The Salvage Liver Transplantation in the Treatment of Hepatocellular Carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) is the fifth most frequent cancer worldwide and in most cases it evolves on a cirrhotic liver, which requires a complex treatment strategy that includes different options. We present the case of a 62 years old patient, suffering from chronic HBV and HDV hepatitis, which was found, in 2011 with a 7 cm HCC located in the sixth segment of the liver and resected. Within less than a year, tumor relapse was detected (multiple nodules in the remaining sixth segment). Systemic chemotherapy (Sorafenib) started being administered and two TACE procedures were performed at one year and seven months difference. Despite that, the CT and MRI showed the evolution of the disease. The therapy was stopped and the patient was listed for liver transplantation and the procedure was performed. The thirteen months post transplantation assessment showed no sign of tumor relapse.

Abbreviations: HCC - hepatocellular carcinoma, HBV - hepatitis B virus, HDV - hepatitis D virus, TACE - transcatheter arterial chemoembolisation, MRI - magnetic resonance imaging, LT - liver transplantation, PEI - percutaneous ethanol injections, UCSF - University of California, San Francisco, MELD - Model for End-Stage Liver Disease, BCLC - Barcelona Clinic Liver Cancer, HKLC - Hong Kong Liver Cancer, SLT - salvage liver transplantation

Key words: hepatocellular carcinoma, salvage, liver transplantation, resection

INTRODUCTION

Hepatocellular carcinoma (HCC) represents 80% (2) of the primary liver tumors, and is, overall, one of the most frequent cancers [(1) is the fifth (2) most frequent cancer in the world]. In most cases, it is associated with chronic liver diseases, especially with cirrhosis (in 80-90% (2,3) of cases HCC evolves on a cirrhotic liver, while 5-9% (2) of the cirrhotic patients will develop a HCC). This association requires a complex treatment. The treatment options available today include surgical resection, liver transplantation (LT), local ablation (using hyper (microwaves, radiofrequency, laser, ultrasound or locally injected hot saline) or hypothermia or local percutaneous ethanol injections (PEI), transcatheter arterial chemoembolization (TACE), chemotherapy and radiotherapy (4,5). The only potentially curative options are the liver transplantation

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(especially for early stage tumor on advanced cirrhosis), which removes both the tumor and the chronic disease that led to it, but is limited by the scarcity of donors and resection (which is recommended whenever possible) (6).

Liver transplantation can be performed as the first procedure or after resection, if tumor relapse occurs (salvage liver transplantation) (2,7-28).

Downstaging and bridging are different strategies used in the HCC management (4,29,30).

Downstaging is a strategy designed reduce the dimensions of tumors from outside of the criteria for resection or liver transplantation so they can meet the criteria and the procedure be performed. The downstaging procedures include percutaneous intratumoral pure alcohol injections, radiofrequency ablation, TACE or internal irradiation.

Bridging is designed to prevent dropout from the waiting list because of the tumor progression (31).

CASE REPORT

We report the case of a 62 years old male patient, who was found in 2004 with HBV and HDV hepatitis treated with Interferon between May 2005 and May 2006 (three doses each week), and then with Entecavir, starting from May 4th 2009 and which is still being administered at present.

In March 2011, as the follow-up revealed a α FP value of 50 ng/ml, a contrast-enhanced CT scan of the upper abdomen was performed, which showed a 7 centimeter tumor located in the 6th segment of the liver

and an increased size of the left lobe; no ascites; the percutaneous tumor biopsy found moderately-poorly differentiated hepatocellular carcinoma grade II-III in Edmondson-Steiner system (*figs. 1, 2*).

The patient was admitted in our center on May 19th 2011 for evaluation and therapeutic management.

Upon admission, physical examination revealed a patient with normal consciousness status and normal weight, normal pulmonary and cardiac auscultation, with a cardiac rate of 65 beats/minute and an arterial pressure on 130/80 mmHg. Abdominal examination showed absence of abdominal distension or ascites, but with a mild pain in the upper-right quadrant, and the inferior border of the liver aligned with the right costal margin.

Laboratory findings revealed a mild liver enzymes elevation and a α FP value of 79 ng/ml.

The upper gastro-intestinal endoscopy and the total colonoscopy were normal.

Taking into account all these findings, the diagnosis was liver tumor (hepatocellular carcinoma) developed on chronic HBV and HDV infection and the therapeutic option was liver resection.

The tumor was surgically removed on May 25th 2011 (non-anatomic liver resection) when cirrhosis was also diagnosed (intraoperative finding).

