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Case Report

Hepatic Arterial Infusion Chemotherapy for Liver Tumor Control in a Patient with Liver Metastasis from Lung Small Cell Carcinoma, a Case Report and Discussion

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Abstract

Hepatic arterial infusion (HAI) chemotherapy was now used in the treatment of liver metastasis in the patients with colorectal cancer and in the treatment of hepatocellular carcinoma. The blood supplies of cancer cells were from hepatic artery instead of portal system which mainly supply normal liver cells. By delivering chemotherapeutic agents directly to cancer cells through catheter in hepatic artery, it provided much more selective treatment and better local tumor control. The feasibility of liver tumor excision was increased after HAI chemotherapy. Theoretically, HAI chemotherapy may be applied to any tumors that mainly get blood supply from hepatic arteries. However, there were few reports of HAI chemotherapy for metastatic liver tumors from other solid tumors. Our report provided a case treated by HAI chemotherapy for liver metastasis from lung small cell carcinoma. This may give us an idea of extended application of HAI chemotherapy to more solid tumors with liver metastasis.

Keywords: Hepatic arterial infusion chemotherapy, metastatic liver tumor, small cell lung cancer

Introduction

Hepatic arterial infusion (HAI) chemotherapy is now used in the treatment of liver metastasis in patients with colorectal cancer[1] and in the treatment of hepatocellular carcinoma.[2] In these patients, blood supply to the cancer cells comes from the hepatic artery instead of the portal system which mainly supplies normal liver cells.[3] Delivering chemotherapeutic agents directly to cancer cells through a catheter in the hepatic artery allow for much more selective treatment and better local tumor control. The feasibility of liver tumor excision is increased after HAI chemotherapy.[1,2] Theoretically, HAI chemotherapy may be applied to any tumors that mainly get blood supply from hepatic arteries. However, there are few reports of HAI chemotherapy for metastatic liver tumors from other solid tumors. We report a case treated with HAI chemotherapy for liver metastasis from lung small cell carcinoma. This case shows the potential application of HAI chemotherapy to more solid tumors with liver metastasis.

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Case Report

This 64-year-old male had underlying diabetes mellitus. He visited our gastrointestinal outpatient department (OPD) on August 18, 2020, due to epigastric pain for 1 week. The symptoms could be aggravated by moving and radiated to the back. His bodyweight had decreased by about 5 kg in 3 months. He received abdominal echo which revealed liver tumors.

Laboratory data revealed hyperbilirubinemia (total bilirubin: 2.1 mg/dL) and elevated aspartate aminotransferase/alanine aminotransferase (ALT) level (around 100 U/L). Abnormal ALK-P (326 U/L) and carcinoembryonic antigen (CEA) levels (318.0 ng/mL) were also noted. Alfa-fetoprotein and CA-199 levels were within normal range, and the creatinine level was 0.84 mg/dl. Hepatitis B virus and hepatitis C virus infection markers were both negative.

He was then referred to our oncology OPD for further tumor survey and staging. Computed tomography (CT) of the liver was arranged, which showed multiple liver and lung nodules along with enlarged portocaval, retroperitoneum, left gastric artery, retrosternal, and right paratracheal lymph nodes [Figure 1]. A tumor scan was also arranged, which revealed tumors involving bilateral lungs, liver, left supraclavicular fossa/mediastinal/abdominal lymph nodes, left adrenal gland, and multiple bones [Figure 2]. A thyroid echo biopsy for primary site survey was arranged, however, the echo showed no definite mass lesion in the right thyroid.

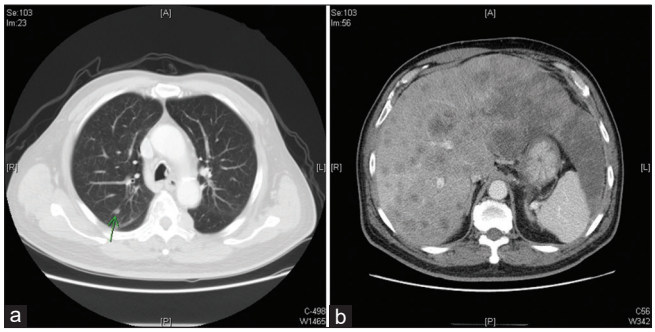

Figure 1: (a and b) Initial computed tomography image on August 21, 2020. Multiple liver metastasis was seen

Echo-guided fine needle aspiration cytology was not performed as no target lesion was found. Because of unclear cancer origin, a liver biopsy was also performed. The liver biopsy was positive for TTF1, CD56, and synaptophysin and focally positive for chromogranin A. The pathology favored metastatic small cell carcinoma of pulmonary origin. Thus, the final diagnosis was lung small cell carcinoma with left supraclavicular fossa/mediastinal/abdominal lymph nodes, left adrenal gland, multiple liver, and multiple bone metastases.

