



## Case Report

## Metronomic chemotherapy with cyclophosphamide for the treatment of advanced hepatocellular cancer: A case report

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## ABSTRACT

**Introduction and importance:** Metronomic chemotherapy entails chronic, equally spaced administration of low doses of various chemotherapeutic drugs without extended rest periods. Its use as a second-line treatment in advanced or metastatic hepatocellular cancer remains under investigation.

**Case presentation:** We report a case of a 49-year-old Caucasian female patient with an enlarged (~14 cm) hepatocellular cancer. In July 2016, she underwent right hepatectomy (after preceding TACE). During the follow-up period, she presented early disease recurrence with lung and peritoneal metastasis. Initially, she received an inhibitor of protein kinase (sorafenib) for six months without response. Afterwards, cyclophosphamide administration at low doses as metronomic chemotherapy provided complete regression of the metastatic lesions. The patient remains in good performance status almost 4 years after initial treatment, without signs of recurrence in her recent follow-up.

**Clinical discussion:** Using cyclophosphamide as metronomic chemotherapy in advanced hepatocellular cancer may have a promising antiangiogenic antitumor effect. Future clinical trials need to demonstrate this effect in terms of tumor suppression and increased disease-free survival.

**Conclusion:** Large multi-centered clinical trials have to be planned to investigate the precise role of cyclophosphamide in the therapy of hepatocellular cancer while defining the patients' profile that will benefit most from cyclophosphamide.

### 1. Introduction

The treatment of hepatocellular carcinoma (HCC) remains challenging for the international scientific community. Till nowadays, advanced hepatocellular cancer is characterized by a low response to systemic therapy. Sorafenib is an orally active multi-kinase inhibitor that targets vascular endothelial growth factor receptor 2 (VEGFR-2) and PDGF receptors. The beneficial role of sorafenib in HCC was confirmed for the first time in phase III SHARP trial (mean survival time 10.7 months) and the Asian-Pacific phase III region trial (mean survival time 6.5 months). Globally sorafenib is the recommended, first-line treatment for advanced/unresectable HCC with vascular invasion or extrahepatic metastasis (BCLC stage C) [1,2].

Regorafenib, an oral multi-kinase inhibitor, is the second-line treatment for HCC. A recent randomized phase III trial showed that

regorafenib provided survival benefit (10.6 months vs 7.8 months placebo) in HCC patients progressing on Sorafenib treatment [2]. Nonetheless, even this second-line treatment remains unsatisfactory, with serious unsettled issues regarding its optimal use.

Due to the co-existent liver cirrhosis, patients with HCC sometimes develop severe side effects during conventional chemotherapy. Metronomic chemotherapy includes low doses of chemotherapeutic agents administered in a frequent schedule with no prolonged intervals and minimizes severe toxicities. Metronomic chemotherapy exerts both direct and indirect effects on tumor cells and their microenvironment. It can inhibit tumor angiogenesis, stimulate an anticancer immune response, and induce tumor dormancy [3,4].

The first work using cyclophosphamide as metronomic chemotherapy in a clinical setting was published in 2002. Colleoni and colleagues evaluated the clinical efficacy of low-dose methotrexate and

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cyclophosphamide in heavily pretreated breast cancer patients, obtaining significant efficacy with minimal toxicity [5]. Latest experimental therapeutic studies in mice with low-dose metronomic chemotherapy (MET) regimens have shown efficacious and promising results for both advanced and early-stage HCC [3,4].

Herein, we report a case of a young woman with advanced, metastatic HCC who showed resistance to sorafenib. MET with cyclophosphamide (CTX) as a second-line treatment agent achieved complete regression of metastatic lesions. This case report has been reported in line with the SCARE criteria [6].

## 2. Presentation of case

A 49-year-old female patient was brought to the outpatient Hepatobiliary Department at University Hospital of Ioannina in early 2016. The patient was in good performance status, without major systemic diseases other than a history of early-stage breast cancer treated with wide local excision and postoperative radiotherapy. At her clinical examination, the patient had an enlarged palpable mass on the right liver lobe.

