Metronomic Chemotherapy: Possible Clinical Application in Advanced Hepatocellular Carcinoma

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Abstract
Hepatocellular carcinoma (HCC) is a hypervascular highly angiogenic tumor usually associated with liver cirrhosis. Vascular endothelial growth factor plays a critical role in vascular development in HCC. In contrast to the treatment of early-stage HCC, the treatment options for advanced HCC are limited and prognosis is often poor, which contributes to this tumor type being the third leading cause of cancer-related deaths worldwide. Metronomic chemotherapy, which was originally designed to inhibit angiogenesis, involves low-dose chemotherapeutic agents administered in a frequent regular schedule with no prolonged breaks and minimizes severe toxicities. We reviewed the potential effects and impact of metronomic chemotherapy in preclinical studies with HCC models and in patients with advanced HCC, especially when combined with a molecular targeted agent. Metronomic chemotherapy involves multiple mechanisms that include antiangiogenesis and antivasculogenesis, immune stimulation by reducing regulatory T cells and inducing dendritic cell maturation, and possibly some direct tumor cell targeting effects, including the cancer stem cell subpopulation. The total number of preclinical studies with HCC models shows impressive results using metronomic chemotherapy-based protocols, especially in conjunction with molecular targeted agents. Four clinical trials and two case reports evaluating metronomic chemotherapy for HCC indicate it to be a safe and potentially useful treatment for HCC. Several preclinical and clinical HCC studies suggest that metronomic chemotherapy may become an alternative type of chemotherapy for advanced unresectable HCC and postsurgical adjuvant treatment of HCC.

Introduction
Systemic chemotherapy with cytotoxic agents remains the most common systemic therapy to treat patients with metastatic disease. Most anticancer agents are designed to inhibit growth or kill rapidly dividing tumor cells. These drugs are usually administered at the highest doses possible to induce the maximum therapeutic effect; this is referred to as maximum tolerated dose (MTD) therapy [1,2]. However, administration of anticancer agents at MTD requires prolonged breaks between cycles of the therapy to allow recovery from the induced adverse side effects in different tissues and organs. These gaps in chemotherapy can allow or facilitate tumor regrowth including growth of clones resistant to the therapy. The regrowth of tumor or drug resistance clones during such gaps can prevent or compromise improvement of overall survival of patients with advanced cancer even when the first cycle of MTD therapy is effective [1,3–6].

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A new concept of anticancer treatment that targets the tumor vasculature was first proposed by Folkman in 1971 [7]. This treatment concept is based on the indispensable role of the vasculature in tumor growth [8,9]. Antiangiogenic therapy has been investigated extensively in both preclinical and clinical studies [10,11]. In 1991, Kerbel [12] suggested that some conventional cytotoxic anticancer agents can suppress vascular development in tumors based on the immature and proliferative nature of endothelial cells present in the neovasculature. Klement et al. [13] and Browder et al. [14] reported that frequent repetitive low doses of chemotherapy drugs such as cyclophosphamide or vinblastine could markedly suppress tumor growth. Hanahan et al. coined the term metronomic therapy to describe this type of therapeutic schedule [15]. Metronomic therapy generally consists of the continuous administration of low-dose chemotherapeutic agents without extended intervals [2]. It was originally designed with the intention to inhibit tumor growth by antiangiogenic mechanisms, though other mechanisms can contribute to its antitumor efficacy as described below, and is usually associated with much less severe acute toxicities compared to conventional MTD chemotherapy [16].

So, recently, metronomic chemotherapy has been investigated in pediatrie oncology [17]. Most new cancer cases and deaths now occur in low-income and middle-income countries [18]. As metronomic chemotherapy is a low-cost, well-tolerated, and easy-to-access treatment, it will be an attractive therapeutic option in resource-limited countries [19].

Hepatocellular carcinoma (HCC) is the sixth most common solid tumor and the third leading cause of cancer-related death globally [20,21]. Although the major blood supply to HCC is the portal veins at the early stage of hepatocarcinogenesis, the main supply ultimately is provided by neoarteries that develop in parallel with tumor growth [22–24]. For advanced HCC, such as Barcelona Clinic Liver Cancer (BCLC) stage C, classical chemotherapy is sometimes selected [25]. However, HCC is usually associated with liver cirrhosis, and thus aggressive chemotherapy can cause severe side effects [26]. Unfortunately, the prognosis of patients with advanced HCC is usually poor even in those treated with sorafenib [27,28]. To improve the therapeutic efficacy and prognosis of patients with advanced HCC, new strategies are clearly needed.

