Clinical Activity of Metronomic Chemotherapy in Liver Cancers

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Abstract

Treating advanced hepatocellular carcinoma (HCC) remains challenging in clinical practice. Although sorafenib, an antiangiogenic targeted compound, has demonstrated survival benefits as a first-line therapy, the response rate and time to progression are not optimal. Metronomic chemotherapy has demonstrated antiangiogenic effects, and its reduced potential for toxicity renders it more tolerable to most advanced HCC patients. Clinical trials and retrospective studies have examined the use of metronomic chemotherapy, either alone or in combination with other antiangiogenic therapies, for treating advanced HCC. These studies have confirmed the feasibility and safety of metronomic therapy in patients with advanced HCC. Although objective responses were achieved using metronomic chemotherapy alone, it is difficult to discern the actual clinical benefits because of the small sample sizes of these studies. Nevertheless, metronomic chemotherapy can serve as a treatment option for advanced HCC patients who have progressed on or are intolerable to the standard therapy, sorafenib. In single-arm phase II clinical trials, combining metronomic chemotherapy with antiangiogenic targeted therapy has demonstrated improved efficacy for treating advanced HCC without increasing toxicities. Further research is warranted to confirm the benefits of combining metronomic chemotherapy with antiangiogenic targeted therapy for treating advanced HCC.

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13.1 Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the second leading cause of cancer-related mortality worldwide [1]. In areas with a high prevalence of viral hepatitis, HCC has become the leading cause of cancer-related deaths in recent decades. Localized HCC can be cured by resection, local ablation therapies, or liver transplantation [2]. Unfortunately, the majority of localized HCCs develop recurrent or metastatic disease that is no longer treatable by locoregional therapies.

Advanced HCC is defined as locally advanced or metastatic HCC that is no longer amenable to locoregional therapies. Systemic therapy is indicated for advanced HCC. However, cytotoxic chemotherapy, which has been the major type of cancer therapy used in previous years, has been shown to be ineffective for advanced HCC [3–6]. Furthermore, most advanced HCC patients are not amenable to conventional cytotoxic chemotherapy because of cytopenia and diminished liver function caused by chronic hepatitis and cirrhosis.

Such a disappointing condition has changed since 2008. Two large randomized phase III trials have demonstrated that sorafenib, compared to a placebo, improved overall survival in patients with advanced HCC [7, 8]. Sorafenib is a multi-kinase inhibitor that targets the vascular endothelial growth factor (VEGF) receptor and Raf kinase [9], through which it inhibits angiogenesis and cancer cell proliferation. Because sorafenib has clearly demonstrated clinical benefits in treating advanced HCC, it became the first ever and remained the only therapeutic agent approved for the treatment of advanced HCC.

13.2 Challenges in Treating Advanced HCC

However, the efficacy of sorafenib in advanced HCC is modest [7, 8]. The objective tumor response rate of sorafenib is 2–3 %, and the disease stabilization rates range from 34 to 43 % [7, 8]. In a randomized phase III trial conducted in East Asia, the median time to progression for patients with advanced HCC treated with sorafenib as a first-line therapy was only 2.8 months [7]. Thus, improving the efficacy of sorafenib and developing novel therapeutics are crucial for improving systemic therapy for advanced HCC.

However, despite continued efforts, none of the new multi-kinase inhibitors or new classes of targeted therapy have shown improved efficacy in treating advanced HCC. In large-scale randomized phase III trials, sunitinib, brivanib, and linifanib have failed to demonstrate greater clinical benefits as a first-line treatment for advanced HCC than sorafenib has [10–12]. In patients for whom sorafenib had failed, brivanib and everolimus have also failed to show significant survival benefits [13, 14]. Recently, large-scale next generation sequencing analyses of HCC cells were performed [15–18]. However, although a more comprehensive view of the genetic alterations that occur in HCC has begun to emerge, these findings have not yet led to the development of new therapeutic strategies for HCC.

13.3 Scientific Basis and Advantages of Metronomic Chemotherapy for Advanced HCC

Antiangiogenic therapy is considered vital for treating advanced HCC, which is most often characterized by hypervascularity. The imaging findings regarding vascularity are included in the clinical diagnostic criteria of HCC [19]. The only approved treatment for advanced HCC, sorafenib, produces antiangiogenic effects by blocking the VEGF receptor. Other antiangiogenic compounds, such as bevacizumab, sunitinib, and brivanib, have also demonstrated some efficacy in advanced HCC [20–25].

