6).

One patient stopped treatment due to deterioration of the general condition.

No grade IV toxicity was found. Grade III toxicity occurred in the form of hepatic toxicity (hyperbilirubinemia) in 10% of the patients (three patients) and renal toxicity (elevated serum urea) in one patient representing 3.3% (one patient). These four patients stopped the treatment. The most common hematological toxicity as seen from the table was thrombocytopenia (grade I) patients (50%) of the studied group (Tables 7–9).

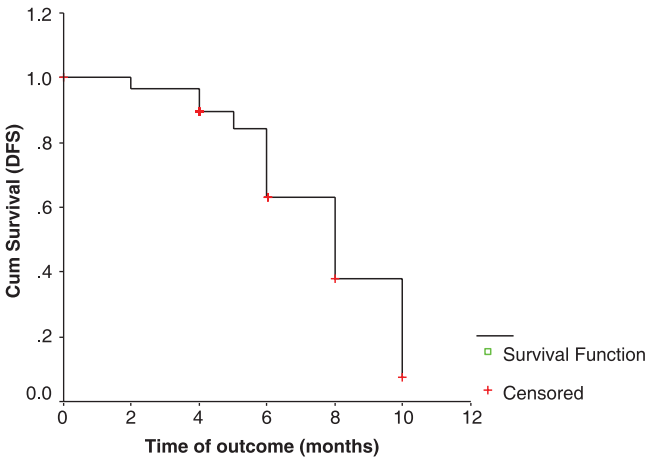
Discussion

HCC is a highly malignant tumor characterized by active neovascularization. It is considered as an intrinsically chemotherapy refractory malignancy [8].

Metronomic chemotherapy, which was originally designed to inhibit angiogenesis, is being tried as a therapeutic option [9].

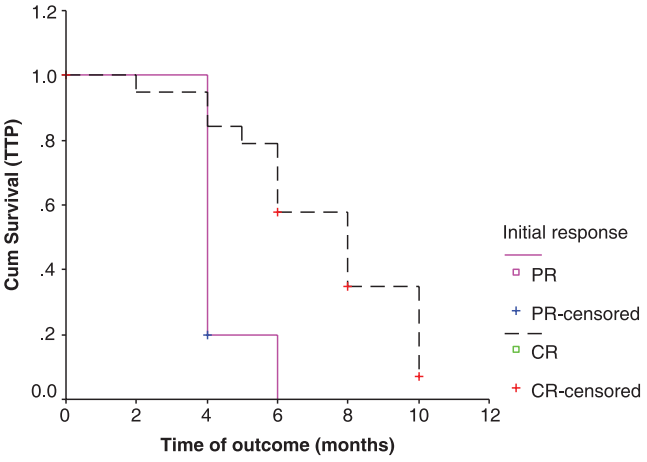
Farrag [10] studied capecitabine with the same metronomic dose given to 22 patients with metastatic HCC for 14 days in cycles repeated every 21 days. The median number of cycles was three ranging from one to nice cycles, whereas in our study the median number of months was 5, ranging 2–10 months. TTP was for all evaluable patients 2.2 months

Figure 1



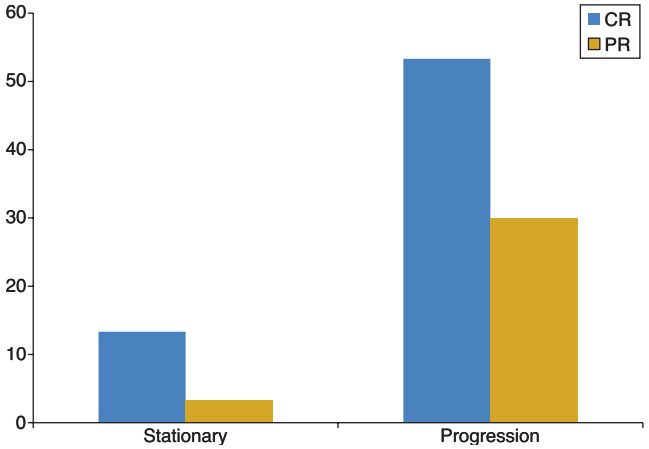
Disease-free survival (DFS) curve in patients with complete response after localized treatment (Kaplan–Meier curve).