In this review, we evaluate the potential effects and impact of metronomic chemotherapy in patients with advanced HCC, especially when combined with a molecular targeted agent such as sorafenib.

**Treatment for Advanced HCC**

The development of sophisticated diagnostic modalities, such as computed tomography, magnetic resonance imaging, and abdominal ultrasonography, has allowed early diagnosis of HCC [29–32]. Patients with small HCCs are usually treated by surgical resection, liver transplantation, percutaneous ethanol injection therapy, microwave coagulation therapy, or percutaneous radiofrequency ablation [33]. The prognosis of patients with small HCCs has improved following the application of these therapeutic modalities [33].

Treatment of advanced HCC includes transhepatic arterial chemembolization, transhepatic arterial infusion chemotherapy, systemic chemotherapy, hormonal therapy, and immunotherapy [32,34–37]. However, only transhepatic arterial chemoembolization has been confirmed to improve long-term survival in BCLC stage B [38–41].

In large randomized trials, the median survival time (MST) of patients treated with doxorubicin were 6.8 and 7.4 months, respectively [42,43]. The MST of patients treated with PIAF regimen (cisplatin, interferon, doxorubicin, and fluorouracil) and FOLFOX4 regimen (oxaliplatin and fluorouracil) was 8.7 and 6.4 months, respectively. In three double-blinded, placebo-controlled trials, no survival benefit of tamoxifen was confirmed [44–46]. In several small studies, the MST of patients with HCC treated with capcitabine and gemcitabine was 10.1 and 6.9 months, respectively [47,48]. Other drugs such as cisplatin, 5-fluorouracil (5-FU), mitoxantrone, etoposide, paclitaxel, irinotecan, and capecitabine have also failed to demonstrate meaningful activity [49–55]. Despite maximum effort by many investigators, any definitive evidences that systemic chemotherapy is effective for advanced HCC have not been provided [56]. Sorafenib is an orally active multi-kinase inhibitor that targets vascular endothelial growth factor receptor 2 (VEGFR-2) and PDGF receptors, among others, and also blocks tumor cell proliferation by targeting the Raf/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinases (ERKs) signaling pathway by virtue of its targeting the intracellular threonine kinase Raf [57–59]. The efficacy of sorafenib for advanced HCC was confirmed for the first time in the phase III SHARP trial (MST; 10.7 months) and the Asian-Pacific phase III region trial (MST; 6.5 months) [27,28]. For advanced unresectable HCC with vascular invasion or extrahepatic metastasis (BCLC stage C), administration of sorafenib is now recommended worldwide [1,60,61]. Several trials with molecular target agents are underway. In the phase III trial, the MST of brivanib was 9.5 months and that of sorafenib was 9.9 months. In another phase III trial, the MST of linifanib and sorafenib was 9.1 and 9.8 months, respectively. In combination therapy, sorafenib and erlotinib (MST; 9.5 months) failed to prove the survival benefit comparing with sorafenib alone (MST; 8.5 months). Any other molecular target agents fail to surpass the efficacy of sorafenib so far. Due to the associated liver cirrhosis, patients with HCC sometimes develop severe side effects during conventional MTD chemotherapy, as noted above. Since metronomic chemotherapy is less toxic and, moreover, inhibits tumor growth through antiangiogenic mechanisms, this new therapeutic strategy using certain conventional chemotherapeutic drugs could be suitable for the treatment of advanced HCC.

**Metronomic Chemotherapy**

**Preclinical Studies**

The first preclinical studies of metronomic chemotherapy came from the laboratories of Folkman and Kerbel [14]. To date, there are more than 300 papers published on the preclinical effects of metronomic chemotherapy, as listed in PubMed. These reports describe the therapeutic efficacy of metronomic chemotherapy against at least 18 different types of cancers in the gastrointestinal tract, respiratory system, blood, brain, skin, and genitourinary systems. The most frequently selected anticancer drug for preclinical metronomic chemotherapy studies is cyclophosphamide. One interesting aspect of some of these studies is the potent antitumor efficacy of metronomic chemotherapy regimens in models of advanced metastatic cancer especially when combined with a targeted antiangiogenic drug which itself has minimal activity in this setting [62,63].