Metronomic chemotherapy refers to administering chemotherapeutics at doses significantly less than the maximum-tolerated dose (MTD), on frequent dosing intervals, for a prolonged period [26]. Preclinical models have demonstrated the antiangiogenic activity of metronomic chemotherapy [27, 28]. In animal studies, metronomic chemotherapy can suppress tumor growth, inhibit distant metastasis, prolong survival, and diminish tumor angiogenesis [29–31]. Combining antiangiogenic targeted therapy with metronomic chemotherapy may improve outcome further. Animal studies have demonstrated that combination therapy inhibited tumor growth, prolonged survival, and delayed resistance to antiangiogenic therapy [32–35]. Thus, metronomic chemotherapy, either alone or in combination with antiangiogenic targeted therapy, may be considered a treatment option for advanced HCC.

A potential advantage of metronomic chemotherapy is minimal bone marrow toxicity, which improves tolerance among patients. Patients with advanced HCC often have cirrhosis of the liver caused by chronic liver disease, which frequently results in cytopenia and impaired organ function. Patients with advanced HCC are usually poor candidates for MTD-type cytotoxic chemotherapy.

13.4 Clinical Trials of Metronomic Chemotherapy for Advanced HCC

Because of its antiangiogenic effects and favorable toxicity profile, metronomic chemotherapy has been considered an option for treating advanced HCC. In recent years, a few clinical trials and retrospective studies have examined the efficacy of metronomic chemotherapy, either alone or in combination with other antiangiogenic therapy, in patients with advanced HCC. The regimens of metronomic chemotherapy used in these studies have consisted primarily of oral fluoropyrimidine derivatives, such as capecitabine or tegafur/uracil. We discuss these studies herein.

13.4.1 Metronomic Chemotherapy Alone

Two prospective clinical trials of the use of metronomic chemotherapy alone for treating advanced HCC have been reported (Table 13.1). The study by Brandi et al. [37] evaluated the efficacy of capecitabine. Capecitabine is an oral prodrug of

Table 13.1 Clinical studies of metronomic chemotherapy with oral fluoropyrimidines alone for hepatocellular carcinoma

Authors	Regimens	*N*	Patients	Prior systemic therapy	Response rate (%)	Disease control rate (%)	Median PFS (months)	Median OS (months)
Clinical trials								
Ishikawa et al. [36]	Supportive care only Tegafur/uracil 400 mg bid (based on tegafur), continually	20 28	Locally advanced HCC[a]	Nil	– 18	– –	– –	6.2 12.1
Brandi et al. [37]	Capecitabine, 500 mg bid, continually Capecitabine, 500 mg bid, continually	59 31	Advanced HCC Advanced HCC	Nil Sorafenib	5 0	56 32	6.0 3.3	14.5 9.8
Retrospective studies/case reports								
Ishikawa et al. [38]	Tegafur/uracil 400 mg/day (based on tegafur), continually	1	Advanced HCC HCV (+)	Nil	Complete response; PFS/OS = 18 months; death due to rectal ulcer bleeding			
Ballardini et al. [39]	Capecitabine, 500 mg bid, continually	1	Advanced HCC HBV (+)	Nil	Partial response; PFS/OS >18 months			

Abbreviations: *PFS* progression-free survival, *OS* overall survival, *HCC* hepatocellular carcinoma, *HBV* hepatitis B virus, *HCV* hepatitis C virus

[a]Include multiple tumors in more than one lobe, a tumor or tumors involving a major branch of the portal or hepatic veins, or lymph node metastasis

5-fluorouracil and is commonly used to treat colorectal, gastric, and breast cancers [40–43]. The study enrolled two cohorts of patients with advanced HCC to be treated with capecitabine (500 mg) twice daily continually [37]. The first cohort consisted of 59 previously untreated patients with advanced HCC. The response rate (RR) was 5 %, and the disease control rate (DCR) was 56 %. The median progression-free survival (PFS) was 6.0 months, and the median overall survival (OS) was 14.5 months. The second cohort consisted of 31 patients who were resistant or intolerant to sorafenib. No response was identified, but 32 % of the patients experienced disease stabilization. The median PFS was 3.3 months, and the median OS was 9.8 months. The disease control rate was comparable with that reported in two phase II trials that have used brivanib (46 %) and tivantinib (42 %) as a second-line treatment for advanced HCC [22, 23].