The pathology examination of the specimen revealed a 6 cm hepatocellular carcinoma (moderately-poorly differentiated hepatocellular carcinoma grade II-III in Edmondson-Steiner system, thus confirming the biopsy). Non-tumoral liver parenchyma showed liver cirrhosis.

Figure 1 - Preoperative CT showing a 7 cm lesion located in the 6th segment of the liver

Figure 2 - The same CT scan, a more caudal CT slice

The postoperative course was uneventful and the patient was discharged in the 12th postoperative day in good clinical condition and having normal laboratory findings.

The follow-up consisted of CT scans each six months, ultra-sound scans between the CTs (three months after each CT) and blood tests each three months, until the next year, as seen further.

In 2012, multiple nodules, sized maximum 13/9 mm were found in the remaining 6th segment. Trans-catheter arterial chemoembolisation was performed on March 27th 2012 and systemic chemotherapy (Sorafenib) started being administered in April 15th 2012 (four tablets daily) and since then, the blood tests were done each month.

In January 18th 2013 the CT scan reveals multiple pulmonary nodules, with the maximum diameters of 9 mm. There was a suspicion of pulmonary metastases. A PET-CT scan was performed, but in could not determine if the nodules were metastases or not, since they were too small. However, the further follow-up showed no change in their number or dimensions (even in April 2016, as seen further), so this suspicion was abandoned.

The patient further assessment revealed a nodule in the 6th segment, which required a new TACE procedure (on October 14th 2013; the chemotherapy continuing being administered).

On January 15th 2016 the RM scan described multiple nodules scattered all over the liver parenchyma some of them suggesting tumoral processes (*fig. 3*).

The chemotherapy administration was stopped in December 1st 2015 and the patient was listed for liver

transplantation (after completing the pre-transplant assessment (cardiologic and psychology evaluation, bacteriology (pharyngeal, nasal, blood, urine, feces) tests-negative- and whole body scintigraphy: no signs of bone metastases)).

The upper gastro-intestinal endoscopy described a sessile polyp measuring 5 mm, 34 cm from the dental arch and 2nd degree esophageal varices; no other findings. The total colonoscopy showed internal hemorrhoids; no other findings.

On April 15th 2016, an isogrup liver graft from a brain-dead donor was available and the patient underwent an orthotopic liver transplantation.

The preoperative laboratory tests showed WBC 5090/mm³, HGB 11.1 g/dl, 115000 PLT /mm³, ALT 229 U/L, AST 394 U/l, ALKP 217 U/l, γ GT 221 U/l, TBil 2.2 mg/dl, urea 34.7 mg/dl, creatinine 0.91 mg/dl, glucose 87 mg/dl, Na 139 mmol/l, K 4.0 mmol/l, INR 1.23, α FP 7.07 ng/ml, CA 19-9 92.80 U/ml and CEA 6.7 ng/ml.

The pathologic examination of the explanted liver showed a 4-centimeter tumor in the right lobe [a well-moderately differentiated hepatocellular carcinoma (Edmondson-Steiner II-III)] and, at quite a distance, a 2 cm nodule which showed high grade dysplasia.

The non-tumoral liver parenchyma presented liver cirrhosis. The lymph nodes did not present metastases (pN0).

The postoperative staging revealed a stage I hepatocellular carcinoma (pT1pN0pMx).

For induction of the immunosuppression, Basiliximab and Methylprednisolone were used, delivered intra-operatively. The patient received the second dose of Basiliximab in the 3rd postoperative day. For the immunosuppression maintenance Tacrolimus and Mycophenolate mofetil were administered.

A total bilirubin level elevation to 5.6 mg/dl called for administration of Dexamethasone, which corrected the bilirubin level. Following that, a elevation of the blood liver enzymes was detected and it was solved with Methylprednisolone and Acetylcysteine.

A minimal operative wound suppuration was found. The bacteriology test revealed MRSA, which was solved with Linezolid and Fluconazole and daily wound lavages.

No other postoperative course events happened and the patient was discharged in the 21st postoperative day, in good clinical condition and having the following liver tests: WBC 7560 /mm³, HGB 10.10 g/dl, 424000 PLT /mm³, ALT 58 U/L, AST 57 U/l, γ GT 163 U/l, TBil 0.5 mg/dl, urea 54.80 mg/dl, creatinine 1.24 mg/dl, glucose 84.70 mg/dl, Na 143 mmol/l, K 5.0 mmol/l.

The Mycophenolate mofetil was stopped three months after transplantation and the patient continued

Figure 3 - MRI image three months before the transplantation showing multiple nodular lesions scattered all over the liver parenchyma

to receive Tacrolimus for the rest of his life.

To avoid HBV recurrence, the patient receives Hepatitis B Immunoglobulin (2000 UI when the plasma level of HBs Ab is less than 200 U/I).