The main antitumor effects caused by metronomic chemotherapy are thought to be inhibition of tumor-associated vascular development and stimulation of immunity rather than direct cytotoxic effects on tumor cells (Figure 1) [12,64–66]. However, intriguingly, some recent reports have implicated direct targeting of cancer stem cells as a possible mechanism of metronomic cyclophosphamide [67], in contrast to MTD cyclophosphamide that does not target this subpopulation [68]. In the following section, we discuss recent information regarding
Inhibition of tumor angiogenesis/vascular development.

Direct cytotoxicity or inhibition of endothelial cell proliferation. Many conventional cytotoxic chemotherapeutic agents, such as cyclophosphamide, vinblastine, paclitaxel, docetaxel, tegafur/uracil (UFT), and tegafur/gimeracil/oteracil potassium (S-1), have antiangiogenic effects [69–75]. S-1 is composed of three compounds, namely, tegafur, gimeracil, and oteracil. UFT and S-1 decrease thymidine phosphorylase that is also called platelet-derived endothelial growth factor. The effect of UFT and S-1 seems to induce the antiangiogenic effect. The activated endothelial cells of newly formed blood capillaries are highly and selectively sensitive in vitro to very low concentrations of many conventional cytotoxic anticancer agents [76–81]. The antiangiogenic effects of conventional cytotoxic anticancer drugs seem to be optimized by administration of smaller doses without long breaks for prolonged periods [12].

Up-regulation of endogenous antiangiogenic factors and down-regulation of endogenous angiogenic factors. Angiogenesis is thought to be switched off or downregulated when levels of endogenous antiangiogenic factors such as thrombospondin-1 (TSP-1) and angiostatin exceed those of angiogenic factors such as VEGF and basic fibroblast growth factor (bFGF) [82]. Bocci et al. [83,84] reported that prolonged exposure of endothelial cells in vitro to low concentrations of various anticancer chemotherapeutic agents and ceramide analog caused marked induction of gene and protein expression of TSP-1. A number of other groups have reported up-regulation of circulating levels of TSP-1 in mice or patients exposed to metronomic chemotherapy [85]. TSP-1, a component of the extracellular matrix produced by endothelial cells, tumor cells, and infiltrating stromal cells, seems to act by binding to CD36 expressed on the cell membrane of endothelial cells [86–88]. TSP-1 also binds to VEGF and sequesters its angiogenic activity [89]. Hypoxia-inducible factor 1 (HIF-1) regulates the expression of angiogenic factors such as VEGF, bFGF, and stromal cell–derived factor 1 (SDF-1). Continuous administration of low-dose topotecan was reported to decrease the expression of HIF-1α [34], VEGF, and SDF-1 [90]. Administration of low-dose anthracycline chemotherapeutic agents also inhibited HIF-1 transcription and the expression of VEGF and SDF-1 [91]. VEGF is the major factor in angiogenesis/vascular development in many tumors [92,93]. A decrease in serum VEGF levels was observed in patients with advanced breast cancer treated with metronomic cyclophosphamide [94]. In addition, metronomic chemotherapy with weekly platinum and daily etoposide administration in patients with non–small cell lung cancer resulted in a decrease in VEGF level during treatment [95].

Inhibition of vasculogenesis by reducing the number and viability of circulating endothelial progenitor cells. Vascular development in tumor tissues consists of angiogenesis and vasculogenesis. Vasculogenesis is generally defined as the contribution to the formation of new blood vessels by circulating bone marrow–derived cells, possibly including endothelial progenitor cells (EPCs) [96,97]. Accumulating evidence suggests that circulating bone marrow–derived EPCs migrate into tumor tissues to support vascular formation and tumor growth [98,99]. In addition, local release of VEGF and SDF-1 induce the migration of EPCs to tumor tissues through VEGFRs and CXCR4 on the cell surfaces of EPCs [100].

Bertolini et al. [101] reported that the administration of MTD cyclophosphamide induced a robust EPC mobilization a few days after the end of treatment in tumor-bearing mice bearing human lymphoma cells. In marked contrast, metronomic chemotherapy of cyclophosphamide, using lower doses given daily, was associated with consistent decreases in the numbers and viability of EPCs, with a much more durable and marked inhibition of tumor growth [101].