Laboratory tests for hepatitis B virus (HBV) and hepatitis C virus (HCV) were between normal ranges, while AFP levels were 742ng/mL. Computed tomography (CT) showed a large mass lesion almost 14 cm in diameter in the right lobe with imaging characteristics of HCC. There was no remarkable lymphadenopathy, while the rest liver parenchyma did not have signs of co-existent cirrhosis. Thorax CT was normal, without metastatic lesions.

Due to the large diameter of the neoplasm and the fact that Transarterial chemoembolization (TACE) is the recommended treatment for asymptomatic, large, or multifocal HCC without macrovascular invasion or extrahepatic metastasis [7]. TACE was held preoperatively in order to downstage the disease. In July 2016, the patient underwent a right hepatectomy, cholecystectomy, and dissection of regional lymph nodes. Histopathological examination of the liver tissue revealed typical histomorphologic features of HCC. R0 (no residual tumor) resection was achieved. Postoperatively, the patient developed mild liver dysfunction and acute renal dysfunction due to hepatorenal syndrome. She was treated conventionally and eventually made a satisfactory recovery and was discharged on the 19th postoperative day.

During the follow-up period (3 months postoperatively), CT of the Abdomen and Thorax indicated early disease progression with new lung and peritoneal metastases (Fig. 1). Subsequently, the patient received adjuvant systemic treatment with sorafenib 400mg twice daily for six months without response. Due to the patients' tolerance to sorafenib, the multidisciplinary team decided alternative treatment with metronomic chemotherapy (MET) as a second-line treatment using low-dose (50mg orally/day) cyclophosphamide (CTX). The patient responded extremely

well to CTX administration, and her surveillance follow-up CTs showed full subsidence of both lung and peritoneal metastasis (Figs. 2 and 3). In total, the CTX regimen was well tolerated, and no side effects other than fatigue were observed. The patient is in complete remission 4 years after the diagnosis of advanced HCC without signs of recurrence in her recent follow-up.

## 3. Discussion

The treatment of HCC is a challenge for the international scientific community, with surgery being the only treatment that can provide potential healing even in advanced stages of the disease. According to BCLC guidelines, surgery is the appropriate therapy for patients at very early and early-stage HCC (BCLC stage 0 and BCLC stage A), whereas patients at intermediate stage (BCLC stage B) should be submitted to TACE. Last, patients with advanced-stage disease (BCLC stage C) should receive sorafenib as a first-line treatment option. Nonetheless, recent studies show that liver resection in selected patients may provide better results in survival even in advanced stage HCC in comparison with TACE and Sorafenib [3,8].

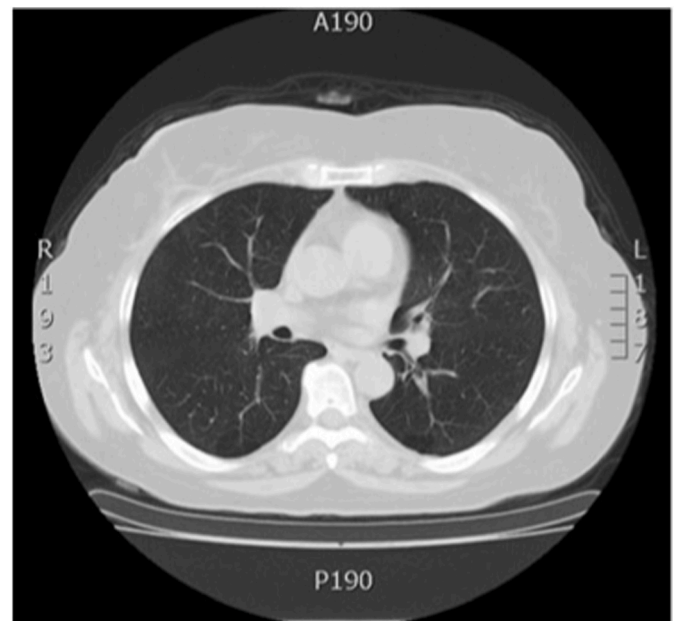


Fig. 2. Computed Tomography of the thorax after metronomic therapy (02/2018). Complete remission of metastatic lesions.