He received the standard regimen for small cell carcinoma with the etoposide/cisplatin regimen with IV injections. However, rapidly progressive liver failure with severe obstructive jaundice (8/18, total bilirubin: 2.1 mg/dl; 8/26, total bilirubin: 4.1 mg/dl) and acute hepatitis (8/26, ALT: 213 U/L) developed. Diffuse tumor infiltration of the liver, especially on the right side, was seen in the previous CT image. Biliary stent and extrahepatic drainage for the obstructive jaundice would be less effective as no obvious main biliary tract dilatation was seen in the CT scan.

Due to the rapidly deteriorating uncontrolled liver function, we decided to give him HAI chemotherapy for prompt focal tumor control combined with systemic chemotherapy. Thus, we arranged both venous port-A and right femoral artery port-A insertion. Arterial port-A was placed into the right hepatic artery for drug infusion access to the right side liver tumors [Figure 3].

The regimen was systemic etoposide 100 mg/m^2 per day through venous port-A for 3 days, and cisplatin 7 mg/m^2 per day for Day 1-Day 5/Day 8-Day 12, through IA port-A every 3 weeks for a cycle. The total cisplatin dose in one cycle was 70 mg/m^2, which is similar to a cycle of conventional EP regimen. The first cycle of chemotherapy was completed on August 31, 2020. After the 1st week of treatment, the total bilirubin level fell to 1.3 mg/dl and the ALT level also reached 123 U/L. After the first cycle of chemotherapy, the liver function and liver enzymes were both in normal range.

For better liver tumors control in the second cycle, we changed the cisplatin (HAIC) dose to 20 mg/m^2 for 3 days, Day 1-Day 3, every 3-week cycle on October 1, 2020. Durvalumab 1500 mg on day 1 was also added in the second cycle.

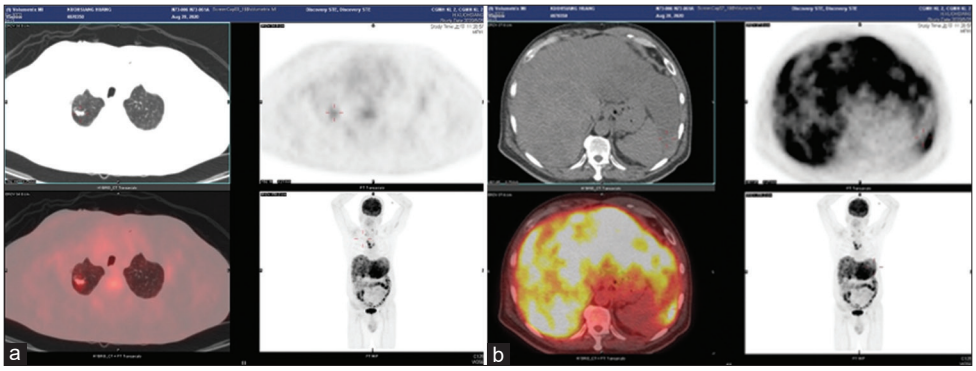

Figure 2: (a an b) Increased fluorodeoxyglucose uptake over right lung and liver was seen in positron emission tomography scan on August 28, 2020

After four cycles of IV etoposide and IA cisplatin treatment, marked regression of multiple right liver tumors was seen [Figure 4]. In addition, the CEA level decreased from 318.0 ng/ml to 45.1 ng/ml [Figure 5]. Brain magnetic resonance imaging showed no evidence of brain metastasis after four cycles of chemotherapy. He received brain CT with contrast regularly without prophylactic cranial irradiation. Durvalumab was then added for maintenance therapy after the whole EP regimen for a 28-day cycle. Only small residual tumors and lung tumors were seen in CT on February 22, 2021 [Figure 6]. His disease has since remained stable.