Stimulation of Immunity

Metronomic chemotherapy with certain chemotherapeutic agents can stimulate the immune response by reducing regulatory T (Treg) cells and inducing dendritic cell maturation [65,66,102]. Treg cells are CD4⁺CD25⁺ lymphocytes known to accumulate in variety of cancers [103]. Increased frequency of Treg cells correlate with tumor progression and lack of treatment response [103]. Metronomic chemotherapy with cyclophosphamide and temozolomide was shown to increase the antitumor immune responses by suppressing the number and activity of Treg cells and also by increasing lymphocyte proliferation and memory T cells [65,66,104–106]. The reduction in Treg cell number was specific, and the treatment had no effects on other types of lymphocytes [106]. This effect was specific for metronomic chemotherapy. However, conventional MTD or high-dose chemotherapy can result in depletion of all types of lymphocytes. Reduction of Treg cells by metronomic chemotherapy restored the antitumor immune response by recovering the activity of both tumor-specific (cytotoxic T lymphocytes and helper T cells) and tumor-nonspecific effect cells (natural killer and natural killer T cells) [106]. Other immunostimulatory effects of metronomic chemotherapy have been proposed recently.
As an example, Tanaka et al. [102] reported that vinblastine, paclitaxel, and etoposide promoted dendritic cell maturation at nontoxic concentrations. They also found that local injection of low-dose vinblastine induced the maturation of tumor-infiltrating dendritic cells and stimulated antitumor immune responses in vivo [107]. However, the involvement of dendritic cell maturation by metronomic chemotherapy needs to be further investigated and confirmed. Preclinical studies using immunodeficient mice have shown that metronomic chemotherapy can result in marked tumor growth suppression. Such results indicate that the involvement of the immune system in metronomic chemotherapy is not necessarily critical [108,109]. Nevertheless, it is interesting to consider the potential benefits of combining metronomic chemotherapy with immunotherapeutic treatments, e.g., tumor vaccines [110].

**Metronomic Chemotherapy: Studies Using HCC Models**

The potential efficacy of various metronomic chemotherapy protocols using cyclophosphamide, UFT, cisplatin, and doxorubicin have been investigated in animal models of HCC [111,112], as summarized in Table 1. Park et al. [113] reported that metronomic chemotherapy with cyclophosphamide inhibited HCC growth and prolonged survival without inducing major toxicities using a rat HCC model with accompanying liver cirrhosis. Tang et al. [111] reported that single or doublet metronomic chemotherapy using cyclophosphamide, UFT, and/or doxorubicin without any added antiangiogenic agents did not have survival benefits. In contrast, they reported a significant improvement of overall survival in animals that received various combinations of metronomic chemotherapeutic regimens with DC101, an anti-VEGFR-2 targeting antibody that potently inhibits angiogenesis. They also reported that metronomic chemotherapy with metronomic UFT and sorafenib delayed the onset of tumor progression (i.e., delayed development of resistance to chemotherapy) [114]. Zhou et al. [115] also reported that metronomic doxorubicin in combination with bevacizumab had a profound effect on tumor growth inhibition and survival of HCC xenograft model. The appearance of resistance to molecular targeted agents, such as sorafenib, is an inevitable problem in the treatment of advanced unresectable HCC. Thus, this report may be hopeful with respect to the clinical application of metronomic chemotherapy with sorafenib for advanced HCC. Iwamoto et al. [116] demonstrated that metronomic chemotherapy with S-1 inhibited tumor growth and prolonged survival of hepatoma tumor–bearing mice and that these effects were enhanced by the addition of vandetanib, an oral inhibitor of both the epidermal growth factor receptor and VEGFR-2. The antitumor effects of metronomic chemotherapy with S-1 alone were shown to be mediated mainly through inhibition of angiogenesis by up-regulation of TSP-1 expression and direct inhibition of endothelial cell proliferation in tumor tissues. With regard to the toxic effects of such therapies, the use of MTD S-1 caused body weight loss and myelosuppression, whereas S-1 metronomic chemotherapy or S-1 metronomic chemotherapy with vandetanib did not cause any severe toxicity. Metronomic chemotherapy with a single agent did not cause an antitumor effect in one study by Tang et al. [111]. However, not only S-1 metronomic chemotherapy with vandetanib but also metronomic S-1 monotherapy caused significant antitumor effects in the study by Iwamoto et al. Perhaps these differences might be due to greater antitumor effects caused by S-1 compared with UFT [116], although the different models could be another explanation.