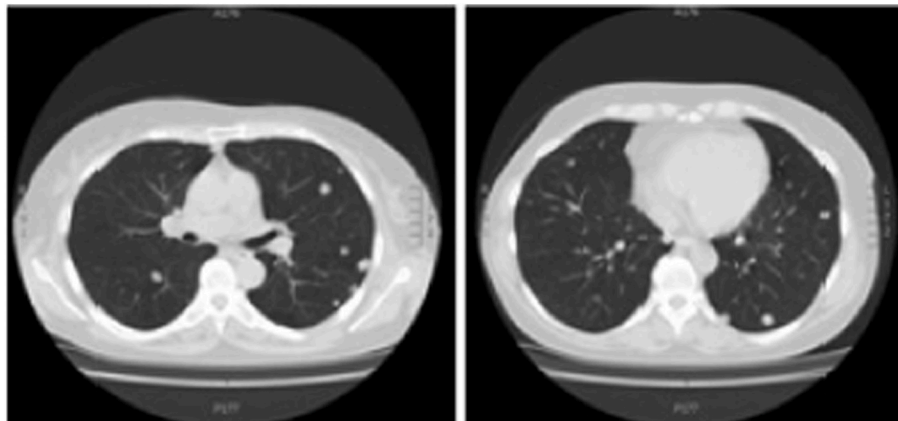
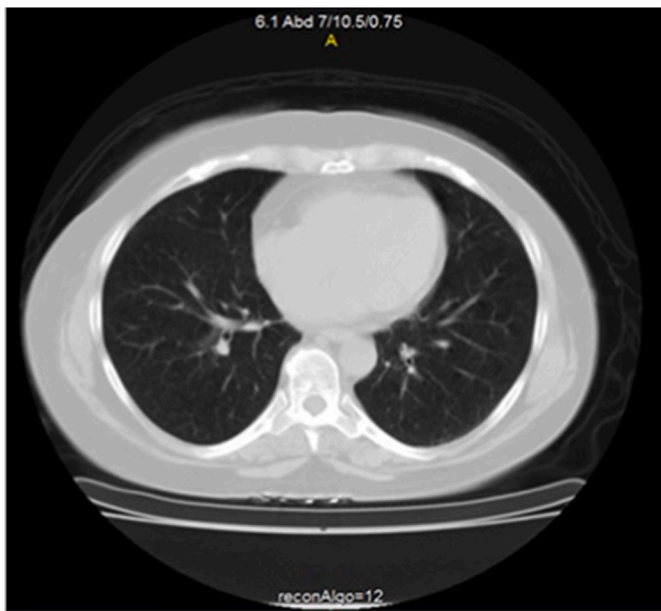


Fig. 1. Computed Tomography of the thorax during the follow-up period (10/2016). Pulmonary metastatic lesions.



**Fig. 3.** Computed Tomography of the thorax almost five years post-operatively (10/2020). Complete remission of metastatic lesions.

The favorable systemic therapy for metastatic cancer is the administration of cytotoxic agents. In general, these agents impede tumor's growth or destroy rapidly dividing cancer cells. In order to produce the maximum therapeutic effect, drugs are usually administered at the highest dose, which is called the maximum tolerated dose (MTD). The main drawback is the need for a prolonged break between cycles of the therapy to allow different tissue and organs to restore from the therapy's induced side effect. Surviving cancer cells may proliferate during the intervals of treatment or develop clones resistant to therapy. Repopulation and drug-resistant clones are important causes of treatment failure as they jeopardize the overall survival benefit of patients with advanced cancer despite the effectiveness of the first cycle of chemotherapy [9].