Figure 2



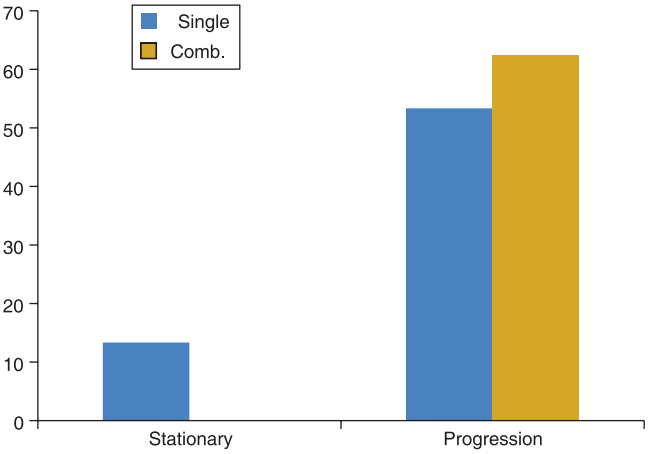
Time to disease progression or recurrence to partial response (PR) or complete response (CR) patients, respectively, as an initial response at the end of the study period (Kaplan–Meier method).

Figure 3



Evaluation of the effect of initial response to localized treatment [complete response (CR), partial response (PR)] and the outcome (stationary disease or progression) at the end of follow-up period.

Figure 4



Single and combined radiofrequency (% of patients in vertical line) with respect to outcome (stationary or progression) at the end of the follow-up period.

Table 1 Characteristics of patients during the study period

Tested paramters	*N* (%)
Child	
Child A	7 (23.33)
Child B	23 (76.67)
Sex	
Male	26 (86.67)
Female	4 (13.33)
Initial response	
CR	20 (66.67)
PR	10 (33.33)
Comorbidities	
DM	8 (26.67)
HTN	5 (16.67)
IHD	2 (6.67)
HCV	22 (73.33)
HBV	5 (16.67)
B	3 (10.00)
Comorbidity	29 (96.67)

B, bilharziasis; CR, complete response; DM, diabetis mellitus; HCV, hepatitis C virus; HTN, hypertention; IHD, ischemic heart disease; PR, partial response.

Table 2 Median time to disease progression in the studied group

Tested paramters	Median	SE	Log rank	*P*-value
CR	8	0.97	11.030	0.001
PR	4.4	0.27		

CR, complete response; PR, partial response.

Table 3 Evaluation of initial response to localized treatment with respect to outcome at the end of follow-up period (stationary or progression)

Response to initial localized treatment	Outcome [*N* (%)]			χ^2	*P*-value
	Stationary	Progression	Total		
CR	4 (13.33)	16 (53.33)	20 (66.67)	0.516	0.473
PR	1 (3.33)	9 (30.00)	10 (33.33)		
Total	5 (16.67)	25 (83.33)	30 (100.00)		

CR, complete response; PR, partial response.

Table 4 Correlation between radiofrequency as a model of initial localized treatment alone or combined with TACE with respect to outcome at the end of follow-up period

RF	Outcome [*N* (%)]		
	Stationary	Progression	Total
Single	3 (100.00)	3 (37.50)	6 (54.55)
Combined	0[a] (0.00[b])	5 (62.50)	5 (45.45)
Total	3 (100.00)	8 (100.00)	11 (100.00)
Fisher's exact test		0.121	

RF, radiofrequency. [a,b]There was no patient with combined initial treatment (RF and TACE) who had stationary disease by the end of follow-up period.