Jang et al. [117] used a chemically induced model of HCC in rats and compared an MTD versus metronomic chemotherapy protocol using cyclophosphamide. The metronomic protocol was more effective in prolonging survival than the MTD method and also suppressed metastasis formation, not just intrahepatic tumor growth. Among the mechanisms implicated for the results included suppression of HIF-1α levels and matrix metalloproteinases (MMPs), including MMP-2 and MMP-9, and also of the MMP-2 activator, tissue inhibitor of metalloproteinase-2 (TIMP-2). In a previous study by the same group using the rat HCC model, suppression of VEGFR-2 caused by metronomic cyclophosphamide was also reported [113].

**Metronomic Chemotherapy: Clinical Studies**

To date, more than 50 clinical trials, mostly phase II trials, of metronomic chemotherapy have been reported in adult patients with breast cancer, lung cancer, prostate cancer, malignant brain tumor, colon cancer, multiple melanoma, malignant lymphoma, HCC, and other types of tumors [118–120]. Many of those clinical trials included both chemotherapeutic and antiangiogenic agents. About 80% of the trials have reported positive efficacy of metronomic chemotherapy. In addition to the improvement in therapeutic response rate (complete response + partial response) and/or clinical benefit (complete response + partial response + stable disease), Orlando et al. [121] showed that 27% of patients with advanced breast cancer who were already resistant to trastuzumab responded to treatment using doublet metronomic cyclophosphamide and methotrexate, in combination with trastuzumab. Furthermore, Kato et al. [122] and Watanabe et al. [123] reported that continuous daily administration of nontoxic doses of UFT was safe and effective as postoperative adjuvant treatment in randomized phase III adjuvant trials undertaken in patients with non–small cell lung cancer and breast cancer, respectively. UFT was administered daily with no breaks for 2 years and can be viewed as a neutralizing monoclonal antibody.

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**Table 1.** Preclinical Studies Evaluating Metronomic Chemotherapy Regimens in Rodent Models of HCC.

<table>
<thead>
<tr>
<th>Animal Model</th>
<th>Drug Used</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human HCC cell line orthotopic xenografts in SCID mice</td>
<td>Oral UFT + cyclophosphamide plus sorafenib or DC101</td>
<td>Tang et al. [111]</td>
</tr>
<tr>
<td>Human HCC cell line orthotopic xenografts in SCID mice</td>
<td>Oral UFT + sorafenib</td>
<td>Tang et al. [114]</td>
</tr>
<tr>
<td>Human HCC cell line orthotopic xenografts in nude mice</td>
<td>Intravenous doxorubicin plus bevacizumab</td>
<td>Park et al. [113]</td>
</tr>
<tr>
<td>Chemically induced HCC in rats</td>
<td>Oral cyclophosphamide</td>
<td>Jang et al. [117]</td>
</tr>
<tr>
<td>Chemically induced HCC in rats</td>
<td>Cyclophosphamide</td>
<td>Zhou et al. [115]</td>
</tr>
<tr>
<td>Human HCC cell line subcutaneous xenografts in nude mice</td>
<td>Oral S-1 + vandetanib</td>
<td>Iwamoto et al. [116]</td>
</tr>
<tr>
<td>Human HCC cell line xenografts and primary HCC cells from patients in Nonobese diabetic/SCID/interleukin-2 (IL-2) receptor γ null mice</td>
<td>Oral cyclophosphamide</td>
<td>Martin-Padura et al. [67]</td>
</tr>
</tbody>
</table>

SCID indicates severe combined immunodeficiency.

