Austin Journal of Cancer and Clinical Research

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Case Report

Long-Time Survival Experience of Sirolimus in Combination with Thymosin Alpha -1 and Huai'er Granule for Prevention Tumor-Recurrence in Liver Transplantation Recipient of Advanced Intrahepatic Cholangiocarcinoma: A Case Report

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Received: March 03, 2017; **Accepted:** April 03, 2017; **Published:** April 25, 2017

Abstract

Objective: To summarize the curative effect of the combined application of Sirolimus (SRL) plus Thymosin alpha-1 and Huaier Granule (PS-T) therapy to prevent the advanced intrahepatic cholangiocarcinoma (ICC) after liver transplantation (LT).

Methods: A 72-year-old woman with multiple ICC recurrence only within 1 year after the first surgical resection and was performed liver transplantation. Methylprednisolone (500 mg) plus Basiliximab (OTC) was used as the induction program, and small doses of hormone also used and were withdrawal 1 week postoperative. Tacrolimus (FK506) plus Mycophenolate Mofetil (MMF) was the initial scheme. And then switched to a SRL based replacement therapy within 1 month after LT. Moreover, received anti-HBV therapy to prevent relapse. The Thymosin alpha -1 subcutaneous injecting 10 days successively, 1.6 mg per time, once a day, and after that, twice a week; Huai'er Granule, 20 g per time, three times a day. The combined application therapy has been kept for long-time and she was followed-up regularly.

Results: The patient recovered well, liver function was recover smoothly, discharged 15 days after operation. Followed-up regularly and she survived well beyond 5 years till now. Compared with preoperative level (AFP112.8 ng/ml, CA199 2396 U/ml), there was a significant difference at every time point after LT, and staying at a steady level for long time (P<0.05).The recently results of clinical laboratory and examination have no evidence to confirm the tumor recurrence.

Conclusion: This advanced ICC patient after LT who accepted the combined application of SRL plus Thymosin alpha -1 and PS-T therapy has long-term survival benefit with no relapse. Therefore, this combined therapeutic plan maybe an effective neoadjuvant therapy for ICC patients after LT.

Keywords: Intrahepatic cholangiocarcinoma; Liver transplantation; Sirolimus; Thymosin alpha -1; Huaier Granule; Tumor-recurrence

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary tumor of the liver which originated from the intrahepatic bile duct epithelial and accounted for about 10%-15% of primary hepatic carcinoma (PHC) [1,2]. The morbidity of ICC is second only to hepatocellular carcinoma, and also the incidence of ICC is gradually increasing worldwide [3,4]. Although the ICC occupies only a rare proportion in PHC [1-2], but the even more higher grade malignancy and relapse rate postoperative were the main factors influencing the prognosis of patients [5-9], which also leads to tumor-recurrence at early phase on most patient and die rapidly [7-9]. Currently, surgery resection is regard as the only curative treatment strategies, however, because of the high malignant degree, the radical resection rate is rather low (15%-20%) [4,10], and the relapse rate postoperative is rather higher (up to 70%) [7,8], therefore, the postoperative 5-year survival rate is only 14%-40% [11].

Besides that, as its prognosis is poor due to poor outcomes from high recurrence rates, even after macroscopic curative resection, patients with ICC are usually typically excluded from liver transplantation (LT). Although, there currently has quite a few reports on the liver transplantation in the treatment of ICC [12,13], but efficacy remains controversial. Recently, several studies have proved that the selected patients with ICC who met the UCSF criteria and no lymph node involvement can benefit from LT, and the combined with neoadjuvant treatment for these cases may achieve an improved survival [13]. Despite the sorafenib, gemcitabine, 5-fluorouracil, cis-

Citation: Zhou L, Su X-J, Pan L-C, Du G-S, Zheng Y-G, Xiao L, et al. Long-Time Survival Experience of Sirolimus in Combination with Thymosin Alpha -1 and Huai'er Granule for Prevention Tumor-Recurrence in Liver Transplantation Recipient of Advanced Intrahepatic Cholangiocarcinoma: A Case Report. Austin J Cancer Clin Res. 2017; 4(1): 1075.

