Oral S-1/Leucovorin combination in treatment of patient with an advanced large primary hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is a lethal disease and novel treatment strategies will increase survival of the patients. This study aimed to test a combined chemotherapy regimen of S-1/Leucovorin in treatment ofa patient who had a large primary hepatocellular carcinoma and was not suitable for hepatectomy or transcatheter arterial chemoembolization (TACE). The treatment course consisted of 50 mg S-1 and 25 mg Leucovorin given orally after meals twice daily for every other week. The outcome suggests that S-1/Leucovorin combination regimen on a biweekly course may provide a novel treatment option for advanced hepatocarcinoma patients.
[Feng Xie, MD, Feng Xu, MM, Rongxi Shen, MM, Long Yan, MM, Jiamei Yang, MM. **Oral S-1/Leucovorin combination in treatment of patient with an advanced large primary hepatocellular carcinoma.** *Life Sci J* 2012;9(3):1353-1355] (ISSN:1097-8135). http://www.lifesciencesite.com. 195

Keywords: large primary hepatocellular carcinoma; S-1; Leucovorin; oral chemotherapy

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common and lethal diseases in the world. HCC most occurs in patients with chronic hepatitis B or C and with cirrhosis, which makes clinical treatment more difficult because the patients have concomitant liver function impairment, poor general health, and are unable to tolerate arterial or intravenous chemotherapy. To date, surgery resection and liver transplantation are the most effective treatments for HCC patients; however, advanced tumor stages and limited sources of liver donors can make these options unfeasible.

Recently, the chemotherapy agent S-1 was successfully applied as an HCC treatment, and studies in different clinical trials (Diasio 1999; Shirasaka et al, 1996) have indicated a good response rate. S-1 is an oral combination regime of tegafur (that is a prodrug of 5-FU, which the liver and other organs convert to 5-FU), gimeracil (that is an inhibitor of the dihydropyrimidine dehydrogenase that degrades 5-FU), and oteracil (that is an inhibitor of the phosphorylation of 5-FU in the gastrointestinal tract, which thereby reduces the toxic gastrointestinal effects of 5-FU) at molar ratios of 1:0.4:1 (Diasio 1999; Shirasaka et al, 1996). This combination was first used for the treatment of advanced or metastatic gastric cancer and colorectal cancer (Koizumi et al, 2008; Ohtsu et al, 2000). In addition, Leucovorin, a folinic acid, was reported to synergistically enhance the effects of 5-FU and other chemotherapy agents due to its ability to suppress the 5-FU inhibitor thymidylate synthase.

In this study, we describe an HCC patient who presented at our clinic with a large primary tumor, but who was not suitable for the standard hepatectomy or transcatheter arterial chemoembolization (TACE) treatment. Thus, we treated this patient with combination of S-1/Leucovorin. After three months of treatment, the patient had achieved a stable disease status.

2. Case report

A 67-year old male Han patient was admitted to our hospital with complaints of flank and back discomfort and pain for a week" in August of 2010. The patient had a history of hepatitis B infection from 25 years past, but had normal AFP levels upon admission. Physical examinations showed mass on the right - upper quarter of abdomen. Magnetic resonance imaging (MRI) on August 23, 2010 revealed an irregular massive low-signal shadow in the right posterior lobe of the liver. T2W1 focus demonstrated an uneven high-signal shadow of 10.9 × 6.4 cm. Several nodular high-signal shadows were also found in the upper segment of right lobe (Figure 1). Thus, the patient was diagnosed with a large primary hepatocellular carcinoma of the right liver lobe with multiple foci and hepatic cirrhosis.

The patient had Child-Pugh class B liver functions, specifically: TBil, 31.8 μmoL/L; DBil, 11.9 μmoL/L; IBil, 19.9 μmoL/L; ALB, 29.4 g/L; GLB, 41.1 g/L; ALT, 70 U/L; G-GT, 140.0 U/L; HB, 134 g/L; WBC, 4.35 x 10^9/L; PLT, 46 x 10^9/L; PT, 15.0 s; APTT, 36.1 s; immunoreactivity-positive HBsAg, but -negative HBsAb, HBeAg, HBeAb, and BcAb; and, HBV-DNA $<10^3$. The multiple lesions of the tumor and the patient's condition made surgical resection not feasible. Therefore, an oral S-1/Leucovorin combination treatment regimen was designed and administrated to the patient starting on August 25, 2010. The treatment course consisted of 50 mg S-1 and 25 mg Leucovorin

after meals twice daily for seven days for every other week.

Liver functions, routine blood and coagulation tests, and MRI were performed every six weeks during this treatment course. The MRI images obtained on November 22, 2010 showed that the tumor in the right posterior lobe of the liver had reduced to 9.6 × 5.9 cm (Figure 2). During treatment, there was no decrease in neutrophils and platelet count or increase in serum creatinine levels. Clinically, no other adverse effects were observed, such as infection, diarrhea, or stomatitis. To date, the patient retains the Child-Pugh class B liver function and is continuing the combined chemotherapy regimen; however, a recent chest X-ray examination yielded a suspicious finding which may be a potential pulmonary metastasis, despite the intrahepatic tumors appearing otherwise as stable.