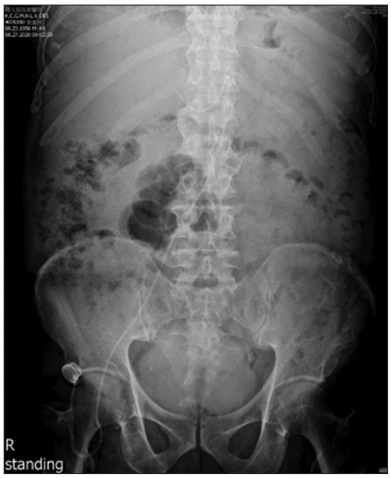

Figure 3: Intra-arterial port A was inserted into right femoral artery, reaching right hepatic artery

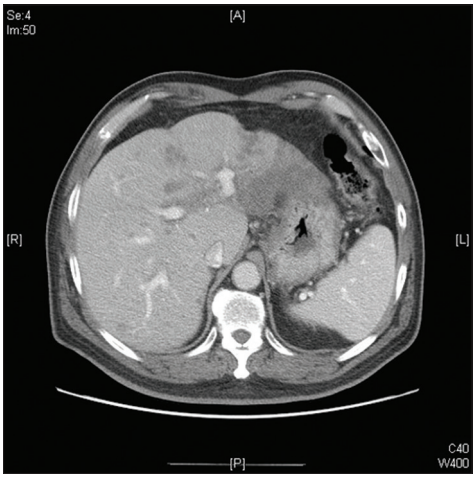

Figure 4: Follow-up computed tomography scan revealed regression of right liver tumors on November 18, 2020

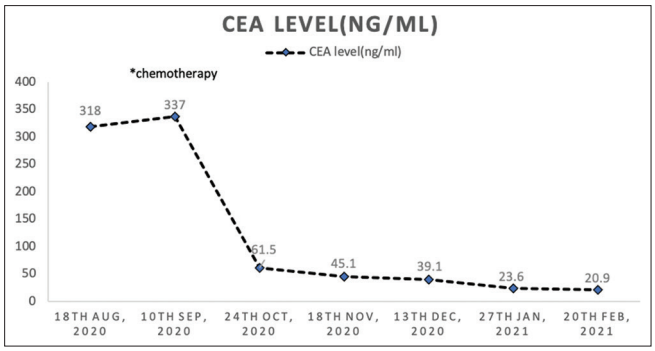

Figure 5: The further follow-up of carcinoembryonic antigen level, the first cycle of chemotherapy was initiated on August 31, 2020 and finished on November 2020. Carcinoembryonic antigen level was then dropped gradually

Discussion

This patient had extensive stage small cell lung cancer. Systemic therapy was suggested for first-line treatment. Etoposide 100 mg/m^2 + cisplatin 75 mg/m^2 combined with immunotherapy is currently the preferred regimen.[4,5] Before the availability of immunotherapy, the EP or E/carboplatin regimen played an important role in the treatment of small cell carcinoma with a good response rate of over 60%.[6,7] However, limited progress has been made in more than two decades, with a median overall survival of about 10 months. This may be due to the high recurrence rate after the first course of the EP regimen. Despite the high response rate and good tumor control with the EP regimen, small cell carcinoma progresses rapidly after completion of the EP regimen due to high mutation and production rates. Immunotherapy was then added for the high mutation rate of small cell lung cancer, which suggests that these tumors may be immunogenic and may respond to immune-checkpoint inhibitors.[8] EP-based regimens with immunotherapy are now the main treatment regimen for better overall survival because of good maintenance with immunotherapy.