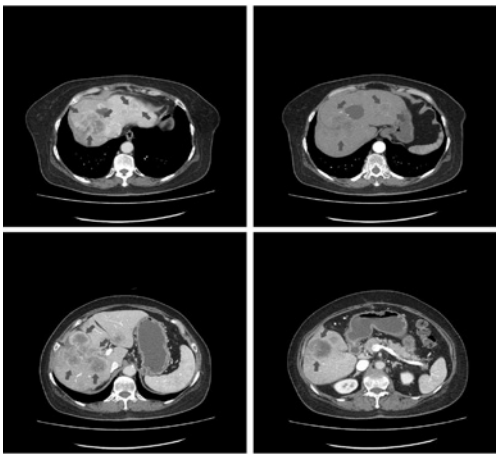

Figure 1: The image of abdominal enhanced CT preoperative indicated multiple space-occupying lesions in liver (displayed by red arrow). In accordance with the patients' medical history, was considered as ICC relapse.

Table 1: The changes of AFP and CA-199 pre- and post-operative.

Time(m)	Pre-LT	Post-LT							
		1	6	12	18	24	36	48	60
AFP(ng/ml)	112.8	23.2	10	7.8	7.5	7.05	6.9	6.17	4.9
CA-199 (U/ml)	2396	60.85	22.72	16.38	16.05	14.75	13.79	9.59	7.81

platinum, can play some effective role in treating tumor recurrence [13-15], but the result unsatisfactory and the adverse events also difficult to bear in some degree. To improve the survival benefit and decrease the recurrence rate, we probe and firstly proposed the application of combined therapy based on Sirolimus (SRL), Thymosin alpha -1 and Huaier Granule (PS-T) in preventing the tumor recurrence for advanced PHC after LT as the new neoadjuvant treatment. Here in, we have reported our initial experience of an advanced ICC patient who treated with SRL plus Thymosin alpha -1 and PS-T survival beyond 5 years.

Case Presentation

A 72-year-old woman was diagnosed intrahepatic cholangiocarcinoma (ICC) 7 years ago, and performed partial hepatectomy resection 1 year later, without regularly undertaking radiotherapy and chemotherapy. Then she underwent multiple tumor recurrence for 4 months, emergency hospitalized at 309th Hospital of PLA.

The Enhanced Computed Tomography (CT) and abdominal ultrasound all indicated multiple space-occupying lesions in the remnant liver, preoperatively. In accordance with the patients' medical history, it was considered as ICC relapse (Figure 1). The PET/CT detection also demonstrated that ICC relapse and no evidence for involvement of the hilar lymph node or vascular or bile duct and distant metastases. Furthermore, the tumor marker level of Alpha Fetal Protein (AFP) and CA-199 were promoted significantly with 112.8 ng/ml and 2396 U/ml respectively.

She underwent liver transplantation at December 28, 2011 successfully, and then, switched to intensive care units for the further treatment for 4 days. The patient recovered well, liver function was recover smoothly, discharged 15 days after operation. Follow-up regularly, and survival well till the paper drafted, also no obvious graft rejection and tumor recurrence occurred.

This study was approved by the Ethics Committee of Human Experimentation of the PLA 309th hospital. Written informed consent was obtained in accordance with the Declaration of Helsinki of the World Medical Association.

Pathology results

The volume of the resected liver was 24 cm*14 cm*9 cm with part liver velamen and dust color, there were many grayish white nodules in the incisal section. In accordance with the history of cholangiocarcinoma, it was diagnosis as multifocal, highly-moderately differentiated ICC with the minimum and maximum disease lesions was 0.9 cm*0.9 cm*0.9 cm and 6 cm*4 cm*4 cm respectively. Furthermore, there was no cancer embolus in portal vein.