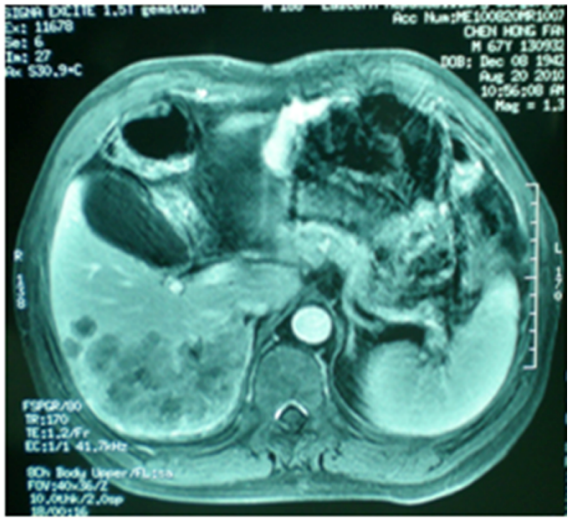

Figure 1. MRI on Aug 23, 2010. The image shows an irregular, massive low-signal shadow in the right posterior lobe of the liver. T2W1 focus demonstrated an uneven high-signal shadow of 10.9 × 6.4 cm in size. In addition, several nodular high-signal shadows were found in the upper segment of the right lobe.

3. Discussion

CT scan and MRI are the most frequently used tools for HCC diagnosis. If they are used correctly, a biopsy is not needed to confirm HCC diagnosis (Talwalkar and Gores, 2004). Nevertheless, although these cost-efficient diagnostic means are used in clinic, most HCCs are diagnosed in the late stages. This may because of the preexisting conditions and non-specific symptoms or lab tests that delay suspicion of HCC.

To date, management of HCC patients usually includes surgical resection and liver transplantation. Neoadjuvant or adjuvant systemic chemotherapy has not yet been shown to have any survival benefit, although 5-FU has been used as the basic drug in treatment of advanced hepatocarcinoma since the 1960s. The underlying mechanism that limits 5-FU efficacy in HCC has been determined. Dihydropyrimidine dehydrogenase (DPD), which is highly expressed in tumor cells, is a rate-limiting enzyme for 5-FU catabolism; in hepatocarcinoma cells, DPD decomposes 5-FU into a toxic metabolite, thereby significantly reducing the 5-Fu concentration and its functional potential. More recently, Leucovorin was found to increase the therapeutic efficacy of 5-FU in HCC patients. This positive effect on 5-FU is due to Leucovorin suppressing the 5-FU inhibitor thymidylate synthase.

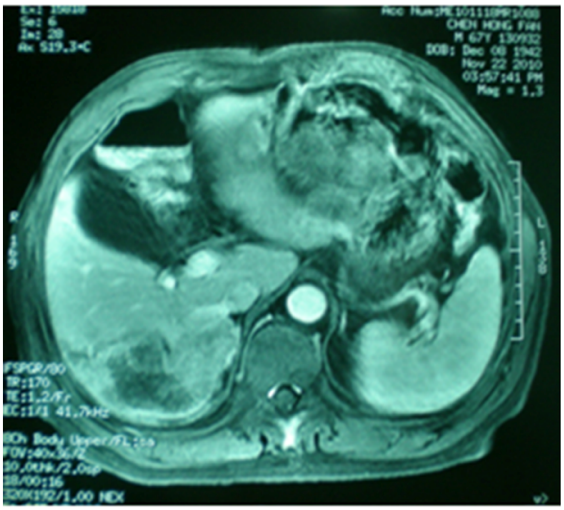

Figure 2. MRI on Nov 22, 2010. The image shows that the tumor in the right posterior lobe of the liver had reduced to 9.6 × 5.9 cm.

Indeed, S-1/Leucovorin has been used to treat advanced or metastatic gastric cancer and colorectal cancer [3,4]. However, to the best of our knowledge, no reports in the literature have described S-1/Leucovorin combination therapy for HCC treatment. Several phase II clinical trials of single agent S-1, however, have been conducted for advanced hepatocellular carcinoma, and have indicated a high clinical response rate, longer disease-free survival, and improved overall survival rate. For example, a phase I/II clinical trial in Japan showed that the partial response rate of advanced HCC to S-1 monotherapy reached up to 21.7%, with a progression-free survival and overall survival of 3.7 and 16.6 months, respectively (Furuse et al, 2010). Another phase II clinical trial in Korea reported similar results, in that the partial response rate reached 23.8%,

with time to progression and overall survival of 4 and 14 months, respectively (Kim et al, 2010). These data are impressive and rare in HCC management history, which brings hope for advanced HCC patients.

The S-1/Leucovorin regimen has been widely utilized for head and neck cancer and recurrent colorectal cancer to increase survival of these patients. This particular drug combination was also found to be more tolerable than S-1 monotherapy (Shin et al, 2011; Koizumi et al, 2010). The S-1/Leucovorin biweekly treatment course has showed better efficacy and safety than that of two weeks' administration with two weeks break in treatment of advanced colorectal carcinoma (Shirasaka 2009). We, therefore, copied this regimen treatment course for our patient since he had advanced hepatocarcinoma with liver function impairments.

Our data showed that the patient had a very stable disease with slightly decreased tumor mass in response to treatment. In addition, the neutrophils and platelet count remained stable and there was no increase in serum creatinine levels. Our case report may provide a novel option for treatment of advanced HCC patients in the future.

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7/22/2012