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Original research

Prior Trans-arterial chemoembolization - A protective factor against rapid HCV recurrence post liver transplant in patients with HCV with HCC? - A Retrospective Cohort Study

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HIGHLIGHTS

- There are very few studies comparing impact of pretransplant HCC therapies either as a bridge to transplant or to downstage.
- HCV-recurrence after LT is one of the most important issues. Histologic recurrence is seen in more than 50% of HCV-infected grafts within the first year and is responsible for allograft failure in 10% of the recipients within 5 years of transplantation.
- In our study on multivariate analysis only patient without TACE was associated with increased risk of rapid histological recurrence of hepatitis c.
- In our study patient who did not underwent TACE were having significantly increased risk of rapid histological recurrent of hepatitis c post transplant.
- To our knowledge it is one of the initial studies on effect of chemoembolization on the post transplant HCV recurrence.

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ABSTRACT

Background: HCV recurrence after liver transplant is nearly universal and results in progressive fibrosis, cirrhosis, graft loss, retransplantation and mortality. There are very few studies comparing impact of pretransplant HCC therapies either as a bridge to transplant or to downstage like TACE, hepatectomy, RFA, PEI on HCV recurrence post transplant. Primary aim of the study was studying prognostic factors associated with HCV recurrence including pre transplant HCC therapies.

Material and methods: All the patients who have undergone living donor liver transplantation at Kaohsiung Chang gung memorial hospital, Taiwan for HCV related HCC between July 2002 and June 2012 were analyzed retrospectively. Severity of HCV histological recurrence was categorized according to the ISHAK hepatitis activity index score. Rapid HCV recurrence was defined ISHAK hepatitis activity index (HAI) score greater than 4 at one year. Statistical analysis was done using SPSS version 21. (IBM).

Results: One hundred and nine patients with HCC associated with HCV undergo living donor liver transplant from July 2002 to June 2012. Median follow up time was 31 months. Forty nine patient had significant hepatitis c recurrence at the end of one year (HAI >4) and were included in study group.60 patients without significant hepatitis c recurrence were included in control group. On univariate analysis patients who did not undergo pre-transplant trans arterial chemoembolization (0.035), primary transplant (without prior hepatectomy) ($p = 0.031$), high meld score ($p = 0.036$), high viral load pretransplant (0.007), High AFP levels (0.013) were significantly associated with rapid histological recurrence of HCV (HAI greater than 4 at one year post transplant). Total 61 patient underwent prior transarterial chemoembolization, 22 of these patients developed significant HCV recurrence while 39 patient did not developed HCV recurrence. On multivariate analysis only patient who did not undergo TACE were significantly associated with rapid histological recurrence of HCV (odds ratio 3.310, $p = 0.018$ 95% confidence interval 1.22–8.94).

Conclusion: Prior TACE do not increase post transplant HCV recurrence but may be beneficial for it.

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1. Introduction

HCV-related end stage liver disease continues to be the leading cause of hepatocellular carcinoma (HCC) and one of the most common indications for liver transplantation (LT) [1]. Hepatitis C virus (HCV) infection is one of the causative factors for the development of HCC [1]. Although the mechanism of carcinogenesis by HCV is still unknown, chronic inflammation, liver cell necrosis and regeneration, and extensive fibrosis are mentioned as probable causative factors of HCC [2].

HCV recurrence after liver transplant is nearly universal and results in progressive fibrosis, cirrhosis, graft loss, re transplantation and mortality [3]. HCV-recurrence after LT is one of the most important issues, the course of graft hepatitis is usually more progressive compared to the natural setting of HCV-infection [4–7]. Histologic recurrence is seen in more than 50% of HCV-infected grafts within the first year and is responsible for allograft failure in 10% of the recipients within 5 years of transplantation [8].

There are very few studies comparing impact of pre transplant HCC therapies either as a bridge to transplant or to downstage like TACE, hepatectomy,RFA, PEI on HCV recurrence post transplant.

2. Aim of the study

Primary aim of the study was studying prognostic factors associated with HCV recurrence including pre transplant HCC therapies.