S-1 is an oral 5-FU prodrug; UFT is an oral 5-FU prodrug; vandetanib is an oral tyrosine kinase inhibitor that targets VEGFRs and epidermal growth factor receptors; DC101 is an anti-mouse VEGFR-2 neutralizing monoclonal antibody.
metronomic chemotherapy-like trial. In contrast, a few other clinical trials of metronomic chemotherapy reported negative outcomes. In particular, malignant brain tumors seem to be resistant to metronomic chemotherapy [124–127]. With regard to adverse effects, metronomic chemotherapy was associated with minimal toxicity and severe adverse events are rare. The most common mild side effects were nausea, vomiting, fatigue, and bone marrow suppression [128,129]. In view of the encouraging preclinical and clinical findings evaluating metronomic chemotherapy or metronomic chemotherapy combined with targeted agents—especially antiangiogenic drugs—a number of randomized phase III trials have been initiated, four in breast cancer and two in colorectal cancer (www.clinicaltrials.gov) [130]. Two are adjuvant trials. The chemotherapy drugs involved include cyclophosphamide, methotrexate, and capecitabine, and the antiangiogenic drug, when used, is bevacizumab (Avastin), the monoclonal anti-VEGF antibody.

**Metronomic Chemotherapy: Clinical Setting of HCC**

To date, there are only four clinical trials evaluating metronomic chemotherapy for HCC (Table 2). One reported negative result, whereas others reported positive natures. Treiber et al. [131] randomly classified 38 patients with advanced HCC into the following four treatment groups: patients of group 1 received 30 mg of octreotide on day 1, group 2 received octreotide on day 1 and 400 mg of imatinib daily, group 3 received oxaliplatin (60–90 mg/m²) on day 1, and group 4 received oxaliplatin (20–30 mg/m²) on days 1, 8, and 15 combined with 30 mg of octreotide on day 1 and 400 mg of imatinib daily. The time to progression and overall survival were not different among the groups in this phase I/II trial. Hsu et al. [132,133] conducted another phase II study of the combination of sorafenib (400 mg twice daily) with metronomic UFT (125 mg/m² based on tegafur twice daily) for advanced HCC. They evaluated the efficacy and safety in 53 patients with Child-Pugh class A. The median progression-free survival was 3.7 months, and median survival was 7.4 months. Four patients showed partial response and 26 had stable disease. Treatment was associated with some severe toxicity including fatigue (15%), abnormal liver function (13%), elevated serum lipase (10%), hand-foot skin reaction (9%), and bleeding (8%). The authors concluded that metronomic chemotherapy with UFT could be safely combined with sorafenib and that such combination could improve the efficacy of sorafenib in patients with advanced HCC when compared to previous reports in similar patient cohorts treated with sorafenib alone [28,134]. The concurrent use of metronomic chemotherapy and sorafenib might augment antitumor efficacy but without a high incidence of severe side effects. Woo et al. [135] reported the results of a phase II trial involving infusion of metronomic epirubicin with cisplatin and 5-FU and found it to be a safe and potentially useful treatment for HCC patients with portal vein thrombosis (MST; 162 days). In addition, Shao et al. [136–138] undertook a metronomic UFT plus thalidomide, sorafenib, or bevacizumab trial in patients with advanced HCC and observed it to be safe, demonstrating modest activity (MST; 4.8 months). There are also two case reports reporting encouraging results in individual HCC patients treated with metronomic capcitabine [139,140]. In addition, Allegreni et al. [141] reported that metronomic UFT and cyclophosphamide plus celecoxib in heavily pretreated gastrointestinal patients including two patients with HCC were well tolerated and associated with interesting activity. To confirm the therapeutic efficacy and safety of metronomic chemotherapy in patients with advanced HCC, more (randomized) phase II trials with other anticancer agents and molecular targeted agents, including randomized controlled trials in larger populations, will be required.

**Conclusions**

In this review, we have attempted to outline the many reasons why we feel metronomic chemotherapy, especially when used in conjunction with an antiangiogenic drug such as sorafenib, is a potentially promising strategy to consider for the treatment of patients with advanced HCC. In summary, these reasons are given as follows:

1. HCC is a highly angiogenic tumor, driven by such proangiogenic growth factors such as VEGF and bFGF.
2. Sorafenib is already approved for treatment of patients with HCC.

