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Case Report
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A middle-aged man with a troubled liver: Combination therapy in advanced (BCLC Stage C) hepatocellular carcinoma

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ABSTRACT

Advanced hepatocellular carcinoma carries a bad prognosis with a survival of only few months. Barcelona Clinic Liver Cancer (BCLC) Guidelines recommended sorafenib monotherapy as the treatment modality for advanced BCLC Stage C disease, citing a two-month increase in survival rates. Here, we highlight a case with advanced HCC (BCLC Stage C) treated with combination therapy of liver resection and Sorafenib therapy. The patient's current survival rate was beyond 10 months. We also discuss the current evidence on liver resection with Sorafenib therapy in hepatocellular carcinoma. The description of the case may benefit in future diagnosis and treatment.

Key words: *Hepatocellular carcinoma, sorafenib, hepatectomy*

Introduction

The fifth most common cancer in the world is hepatocellular carcinoma [1]. Various authors have highlighted the multidisciplinary approach to treat such a condition because of the underlying cirrhosis [2]. Clinicians reported that patients, in earlier stages of cancer, may be treated with radiofrequency ablation and in the intermediate stage to be treated by transarterial chemoembolization [1]. In the present case, we discuss the current evidence on liver resection with Sorafenib therapy in hepatocellular carcinoma.

Case Report

A 37-year-old doctor, who was fit and well otherwise, developed intermittent abdominal pain for two months. This was associated with lethargy, weight loss, and having a poor appetite. He denied any high risk behaviors or significant needle stick injury. His mother was previously noted to be Hepatitis B positive and treated, accordingly.

He experienced sudden worsening of abdominal pain, prompting a hospital admission. Oesophagoduodenoscopy (OGDS) examination revealed a peptic ulcer (Forrest III) and a positive Campylobacter-Like Organism (CLO) test. He received treatment with proton pump inhibitor (PPI) and eradication triple therapy.

He was presented two weeks later in another hospital with persistent abdominal pain. Upon examination, a firm and smooth epigastric mass measuring 6 x 4 cm was palpated below the left costal margin. There was no

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jaundice or ascites detected clinically. Blood investigations showed significant anaemia with haemoglobin (Hb) level of 8.3 g /dl. The renal function, liver function, and coagulation profile was normal.

Hepatitis screen showed HBs Ag reactivity. Abdominal ultrasonography and subsequent multiphase Computed Topography (CT) scan showed a large, 10 cm x 12 cm liver mass at segment II and III with subcapsular haematoma. The mass was heterogeneously enhancing in the arterial phase and washout in the portovenous phase (Figure 1). The left portal vein was thrombosed with evidence of portal lymphadenopathy. The liver however, was non-cirrhotic. A raised α-fetoprotein of 10.66 ng/ml confirmed a diagnosis of hepatocellular carcinoma, with radiological evidence of subcapsular rupture and macrovascular invasion. Further assessments revealed Child Pugh score of A (5) and the Eastern Cooperative Oncology Group (ECOG) performance status was 0. This patient was staged at BCLC Stage C.

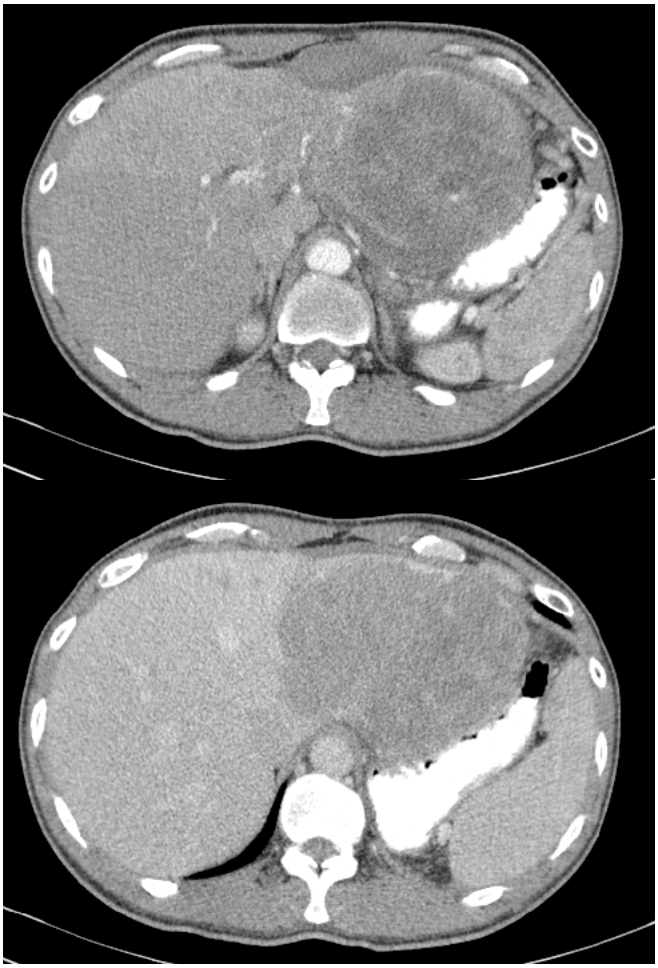

Figure 1. Heterogeneous enhancement in the arterial phase (above) and washout in the portovenous phase (below).