3. Material and methods

All the patients who have undergone living donor liver transplantation at Kaohsiung Chang gung memorial hospital, Taiwan for HCV related HCC between July 2002 and June 2012 were analyzed retrospectively. Recurrent HCV and acute cellular rejection (ACR) were diagnosed based on liver biopsy results. Banff criteria were applied to the diagnosis of ACR and diagnosis of HCV recurrence. Severity of HCV histological recurrence was categorized according to the ISHAK hepatitis activity index score. Rapid HCV recurrence was defined ISHAK hepatitis activity index (HAI) score [9] greater than 4 at one year.

One hundred and nine patients with HCC associated with HCV underwent living donor liver transplant from July 2002 to June 2012. Median follow up time was 31 months. Forty nine patient had significant hepatitis c recurrence at the end of one year (HAI >4) and were included in study group.60 patients without significant hepatitis c recurrence were included in control group.

4. Protocol biopsies

We perform protocol biopsy 4 month and one year post liver transplant for HCV. Biopsies are done in between if HCV recurrence is suspected. Hepatitis activity score is noted as per Ishak hepatitis activity score and fibrosis as per Ishak fibrosis score.

5. Follow up protocol

We follow up patients with HCC with Ultrasonography and CT scanning every 3-month for first year every 6 month for second year and yearly there after.

6. Loco regional therapies protocol

Liver resection or transplantation was done according to BCLC liver staging. RFA was done when patients were not suitable for liver resection or transplantation or patient refused either of the above therapy.

7. TACE protocol

TACE was performed according to National Cancer Center protocol. Briefly, an arterial catheter was inserted into the femoral artery by the Seldinger method and placed in the hepatic artery. Tumor feeding vessels were superselected where possible; the catheter was inserted to the level of the segmental arteries, subsegmental arteries, or lobar branches, and a solution containing doxorubicin hydrochloride and of iodized oil (lipiodol) was infused.

. The dosage of doxorubicin and lipiodol was determined according to the tumor size, the presence of arteriovenous shunts or extrahepatic collateral vessels, and the underlying liver functions on a case-by-case basis. The endpoint of infusion was stasis of.

the lipiodol mixture in the feeding arteries with or without the appearance of iodized oil in the portal vein adjacent to the tumor. TACE efficacy was evaluated in all patients after 4–8 week by dynamic spiral CT of livers for evaluation of response and recurrence.

8. Immunosuppression protocol

We use baciliximab induction and another dose at postoperative day 7. Intraoperative methyl prednisolone 500 mg iv before revascularization and then we gradually taper it over 3 month. We start low dose tacrolimus on first post operative day and gradually increase with target tacrolimus levels of 5–10 ng/ml we use mycophenolate mofetil as a third agent. In rejection episodes particularly with HCV cases steroid are given only for biopsy proven rejections.

9. Statistical analysis

Categorical variables were analyzed by chi square test and fisher *t*-test; continuous variables were analyzed by Mann Whitney *U* test. P value < 0.05 was considered statistically significant. Statistical analysis was done by SPSS version 21 (IBM).

10. Results

Patients' characteristics of both groups and univariate analysis are described in Table 1.

11. Univariate and multivariate analysis

On univariate analysis patients who did not undergo pretransplant trans arterial chemoembolization (0.035), primary transplant (without prior hepatectomy) ($p = 0.031$), high meld score ($p = 0.036$), high viral load pretransplant (0.007), High AFP levels (0.013) were significantly associated with rapid histological recurrence of HCV (HAI greater than 4 at one year post transplant).

On multivariate analysis only patient who did not underwent TACE were significantly associated with rapid histological recurrence of HCV (odds ratio 3.310, $p = 0.018$ 95% confidence interval 1.22–8.94) [Table 2].

12. Discussion

Studies have shown that prior trans arterial chemoembolization have no beneficial effects on post transplant HCC recurrence [10] but very few studies have shown effect of trans arterial chemoembolization on post transplant HCV recurrence.

Park et al. [11] showed that single session of TACE does not significantly aggravates Hepatitis B hepatitis however no such study is found on hepatitis C.

In our study patients who did not undergo pre-transplant trans arterial chemoembolization (0.035), primary transplant (without