Another prospective study evaluated metronomic chemotherapy using tegafur/uracil for advanced HCC. Tegafur/uracil is an oral fluoropyrimidine that is approved for and commonly used in treating gastric, colorectal, and non-small cell lung cancers in patients in Asian countries [44–46] (Table 13.1). Ishikawa et al. [36] randomized 48 patients with locally advanced HCC to receive supportive care only or to continually receive 400 mg of tegafur/uracil (based on tegafur) twice daily. Among the 28 patients who received tegafur/uracil, the RR was 18 %, and the median OS was 12.1 months. By contrast, the median OS of patients receiving supportive care was 6.2 months.

Overall, these phase II metronomic chemotherapy studies have demonstrated the safety and feasibility of treating advanced HCC patients with metronomic oral fluoropyrimidines. They have demonstrated that either capecitabine or tegafur/uracil could induce objective tumor response in treatment-naïve patients with advanced HCC. For patients who were resistant or intolerant to sorafenib, one study demonstrated that metronomic capecitabine induced disease stabilization in 32 % of advanced HCC patients. These data and those from case reports, which demonstrated significant tumor response for a prolonged period in HCC patients treated with metronomic chemotherapy using either capecitabine or tegafur/uracil [38, 39], collectively indicate that metronomic chemotherapy with oral fluoropyrimidines is clinically effective in certain HCC patients. However, because each of these studies has relatively few patients, caution must be exercised when interpreting the results.

13.4.2 Metronomic-Like Use of Oral Fluoropyrimidine Chemotherapy

Additional clinical studies have evaluated oral fluoropyrimidines by using schedules that deviated from a typical metronomic schedule [26], such as treatment for multiple weeks followed by 1 week of no treatment. The results of these studies on the metronomic-like use of oral fluoropyrimidines in advanced HCC patients are summarized in Table 13.2.

Three studies have evaluated the use of capecitabine (1,000 mg/m^2) twice daily from day 1 to day 14 (2 weeks “on”), followed by no treatment from day 15 to day

Table 13.2 Clinical studies of oral fluoropyrimidine chemotherapy in a metronomic-like schedule for hepatocellular carcinoma

Authors	Regimens	*N*	Patients	Prior systemic therapy	Response rate (%)	Disease control rate (%)	Median PFS (months)	Median OS (months)
Clinical trials								
Abdel-Rahman et al. [47]	Capecitabine, 1,000 mg/m^2 bid, D1–14, every 21 days Sorafenib 400 mg bid	26 26	Advanced HCC	Nil	3 15	58 77	4.0 6.0	5.1 7.1
Retrospective studies/case reports								
Mani et al. [48]	Tegafur/uracil 300 mg/m^2/day and leucovorin 90 mg/day D1–28, every 35 days	14	Advanced HCC HBV (+) 0 %; HCV (+) 29 %	Nil	0	21	4.5[a]	> 10
Patt et al. [49]	Capecitabine, 1,000 mg/m^2 bid, D1–14, every 21 days	37	Advanced HCC HBV (+) 19 %; HCV (+) 32 %	Yes 41 % No 59 %	11	22	–	10.1
von Delius et al. [50]	Capecitabine, 1,000 mg/m^2 bid, D1–14, every 21 days	11	Advanced HCC HBV (+) 9 %; HCV (+) 18 %	Yes 27 % No 73 %	9	27	2.2	10.1
Di Meglio et al. [51]	Tegafur/uracil 500 mg/day (based on tegafur), D1–28, every 35 days	1	Advanced HCC HCV (+)	Nil	Partial response; PFS ~ 32 months; OS > 44 months			

Abbreviations: *PFS* progression-free survival, *OS* overall survival, *HCC* hepatocellular carcinoma, *HBV* hepatitis B virus, *HCV* hepatitis C virus
[a]Time to progression reported in the study

21 (1 week "off") [47, 49, 50]. Patt et al. [49] retrospectively analyzed 37 patients with HCC who were not amenable to locoregional therapies and found that capecitabine treatment induced a partial response rate of 11 % and a disease stabilization rate of 22 %. In a retrospective analysis of 11 patients with advanced HCC, von Delius et al. [50] reported that one patient experienced partial response (9 %) lasting 13 months and two other patients experienced disease stabilization.

The only prospective study was conducted by Abdel-Rahman et al. [47], who enrolled 52 patients with advanced HCC and randomized them to receive either capecitabine or sorafenib as a first-line therapy. Among the 26 patients who received capecitabine, the RR was 3 %, and the median PFS and OS were 4.0 and 5.1 months, respectively. Compared with patients treated using sorafenib, those treated using capecitabine had poorer outcomes, including poorer RR and shorter PFS and OS.