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**Table 2. Clinical Studies Evaluating the Therapeutic Efficacy of Metronomic Chemotherapy in Patients with HCC.**

<table>
<thead>
<tr>
<th>Drugs Used</th>
<th>Results/Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide, imatinib, oxaliplatin</td>
<td>Phase I/II study. Metronomic chemotherapy with oxaliplatin in combination with antiangiogenic drugs suppressed the increase of serum E-selectin, VEGF-A, PDGF-BB, and α-fetoprotein levels.</td>
<td>Treiber et al. [131]</td>
</tr>
<tr>
<td>UFT, sorafenib</td>
<td>Phase II study. Metronomic chemotherapy with UFT was safely combined with sorafenib and showed activity to improve the efficacy of sorafenib.</td>
<td>Hsu et al. [132]</td>
</tr>
<tr>
<td>5-FU, sorafenib, bevacizumab, thalidomide</td>
<td>Phase II study. An early α-fetoprotein response was a useful surrogate marker to predict treatment efficacy and prognosis of metronomic chemotherapy with 5-FU in combination with antiangiogenic agents.</td>
<td>Shao et al. [136]</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Case report. Metronomic chemotherapy with capcitabine induced complete remission with minimal toxicity.</td>
<td>Brandi et al. [140]</td>
</tr>
<tr>
<td>UFT, sorafenib</td>
<td>Phase II study. Vascular response measured by dynamic contrast-enhanced MRI predicted tumor response and survival by metronomic UFT therapy with sorafenib.</td>
<td>Hsu et al. [133]</td>
</tr>
<tr>
<td>UFT, sorafenib</td>
<td>Phase II study. High baseline circulating EPC levels were associated with poor prognosis by sorafenib and metronomic chemotherapy with UFT.</td>
<td>Shao et al. [138]</td>
</tr>
<tr>
<td>Epirubicin, cisplatin, 5-FU</td>
<td>Prospective study. Metronomic chemotherapy might be a safe and useful palliative treatment for HCC patients with major portal vein tumor thrombosis.</td>
<td>Woo et al. [135]</td>
</tr>
<tr>
<td>UFT, thalidomide</td>
<td>Phase II study. High baseline IL-6 and IL-8 levels were associated with poor prognosis. Metronomic chemotherapy with UFT and thalidomide was safe and demonstrated modest activity.</td>
<td>Shao et al. [137]</td>
</tr>
</tbody>
</table>

MRI indicates magnetic resonance imaging.

UFT is an oral 5-FU prodrug.
3. Antiangiogenic drugs can augment the efficacy of metronomic chemotherapy and vice versa, as shown in a very large number of diverse preclinical studies—especially those involving treatment of mice with advanced metastatic disease—and also as suggested, or shown, in a number of phase II clinical trial results of other types of cancer.

4. Metronomic chemotherapy, which functions more as a biologic therapy, is now known to involve multiple mechanisms that include antiangiogenesis and antivasculogenesis, immune stimulation, and possibly some direct tumor cell targeting effects, including of the cancer stem cell subpopulation.

5. There is no effective standard chemotherapy for HCC when using conventional MTD treatment protocols, and in part, this is related to the toxicity of such treatments in patients with HCC who have the underlying comorbidity of liver cirrhosis; in contrast, the less toxic regimens associated with metronomic chemotherapy and the different cellular targets and mechanisms of action involved may make this an attractive and alternative type of chemotherapy to consider, especially for treatment of advanced HCC, but perhaps also for postsurgical adjuvant treatment of early-stage HCC, given the successes of metronomic-like protocol of UFT reported in adjuvant phase III breast and lung cancer trials.

6. The total number of preclinical studies showing impressive results using metronomic chemotherapy-based protocols, especially in conjunction with antiangiogenic drugs (even in models of advanced metastatic disease) along with the number of promising clinical study and trial results that have been published to date, argues strongly for giving more consideration to testing more extensively this type of treatment strategy for advanced HCC.

7. Some limited preliminary results of several preclinical HCC studies using metronomic chemotherapy in conjunction with antiangiogenic drugs indeed suggest that this treatment strategy can be highly active and, as such, should be given proactive clinical consideration.

**Perspective for Future Directions**

In unresectable advanced HCC (BCLC stage C), sorafenib is recommended as the standard treatment. As HCC is usually accompanied with liver cirrhosis, a combination treatment with less adverse events will be required to improve the survival benefit of sorafenib. Metronomic chemotherapy will be a candidate treatment that meets these criteria. To confirm the synergy of metronomic chemotherapy, prospective trials of metronomic chemotherapy with sorafenib compared with sorafenib alone as the control arm will be necessary as soon as possible.

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