Immunosuppressant protocol

She was informed about the therapeutic protocol, accepted the treatment, and gave their written informed consent. Methylprednisolone plus OTC was used as the preoperative induction treatment, FK506 plus Mycophenolate Mofetil (MMF) and hormone was utilized as the initial scheme in the early stage postoperative period, with hormone withdrawal 1 week after LT. And then gradually switched to a SRL based replacement therapy (SRL plus Thymosin alpha -1 and PS-T) within 1 month after LT. Moreover, FK506 was gradually reduced and withdrawn at six months after LT. Moreover, she received anti-HBV therapy to prevent Hepatitis B recurrence via intravenous injection of Human Hepatitis B immunoglobulin (HBIG) to maintain effective blood antibody titers.

The Thymosin alpha-1 was subcutaneous injected 10 days successively, 1.6 mg per time, once a day, and after that, twice a week, the dosage was the same as the previous; meanwhile, the PS-T taken orally with 20 g per time, three times a day.

Follow-up

Regular postoperative follow-up. The AFP and CA-199 level was detected at 1 week, 2 weeks, 1 month, 3 months, 6 months, 1 year and 1.5 years until 5 years, respectively. Regularly detected the blood drug level of the immunosuppressant. Recheck the abdominal ultrasound every 3 month as well as the CT of lung and abdomen every 6 month.

Results

Variation of AFP and CA199 level postoperative

Compared with preoperative level (AFP112.8 ng/ml, CA199 2396 U/ml), there was a significant difference at every time point after LT, and staying at a steady level for long time ($P<0.05$) (Table 1) (Figure 2).

Variation of imaging postoperative

The regularly abdominal ultrasound suggested that blood flow of liver graft was normal, with no obvious Bile duct stenosis and no signal of the tumor-recurrence and metastasis. The CT scan of lung and abdomen at 12 (Figure 3) and 24 months (Figure 4,5) emphasized that no performance of tumor-recurrence and metastasis in liver, celiac lymph nodes and bilateral lung.

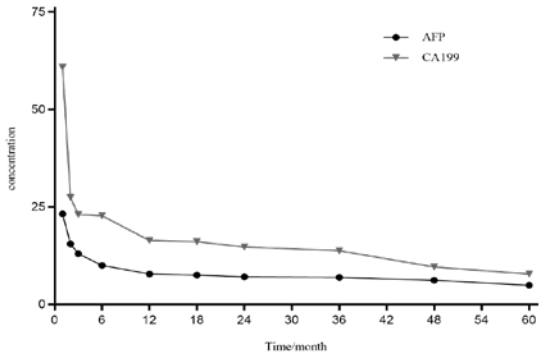

Figure 2: The diversity of AFP and CA-199 for long-time survival after transplantation.

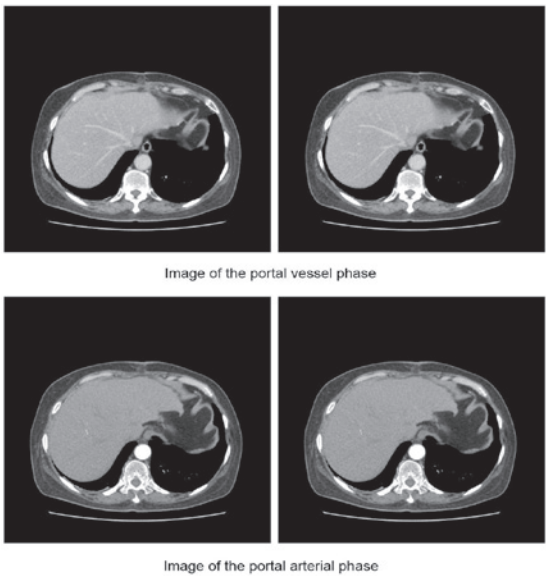

Figure 3: The image of abdominal enhanced scan of the patient 12 m after transplantation.