Our case had extensive stage of small cell lung cancer (ES-SCLC) with liver metastasis. Severe obstructive jaundice may have gradually caused liver failure without good focal control of the tumor-related obstruction. This required effective liver tumor control as soon as possible. Few studies have mentioned the management of localized treatment for small cell lung cancer with liver metastasis. One study suggested that radiotherapy (RT) may improve the survival rate of patients with ES-SCLC with distant metastasis, particularly in those with only one metastatic site.[9] The total study population was 8595, of whom 56.8% had liver metastasis. These patients received liver RT to control the liver metastasis. The liver metastasis only group had survival benefit ($P < 0.001$). However, the liver and bone metastasis group had no obvious survival benefit ($P = 0.227$). The hazard ratio (HR) of overall survival with only one metastasis site in the whole population was 0.63, but there was no statistical difference in the group with more than one metastasis site (HR: 0.90). In addition, the study did not mention focal response rate or treatment-related toxicities. Our patient had ES-SCLC with more than one metastasis site and impending hepatic failure. Radiation-induced liver injury can cause acute hepatitis and liver fibrosis and should be considered in patients with impending liver failure.[10] Thus, liver RT was less favored in our case due to the lack of survival benefit and the potential for advanced liver damage with poor liver function.

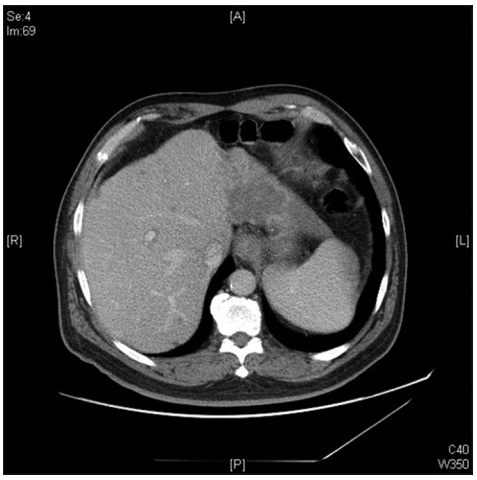

Figure 6: Follow-up computed tomography scan revealed only few residual tumors seen in the right liver on February 22, 2021

Based on previous studies on HAI treatment for colorectal cancer with liver metastasis, HAI chemotherapy to control liver metastasis can also be considered. HAI chemotherapy has been shown to be a good treatment method for local liver metastasis with fewer systemic adverse events from chemotherapy. A meta-analysis conducted in 2014 found that the response rate with HAI chemotherapy combined with systemic therapy was around 62%–85%, although it included heterogenous studies and regimen choice.[1] Possible treatment-related adverse events included abdominal pain, neurotoxicity, and biliary sclerosis, which were related to the choice of HAI chemotherapy regimen, dosage, and HAI catheter insertion technique. The incidence of systemic adverse events is relatively low compared with systemic chemotherapy.[1,11-14] The regimen choice is another important issue but varies in many studies. The most commonly used regimen is FOLFOX6. Several studies have directly separated the regimen into oxaliplatin 100 mg/m^2 with an HAI pump and other medications through IV infusion.[11] We also searched for other HAI treatment protocols including HAI chemotherapy for hepatocellular carcinoma control. IA cisplatin combined with 5-FU was used in several studies,[15,16] and the response rate of most regimens ranged from 10% to 40%. No studies have mentioned the regimens used for liver metastasis from small cell carcinoma. Due to the reported experience of HAI cisplatin treatment for HCC, we decided to use a cisplatin-based HAI chemotherapy regimen. The reported dose of HAI cisplatin has ranged from 7 mg/m^2 to 80 mg/m^2.[15] The lowest dosage was chosen because of possible tumor lysis syndrome and renal impairment. In addition, the low dose of chemotherapy with frequent administration was based on the metronomic chemotherapy concept.[17,18] Minimal toxic doses can still inhibit tumor growth primarily through antiangiogenic mechanisms while significantly reducing undesirable toxic side effect.

After the first cycle of low-dose cisplatin, the tumor response in the liver was acceptable without obvious adverse effects. Moreover, the liver function and bilirubin level both improved. Thus, the dose was escalated in the second cycle. The liver tumors were well controlled after a total of four cycles of HAI-IV etoposide treatment. However, the possible adverse effects of HAI chemotherapy including abdominal pain, neurotoxicity, biliary sclerosis, and HAI catheter insertion-related complications need to be monitored. Further studies are needed to investigate the risk of HAI chemotherapy-related complications.

In conclusion, focal liver tumor control with HAI chemotherapy can be considered for liver metastatic tumors from small cell carcinoma as in our case. More cases and further randomized control trials are needed in the future.

Ethics approval and declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

The study was approved by the Institutional Review Board at Chang Gung Memorial Hospital (#202101536B0).

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Nil.

Conflicts of interest

There are no conflicts of interest.

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