Table 5 Correlation between TACE as a model of initial localized treatment alone or combined with radiofrequency with respect to outcome at the end of follow-up period

TACE	Outcome [*N* (%)]		
	Stationary	Progression	Total
Single	2 (100.00)	17 (77.27)	19 (79.17)
Combined	0[a] (0.00[b])	5 (22.73)	5 (20.83)
Total	2 (100.00)	22 (100.00)	24 (100.00)
Fisher's exact test		0.620	

RF, radiofrequency. [a,b]There was no patient with combined initial treatment (RF and TACE) who had stationary disease by the end of follow-up period.

Table 6 Correlation between initial treatment (TACE or RF) combined and single with respect to outcome at the end of follow-up period

Combined	Outcome [*N* (%)]		
	Stationary	Progression	Total
No	5 (100.00)	20 (80.00)	25 (83.33)
Yes	0[a] (0.00[b])	5 (20.00)	5 (16.67)
Total	5 (100.00)	25 (100.00)	30 (100.00)
Fisher's exact test		0.373	

RF, radiofrequency. [a,b]There was no patient with combined initial treatment (RF and TACE) who had stationary disease by the end of follow-up period.

Table 7 Hematological toxicity during the treatment period

Type	Grades [*N* (%)]	
	G1	G2
Thrombocytopenia	15 (50)	4 (13.3)
Anemia	6 (20)	3 (10)
Leucopenia	1 (3.3)	0

Table 8 Renal toxicity during treatment period

Type	Grades [*N* (%)]	
	G2	G3
Elevated serum creatinine	0	1 (3.33)
Elevated serum urea	0	1 (3.33)

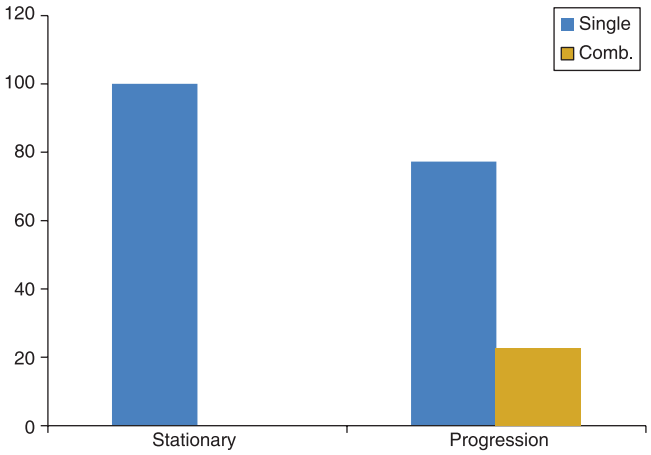
Table 9 Hepatic toxicity during treatment period

Types	Grades [*N* (%)]		
	G1	G2	G3
Elevated serum SGOT, SGPT	6 (20)	0	0
Elevated serum bilirubin	0	4 (13.3)	3 (10)
Decreased serum albumin	1 (3.33)	4 (13.3)	0
Elevated serum INR	0	2 (6.66)	0

Median = 8; SE = 0.97. SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

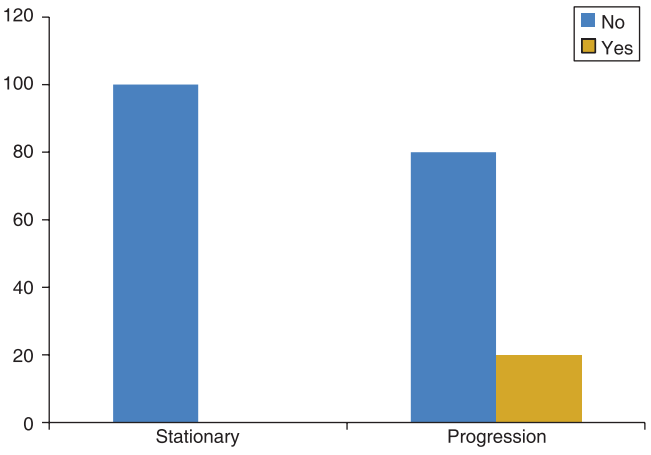
compared with the current study in which it was 4.4 months for PR patients and 8 months for CR patients. This could be explained as his patients had advanced metastatic HCC. Regarding toxicity in Farrag study, no grade III/IV hematological toxic effects were observed. Nonhematological toxic effects included grade III vomiting and diarrhea in one patient and grade III hand–foot syndrome in one patient. There was no treatment-related mortality. Compared with the current study, there were three cases of grade III nonhematological toxicity; there was cases of hand and foot syndrome or drug-related mortality, and there was one case of stopping treatment due to fatigue and deterioration of performance status. He concluded that