Discussion

The ICC is an even higher malignant tumor which originates from the distal bile duct epithelial cells beyond liver first class bile duct. Its morbidity seconds only the hepatocellular carcinoma, accounting 5%~10% for primary hepatic malignant tumor [15,16] as well as 10% for all bile duct cancer. The incidence rate increasingly promoted [17-19] worldwide in recent years. At present, the preferred method for ICC is the radical surgical ablation. However, even worse, most ICC tumors are deemed unresectable at the time of diagnosis and only a limited number (12% to 32%) of patients with confined disease are eligible for surgical treatment including surgical resection, LT or ablative therapy [20,21], because of the disease was often diagnosed at advanced stage or the existence of serious complications. Furthermore, there was high recurrence rate in those who were performed surgical resection, and the long-term survival benefit was still poor. Currently, reported survival rates for these patients at 5 years range from 22% to 40% [11,22].

Interestingly, transplantation, as a treatment for cholangiocarcinoma, was originally thought to provide a good

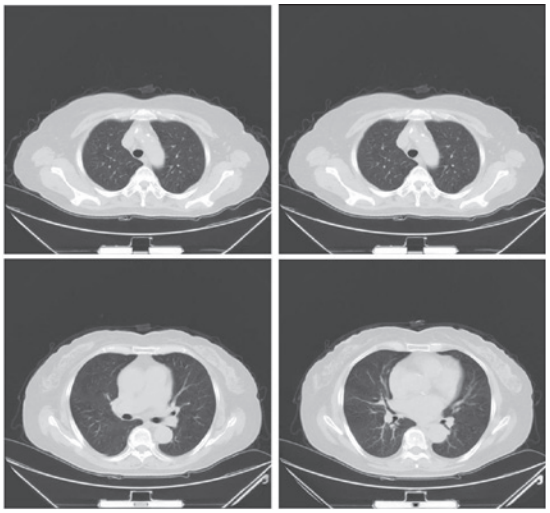

Figure 4: The image of chest computed tomography 2 years after transplantation.

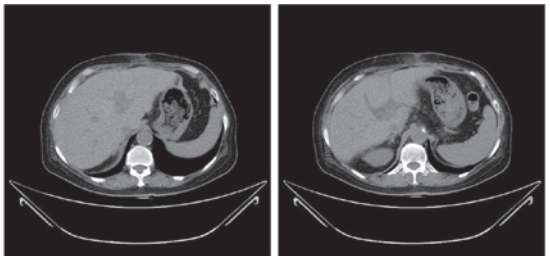

Figure 5: Image of abdominal enhanced scan 2 years after transplantation.

chance for cure. LT theoretically provides the opportunity for wide resection margins, thus potentially expanding the number of patients eligible for surgical intervention. Although, there currently has quite a few reports on the liver transplantation in the treatment of ICC [12,13], however, cholangiocarcinoma has been a controversial indication for LT, with limited results because of a high incidence of recurrent tumor. Based on these experiences, most transplant centers once consider ICC to be a contraindication for liver transplantation [4,5,7,10]. However, recent data show excellent outcomes in a select patient population, thereby justifying transplantation for certain ICC patients [13,23,24]. Moreover, for the selected patients, the role of neoadjuvant therapy in combination with liver transplantation could be promising for ICC treatment [12,25]. These all were the reasons why we try to attempt treat ICC with LT meanwhile with a SRL based replacement therapy.

Expectedly, when the patient in this study who was first diagnosed as the intrahepatic cholangiocarcinoma had performed partial hepatectomy, multiple hepatic tumor recurrence was appeared in liver again only within 1 year postoperative and that the tumor developed even fast than the first time. This is high consistent with the literature reported [7-8]. Therefore, when the patient diagnosed with tumor relapse, we performed LT for her, and selected a SRL based replacement therapy at the early stage postoperative; meanwhile, discontinue to use the FK506 which can increase the risk of tumor relapse. It is encouraging that the tumor makers and the imaging detection were no abnormal for the first 6 to 12 months.