The last viral assessment on October 2016 showed no sign of HVB in the patient's blood.

The post transplantation follow-up consisted of blood samples each two weeks, ultrasound scans each month and CT scans at 3, 6 and 12 months after the transplantation.

At present (13 months after liver transplantation), the patient is disease-free, without evidence of recurrence on CT scan (on May 9th 2017), and normal laboratory tests: WBC 6800 /mm³, HGB 13.9 g/dl, 196000 PLT /mm³, AST 24 U/l, ALKP 140 U/l, γ GT 139 U/l, TBil 0.6 mg/dl, urea 43 mg/dl, creatinine 0.81 mg/dl, glucose 81 mg/dl, Na 142 mmol/l, K 4.3 mmol/l, α FP 3.3 ng/ml, CA 19-9 5.84 U/ml and CEA 1.47 ng/ml, CMV IgM 0.18, tacrolinemia 4.6 ng/ml.

DISCUSSIONS

The association hepatocellular carcinoma-cirrhosis requires a complex treatment management and different protocols were designed in order to assess the tumor, the stage of the cirrhosis and to decide the best strategy (which remains a subject of debate). There are several therapeutic options of which liver transplantation and the resection are the only potentially curative ones. The liver transplantation has the advantage of removing the tumor and the diseased liver (which is a potential source of new tumors), but is impaired by the scarcity of donors, and the difficulties and risks that immuno-suppression brings with it, while the resection allows the patient to continue living with his native liver (with no need for immunosuppression), but has a greater rate of tumor recurrence.

One of the most well known systems used to stage the tumor [and to decide whether or not a liver transplantation can be done for hepatocellular carcinoma on liver cirrhosis with good results (in terms of survival after 5 years or disease-free survival)] is the Milan system (single tumor $\leq$ 5 cm or no more than three tumors none $>$ 3 cm, with no vascular invasion and no extra-hepatic extension of the disease)(32). Since patients with tumors outside the Milan criteria still had good results after undergoing liver transplantation, these criteria were extended. Hence, systems like UCSF (University of California, San Francisco) (single tumor $<$ 6.5 cm or no more than 3 tumors, none bigger than 4.5 cm, and cumulative tumor size $<$ 8 cm, with no vascular invasion and no extra-hepatic extension)(32) or up-to-seven (or

the new Milan criteria: seven as the sum of the largest tumor (in cm) and the number of tumors)(33) have been developed (29,34). And even for tumors outside these criteria down-staging procedures can be used in order to bring tumors inside them. The down-staging protocol inclusion criteria are: 1) one tumor $\leq$ 8 cm, 2) 2-3 tumors $\leq$ 5 cm each and with cumulative tumor size $<$ 8 cm, 3) 4-5 tumors, none bigger than 3 cm, and with cumulative tumor size less than 8 cm (2). These systems can be also used to decide whether or not the resection is a good option (30).

In order to assess the liver function impairment due to cirrhosis are the Child-Pugh-Turcotte and the Model for End-Stage Liver Disease (MELD) scores.

As far as the treatment strategy is concerned, different systems have also been developed, like BCLC (Barcelona Clinic Liver Cancer)-the only system endorsed by the European Association for the Study of the Liver and the American Association for the Study of Liver Disease (35), HKLC (Hong Kong Liver Cancer) and many others which try to indicate the therapy strategy for each combination of disease (cancer and cirrhosis) stage (35). The recent consensus meetings (based on a great body of evidence from studies in Western and Asian countries) stated that HCC involving a single tumor, regardless of its size should be resected, whenever technically possible (35) and, of course, when the volume and function of the remaining liver allows that.

The resection was the first step in our reported case's therapy. Within less than one year, relapse was found and systemic therapy was initiated and two TACE procedures were performed (at more than a year distance). But the disease continued to evolve despite this therapy, therefore the patient was listed for a liver transplantation, which was performed on the 15th of April 2016. The thirteen months post transplantation assessment shows no sign of relapse.

The liver transplant in this case was a salvage liver transplantation (SLT) for relapses within Milan criteria after the resection, which couldn't be controlled by systemic chemotherapy and TACE (28,36-52).

CONCLUSIONS

Hepatocellular carcinoma is the fifth most frequent cancer in the world and in most cases it evolves on a cirrhotic liver. This association requires a complex algorithm for finding the best therapy for the given stage of the tumor and the given stage of the liver disease (plus the patient performance status and other diseases he may have), and there are still debates about which the best option might be.

For the reported case, the patient's evolution so far suggests that the transplantation was an inspired choice for this case.

The systemic therapy and TACE may be seen as bridging therapies.

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