Figure 5



Single and combined TACE (% of patients in vertical line) with respect to outcome (stationary or progression) at the end of follow-up period.

Figure 6



Combined and single initial treatment (% of patients in vertical line) with respect to outcome (stationary or progression) at the end of follow-up period.

metronomic chemotherapy has a modest antitumor efficacy in patients with advanced HCC. These results are similar to most chemotherapeutic agents. However, due to its low toxicity profile, it deserves further studies [10].

In a study by Brandi *et al.* [11], they gave capecitabine with the same dose 1000 mg/day (14 days continuous then 7 days rest and the cycle repeated every 21 days) to 61 patients; in child A unresectable HCC patients, the median TTP was 7.45 months and median OS was 12.94 months. However, in the current study, the median DFS for CR patients was 8 months and the TTP was 4.4 and 8 months for PR and CR patients, respectively. As for toxicities in the study by Brandi *et al.* [11], there were grade III or IV drug-related toxicities thrombocytopenia in patients starting with low baseline platelet, hypertransaminasemia, and hyperbilirubinemia, although the patients were child A but with advanced liver disease. However, in the current study, there was no grade IV toxicity and the toxicities occurring were minimal, which is in agreement with the toxicity profile in different similar studies using metronomic chemotherapy, although there were four patients who stopped treatment due to persistent grade III toxicity, which is due to the combined effect of decompensated liver disease and treatment. It was in the form of hepatic toxicity (hyperbilirubinemia) and renal toxicity (elevated serum urea) [11].

However, in the study conducted by Patt *et al.* [12], they treated 63 patients with nonresectable hepatobiliary carcinoma including nonresectable HCC (37 patients) 11%, cholangiocarcinoma, and gall bladder carcinoma. Patients with HCC were child A or B; some of them had cirrhosis, which is similar to patient characteristics in the current study. The median survival time was 10.1 months for patients with HCC. Patt *et al.* [12] had a better response as they had a CR radiologically confirmed in one patient with HCC and in two patients with GBC. The most common toxicity was hand–foot syndrome (37%). Grade III thrombocytopenia occurred in 8% of patients with HCC. No other significant toxicities were observed. Comparing toxicity profile, grade I and II hand–foot syndrome were the most common side effect, followed by grade I or II nausea, emesis, and fatigue. Grade III thrombocytopenia occurred in 8% of patients with HCC. Other toxic effects were mild. All toxic effects were reversible. Dose adjustments to 25% reduction were required for patients with HCC. All toxicities were related to treatment. As in our study there were no cases of hand and foot syndrome, no dose adjustment was needed. Grade III thrombocytopenia did not occur; only grade I and II occurred. However, we had four patients stopping treatment due to persistent grade III toxicity as mentioned earlier [12].

Metronomic capecitabine has a modest antitumor efficacy on HCC patients in CR or PR after localized intervention whether TACE or RF or both. These results are similar to most chemotherapeutic agents. However, because of its low toxicity profile as no high-grade toxicity was observed, it deserves further attention as a convenient, outpatient-based chemotherapy regimen.

Conclusion

To confirm the therapeutic efficacy and safety of metronomic chemotherapy in patients with HCC, we recommend more randomized controlled trials

and phase III trials with comparative arm in larger populations.

Conflicts of interest

There are no conflicts of interest.

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