The recently reported series from China [12] and other centers [26-28] have indicated that the LT plus neoadjuvant therapy or not can promote the survival rate, but the recurrence time was observed mainly from 12 to 24 months after operation. However, the patient in our center did not undergo the tumor relapse until paper drafted beyond 60 months. All the index associated with tumor recurrence was at normal limits, and also no rejection and biliary complications occurrence.

Compared with the literatures, we analyze the potential reasons as the follows: Firstly, we replace the FK506 switching SRL at the early stage (within 1 month) after LT. Because, Mammalian target of rapamycin (mTOR) inhibitors have been shown to have a direct antitumorigenic effect and to inhibit cell growth through antiangiogenic, antiproliferative effect [29]. The recently "SiLIVER" study has demonstrated that sirolimus (SRL) can "kill two birds with one stone" by acting as an efficacious immunosuppressive drug and an antineoplastic agent for the LT patients with clinical safety and efficacy [30]. Unlike FK506, the therapy concentration of SRL did not rely on drug dosage, but mainly on liver and renal function, as well as rejection status. Therefore, we also suggest that the SRL levels are maintained at or below 10 ng/ml to avoid interstitial pneumonia, thrombocytopenia, and other severe adverse reactions. Secondly, some transplantation centers perform preliminary researches [31,32] have indicated that single application of the PS-T in post-transplantation treatment of liver cancer can significantly improve the patient quality of life and prolong survival time but has a negligible effect on the short-term recurrence rate in patients beyond the Milan and UCSF criteria. So, we advised that 20 g PS-T should be orally taken thrice per day as early as possible and continuously after transplantation. Thirdly, the application of Thymosin alpha -1 in the field of organ transplantation hasn't increased the risk of rejection rate even then theoretically infeasible [33,34]. Related studies indicated that an early single application of Thymosin alpha-1 after liver transplantation can improve the patient's cellular immune function. In this study, the Thymosin alpha-1 was used 2 days after LT, it did not increase the risk of graft rejection during the 5-years survival. To reach the therapy concentration, we recommended an early application and continuous subcutaneous injection firstly lasting for 10 days, 1.6 mg dose per time, once a day, which was later changed to twice per week.

Although intrahepatic cholangiocarcinoma (ICC) is a rare malignancy in PHC, but it carries a poor prognosis due to the lack of both early clinical symptoms and efficient diagnostic modalities. The patient including in this study displayed a multiple tumor relapse only within 1 year and was no possibility for secondary surgery resection. Multi-imaging examinations preoperative showed that the patient had been in the advanced stage of tumor, LT in combination with a SRL based replacement therapy showed a benefited survival results beyond 5 years. The recently results of clinical laboratory and examination have no evidence to confirm the tumor recurrence.

Therefore, this combined therapeutic plan (SRL plus Thymosin alpha-1 and PS-T) maybe an effective neoadjuvant therapy for ICC patients after LT. Due to the case reports, the long-term effect of anti-tumor therapy and prospective clinical study with large sample has been in under way.

Acknowledgment

The authors thank Professor DU Guo-sheng, SHI Xian-jie and XIAO Li for their contribution to the drafting of this article.

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Austin J Cancer Clin Res - Volume 4 Issue 1 - 2017
ISSN : 2381-909X | www.austinpublishinggroup.com

Citation: Zhou L, Su X-J, Pan L-C, Du G-S, Zheng Y-G, Xiao L, et al. Long-Time Survival Experience of Sirolimus in Combination with Thymosin Alpha -1 and Huai'er Granule for Prevention Tumor-Recurrence in Liver Transplantation Recipient of Advanced Intrahepatic Cholangiocarcinoma: A Case Report. Austin J Cancer Clin Res. 2017; 4(1): 1075.