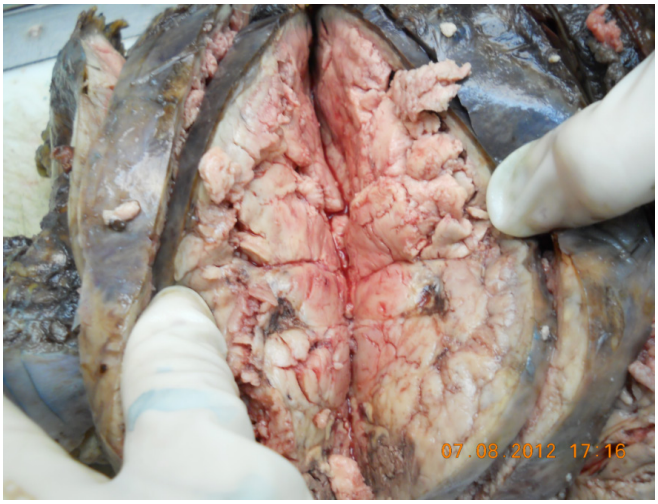

Figure 2. Photograph showing large hepatocellular carcinoma of size 16X14X10 cm.

Regarding the treatment of HCC, we strongly adhered to the BCLC guidelines. According to this guideline, Stage C disease is treated palliatively with Sorafenib monotherapy. However, following a thorough discussion with the patient and his family, and after taking into account the patient's otherwise favorable clinical status, we decided for a combination therapy of surgical resection and Sorafenib.

Intra-operative findings revealed a large left lobe tumour of the liver with rupture and extension to the diaphragm, with invasion to the left lung. A separate segment 4a and 4b mass was discovered. The patient underwent a left hepatectomy (anatomical resection) with excision of the diaphragm, wedge excision of the stomach and cholecystectomy. The left portal vein was flushed, but no tumour thrombus was observed.

The patient had an uneventful recovery with four days of recuperation in the intensive care setting and discharged at day eight, post-operatively. The histopathology examination confirmed a moderate to poorly differentiated classical type hepatocellular carcinoma, with advanced extension to the diaphragm, and vascular invasion to the portal and hepatic veins (Figure 2).

Sorafenib therapy (400 mg twice daily dosing) was initiated four weeks following the operation. He developed dose related drug reaction to sorafenib with maculopapular lesions over the hands, feet, scalp and mouth, and the dose was reduced and maintained at 200mg twice daily with resolution of the lesions. The CT scan at three months was reassuring with no evi-

dence of recurrence. However, at six-month follow up, he complained of back pain. A Positron Emission Tomography (PET) scan revealed disease recurrence and metastasis to the spinal vertebrae. He subsequently underwent posterior instrumentation of the T8-T10 vertebrae with good recovery. The patient survived 13 months, post-operatively.

Discussion

According to few authors, hepatocellular carcinoma (HCC) is the fifth commonest cancer in the world [1]. If one were to follow the American Association for the Study of Liver Diseases (AASLD) practice guidelines, Barcelona Clinic Liver Cancer (BCLC) staging system fulfils the criteria that HCC patients can be classified into different prognostic subgroups, and proper treatments can be offered, accordingly [3]. Early diagnosis allow for potential curative treatment with surgery (liver resection or transplantation) or local ablation therapy (Radiofrequency ablation (RFA), Percutaneous Ethanol Injection (PEI).

However, there is a lack of effective treatment options for advanced stages of HCC, invariably contributing to poor prognosis. The current recommendation for advanced stage (BCLC stage C) is Sorafenib monotherapy, the only systematic therapy to significantly prolong survival in patients with Child-Pugh A cirrhosis and good performance status [4].

This guideline is widely adopted by the major liver societies in North America and Europe, namely the American Association for the Study of Liver Disease (AASLD) and European Association for the Study of Liver (EASL). It was reported earlier that the median overall survival was 10.7 months in the Sorafenib group and 7.9 months in the placebo group [4].

Liver resection in BCLC stage C was not recommended as previous understanding of this disease does not show any additional survival advantage. However, this concept is now being put into question as there is a growing number of data suggesting improved survival in carefully selected BCLC stage C patients who underwent liver resection.

A recently published retrospective analysis showed the result of 68 patients with BCLC stage C with Child A's status, who underwent liver resection alone as the treatment modality [5]. The median survival outcome was noted at 33.4 months (95% CI 11.9, 54.9). These set of patients were carefully selected, with lower rate of extrahepatic spread (5.9%), vascular invasion (39.4%), and number of tumour >3 (19%) [5]. Unfortunately, the specific selection criteria was not documented or analysed, as this decision was made individually by the attending surgeons depending on tumour characteristics, and his or her preference.

This case report also highlighted the current need for refinement of the BCLC stage C stratification. There is a significant variation of long term outcome within this cohort of patients, due to the relevant prognostic heterogeneity of BCLC stage C. Some studies have also challenged the BCLC capacity to provide accurate stratification for clinical trials [6].

Presently, there is no data on the survival benefit in the combination treatment of liver resection and Sorafenib in BCLC stage C patients. However, a recently established observational study has commenced to collect data on the role of Sorafenib for residual disease after resection of curative intent [7]. Interestingly, latest research report showed that Sorafenib suppressed α-smooth muscle actin (α-SMA) expression, inhibited platelet derived growth factor (PDGF)-dependent signalling pathways in hepatic stellate cells (HSCs), down-regulated the PDGF-BB and Tumour growth factor (TGF-β1) expression in the HSCs supernatant, and restrained viability of the HSCs, thereby suppressing the proliferation and invasion in the HepG2 cells [8].

Conclusion

The incidence of hepatocellular carcinoma is always on the rise during recent years. The treatment modalities throw a challenge. The present case report highlighted a case of advanced HCC treated with combination treatment of liver resection and Sorafenib therapy. There is growing evidence on the role of liver resection in advanced HCC, with potential additional benefit from the already proven Sorafenib monotherapy in prolonging survival. Like any surgical procedure, patient selection is paramount to provide the best outcome. We advocate further studies to formulate a reproducible patient selection criterion for future analysis.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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