Metronomic chemotherapy (MET) has been established as a new treatment strategy to control certain types of malignancies, including HCC. It is defined as the continuous administration of low-dose chemotherapeutic agents significantly below the MTD without prolonged intervals or simply "lower doses for a longer time". The potential advantages of MET are the minimal adverse effects and a rare probability of developing drug resistance. As stated in recent preclinical and clinical studies, MET enhances certain drugs' antiangiogenic and anti-tumor properties. The antiangiogenic action is induced by decreasing tumor endothelial cells (TEC) and endothelial progenitor cells (EPC), inhibiting angiogenic HIF-1 $\alpha$  and increasing antiangiogenic protein Thrombospondin-1. The anti-tumor properties encompass decreased tumor immune tolerance, decreased cancer stem cells, increased cytotoxic response, and increased tumor dormancy [3,4].

Several clinical studies have examined the efficacy and safety of MET in patients with advanced/metastatic HCC. Generally, MET was proven to be well tolerated and demonstrated modest activity [3,4]. It appears that MET is active in both treatment-naïve patients and those previously treated with sorafenib [10,11]. In one study, MET plus antiangiogenic caused the least increase in serum biomarkers of angiogenesis than conventional chemotherapy, although time to progression and overall survival were not significantly different [12]. Moreover, in patients with metastatic or locally advanced HCC and Child-Pugh A cirrhosis, MET seemed to improve the efficacy of sorafenib as first-line therapy. However, MET was correlated with some severe toxicity [13].

Cyclophosphamide (CTX) is an alkylating agent that needs hepatic cytochrome P450-catalysed metabolism to attain cytotoxic activity. Low

dose CTX has been widely used in metronomic schedules for many cancer protocols and has demonstrated antiangiogenic and immunomodulatory effects. This evidence suggests that metronomic CTX can act as an antiangiogenic agent and a cytotoxic drug for cancer cells [3]. According to preclinical orthotopic models in many cancer types, metronomic CTX is enhanced with various properties, ranging from antiangiogenic to immunomodulation, and may prevent tumor resistance. Endurance to conventional systemic therapies arises the need to increase the efficacy of targeted therapies with metronomic scheduling. Nevertheless, its beneficial efficacy in HCC is not fully determined in clinical practice yet [14,15].

Optimizing a metronomic anticancer therapy is still a challenging task. Future cancer research should aim to identify the best agents to use according to tumor type, calculate the doses of each agent to be used, and define drug administration's timing. New strategies are being developed in order to combine metronomic chemotherapy with conventional chemotherapy, radiotherapy and/or targeted therapy.

Surgery, chemotherapy, and radiotherapy are the main choices for HCC treatment. However, due to many patients' actual conditions (advanced disease or poor liver function), chemotherapy is often the most appropriate therapeutic procedure. In our patient, metronomic CTX had been proposed by the multidisciplinary team as an alternative therapy to sorafenib. The last had no response to the patient, whereas CTX as MET showed a beneficial effect on overall and disease-free survival.

#### 4. Conclusion

Implementation of CTX as a metronomic chemotherapeutic regimen is already effective against several types of cancer. It is believed that metronomic CTX could be an effective and well-tolerated therapy option in patients with advanced HCC. However, these results need to be clinically verified in larger HCC patients' population in prospective randomized trials.

#### Provenance and peer review

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#### Conflicts of interest

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#### Ethical approval

N/a.

#### Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor – in – Chief of this journal on request.

#### Author contribution

1. Peristeri DV: Study conception and design, drafting of manuscript.
2. Tepelenis K: Literature search and acquisition of data.
3. Karampa A: Literature search and acquisition of data.
4. Kapodistrias N: Analysis and interpretation of data.
5. Goussia AC: Analysis and interpretation of data.
6. Papas-Gogos G: Critical revision.

7. Glantzounis GK: Final approval of the version to be submitted.

All the authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

#### Registration of research studies

1. Name of the registry: N/a
2. Unique Identifying number or registration ID: N/a
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): N/a

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2021.103043>.

#### Abbreviations

|     |                          |
|-----|--------------------------|
| CT  | Computed Tomography      |
| CTX | Cyclophosphamide         |
| HCC | Hepatocellular Carcinoma |
| MET | Metronomic Chemotherapy  |

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