Two trials have evaluated the efficacy of tegafur/uracil by using a 28-day-on, 7-day-off schedule in patients with advanced HCC (Table 13.2). In a phase II study, Mani et al. [48] enrolled 16 advanced HCC patients and treated them with tegafur/uracil (300 mg/m^2/day) and leucovorin (90 mg/day) from day 1 to day 28, followed by no treatment for 1 week, repeated every 35 days. Fourteen patients were evaluable for response. Although no patients experienced objective responses, disease stabilization occurred in three patients for 17–22 weeks. The median time to progression and overall survival time were 4.5 and >10 months, respectively. In another case report, an HCC patient treated using a repeated schedule of tegafur/uracil (500 mg/day) from day 1 to day 28, followed by no treatment for 1 week, showed a partial response [51].

These data collectively suggest that the use of oral fluoropyrimidines in advanced HCC patients following a metronomic-like schedule provides a safe toxicity profile and modest clinical activity (Table 13.2) that are similar to those of the metronomic use of oral fluoropyrimidines in patients with advanced HCC (Table 13.1). However, interpreting the findings of these studies is limited by the retrospective nature of the study design and/or the relatively small sample size. No studies have addressed the dosages and/or schedules of oral fluoropyrimidines regarding antitumor activity in advanced HCC.

13.4.3 Antiangiogenic Therapy Combined with Metronomic Chemotherapy

Preclinical models have demonstrated the synergistic antitumor activity of metronomic chemotherapy combined with other antiangiogenic drugs [28, 32–35]. Three single-arm phase II trials and a retrospective study evaluated various combinations as first-line therapies for patients with advanced HCC in Asian countries (Table 13.3).

Hsu et al. [52] examined the efficacy and safety of combining metronomic tegafur/uracil with sorafenib as a first-line therapy for patients with advanced HCC. Fifty-three patients with Child-Pugh class A liver reserve and adequate organ functions were enrolled to receive continual sorafenib (400 mg) twice daily and tegafur/uracil (125 mg/m^2 based on tegafur) twice daily. The RR was 8 %, and the DCR was 57 %.

Table 13.3 Clinical studies of metronomic chemotherapy combined with antiangiogenic therapy for hepatocellular carcinoma

Authors	Regimens	*N*	Patients	Prior systemic therapy	Response rate (%)	Disease control rate (%)	Median PFS (months)	Median OS (months)
Clinical trials								
Hsu et al. [52]	Sorafenib, 400 mg, bid Tegafur/uracil, 125 mg/m^2 (based on tegafur), bid Both continually	53	Advanced HCC HBV (+) 72 %; HCV (+) 25 %	Nil	8	57	3.7	7.4
Hsu et al. [53]	Bevacizumab, 7.5 mg/kg, day one, triweekly Capecitabine, 800 mg/m^2, bid, D1 to 14, every 21 days	45	Advanced HCC HBV (+) 67 %; HCV (+) 18 %	Nil	9	52	2.7	5.9
Shao et al. [54]	Thalidomide, 200 mg/day Tegafur/uracil, 125 mg/m^2 (based on tegafur), bid Both continually	43	Advanced HCC HBV (+) 72 %; HCV (+) 14 %	Nil	9	33	1.9	4.6
Retrospective studies/case series								
Ang et al. [55]	Thalidomide 50–200 mg/day Capecitabine, 1,000 mg/m^2 bid, D1–14, every 21 days	42	Advanced HCC HBV (+) 60 %; HCV (+) 7 %	Yes (17 %)	14 (CR 7)	45	5.1	9.9

Abbreviations: *PFS* progression-free survival, *OS* overall survival, *HCC* hepatocellular carcinoma, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *CR* complete response

The median PFS was 3.7 months, and the median OS was 7.4 months. The treatment was well tolerated, and the grade 3 or 4 adverse events, including fatigue (15 %), hand-foot skin reaction (9 %), and bleeding (8 %), were relatively infrequent. Compared with other reports using sorafenib alone in treating patients with advanced HCC, the combination therapy demonstrated no increased toxicity.

The second study examined the feasibility and efficacy of using bevacizumab combined with capecitabine as a first-line therapy for advanced HCC [53]. Bevacizumab is a monoclonal antibody that binds the VEGF. It has been approved for treating various malignant diseases, including advanced colorectal and non-small cell lung cancers [56, 57]. Bevacizumab (7.5 mg/kg) was administered intravenously every 3 weeks. Capecitabine (800 mg/m^2) was administered orally twice daily from day 1 to day 14, followed by no treatment for 1 week, and the treatment was repeated every 3 weeks. A total of 45 patients were enrolled. The objective RR was 9 %, and the DCR was 52 %. The median PFS was 2.7 months, and the median OS was 5.9 months. Treatment was well tolerated, with no grade 3 or 4 hematological toxicities. The most frequent grade 3 or 4 adverse reactions were gastrointestinal bleeding (9 %), hand-foot skin reaction (9 %), and diarrhea (4 %).

The third trial evaluated the use of thalidomide combined with tegafur/uracil as a first-line therapy in 43 advanced HCC patients [54]. Thalidomide has been shown to provide clinical benefits to patients with advanced HCC in single-arm phase II trials, which have reported RRs ranging from 3 to 7 % [58–61]. The antitumor activity of thalidomide is partially attributable to its antiangiogenic properties and has been shown to inhibit both basic fibroblast growth factor- and VEGF-induced angiogenesis in corneal micropocket assays [62, 63]. In this study, patients were treated with thalidomide (200 mg/day) and tegafur/uracil (125 mg/m^2 based on tegafur, bid) continuously [54]. An RR of 9 % and a DCR of 33 % have been reported. The median PFS was 1.9 months, and the median OS was 4.6 months. The treatment was well tolerated, with infrequent grade 3 or 4 adverse events. The most common grade 3 or 4 treatment-related adverse events were somnolence (9 %), gastrointestinal hemorrhage (5 %), skin rashes (2 %), and dizziness (2 %).

These three phase II trials have collectively demonstrated the feasibility of combining antiangiogenic therapy with metronomic oral fluoropyrimidine chemotherapy and have shown encouraging clinical efficacy in advanced HCC, with objective RRs of 6–9 % and DCRs ranging from 33 to 57 %. Another retrospective study of 42 patients who received combination therapy with thalidomide and capecitabine reported an RR of 14 % and a DCR of 45 % [55], corroborating the results of the three aforementioned prospective clinical trials.

Nevertheless, it remains difficult to determine whether combining antiangiogenic targeted therapy with metronomic chemotherapy is more effective against advanced HCC than either metronomic chemotherapy or antiangiogenic therapy alone. No randomized studies have directly compared a combination approach with a single treatment modality. Furthermore, a cross-study comparison of various clinical trials of advanced HCC is problematic because of the heterogeneous disease states and variable outcomes among different studies.

Prior studies have shown that patients with advanced HCC may have variable outcomes [64, 65]. Studies on patients from different geographic areas or on patients with various etiological factors may yield distinct outcomes, despite having similarly advanced diseases. In two pivotal studies of sorafenib treatment for advanced HCC, the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) study enrolled patients from Europe, Australia, and New Zealand [8], and the Asia-Pacific study enrolled patients from China, South Korea, and Taiwan [7]. Despite using the same inclusion/exclusion criteria for patient selection and the same dose and schedule of sorafenib, the efficacy outcomes of the two studies differed significantly. Compared with the patients in the Asia-Pacific study, the patients in the SHARP study had longer time to progression (5.5 vs. 2.8 months) and OS (10.7 vs. 6.5 months).

Conclusion

A limited number of clinical trials have thus far been conducted to evaluate the efficacy of metronomic chemotherapy for advanced HCC. The clinical trials that have been performed primarily used oral fluoropyrimidines. The findings of these trials confirm that metronomic chemotherapy is well tolerated by advanced HCC patients and may have modest antitumor activity for advanced HCC. Metronomic chemotherapy using oral fluoropyrimidines can thus serve as a treatment option for advanced HCC patients who have progressed on or cannot tolerate sorafenib, which is the current standard for first-line treatment.

Combining antiangiogenic therapy with metronomic chemotherapy, the sound scientific basis of which has been shown in preclinical models, has been evaluated in three prospective phase II studies. The results indicate that the combination treatment does not increase the potential for toxicity and is well tolerated by advanced HCC patients. The encouraging antitumor activity demonstrated in these phase II studies warrants future investigation to confirm the clinical benefits of combining antiangiogenic therapy with metronomic chemotherapy for treating advanced HCC patients.

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