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Hepatology Highlights

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Outcome of early *vs.* deferred antiviral treatment for recurrent hepatitis C in liver transplant recipients

Campos-Varela I, et al. Cirrhosis due to hepatitis C virus infection has become the most common indication for liver transplantation, however graft infection is virtually a rule leading to cirrhosis in 10% to 30% of patients in 5 to 7 years following transplantation. There are few high quality studies to guide treatment of HCV after liver transplantation. Combination therapy with interferon plus rivabirin has been associated with end of treatment response rates as high as approximately 50% and sustained virological response rates of over 20 % in some series.[1] However the optimal time to begin the antiviral therapy still debatable and its usually based on the fibrosis stage. In this regard Castells evaluated the efficacy and safety of treatment with pegylated interferon and rivabirin in the acute phase of recurrent HCV after liver transplantation, when risk of acute rejection is presumably lower. Treatment with combined therapy yielded a sustained virological response of 34.7%. Although proven safe and effective the limited sample size and comparison with patients who did not receive antiviral therapy precluded identification of patients who might obtain the most benefit from this strategy.[2]

In the present study Campos-Varela *et al.* analyzed early treatment of recurrent HCV and compared with treatment of established chronic HCV recurrence in terms of efficacy, safety and long-term outcome. During 9 consecutive years patients with recurrent VHC after liver transplantation were retrospectively analyzed and classified into early treatment group and deferred treatment group. During 18 consecutive months, patients with acute recurrent HCV were given prompt treatment regardless of their clinical or histological status and subsequently, the indication for treatment was based on clinical and histological criteria.

Final cohort included 105 patients, 60 in the early treatment and 45 in the deferred treatment group. There were no differences in the sustained virological response (23% in the early treatment vs 36% in deferred). Survival analysis showed a trend towards shorter survival in the early treatment group during the first year, but similar long-term survival in both groups.

Genetic variations in the IL28B gene appear to influence response rates to combination therapy with peginterferon and ribavirin. In a study of 67 patients who had undergone liver transplantation for HCV infection, patients who were homozygous for the C allele at the rs8099917 polymorphic site had significantly higher SVR rates than patients with heterozygous CT or homozygous TT alleles (54 *vs.* 11%).[3] In addition, the SVR rate was higher if the donor was homozygous for the C allele (44 *vs.* 9%). The highest SVR rate was seen when both the donor and recipient were homozygous for the C allele (56%). It was low when only one was homozygous (10%), and it was lowest when neither was homozygous (0%).

Although early treatment is a safety and efficiently as deferred treatment, the optimal time to start treatment seems to be more likely to be choosen based on the severity of recurrence. According to this observation further studies to predict variables associated with severe recurrences are needed.

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Is recurrence rate of incidental hepatocellular carcinoma after liver transplantation similar to previously known HCC? Towards a predictive recurrence score

Piñero F, et al. Approximately 30% of all liver transplants are indicated for hepatocellular carcinoma. Also about 30% of patients are diagnosed at early stages with routine hepatocellular monitoring. However despite correct application of the Milan criteria, recurrence after transplantation is diagnosed in 15-40% cases.[4]

With better imaging diagnostic technics hepatocellular detection rates have been enhanced.[5] However, despite this imaging advances very small nodules may only be detected during explant pathology examination, leading to incidental hepatocellular carcinoma, which nowadays remains an unresolved problem and generates uncertainty over risk of recurrence and follow up after liver transplantation.[6]

In the present study Piñero F, *et al*. evaluated the incidence of incidental hepatocellular carcinoma, identify risk factors for recurrence and compare recurrence rates between incidental and confirmed hepatocellular carcinoma.

All explanted livers were examinated by two different pathologists. A total of 309 cirrhotic patients were transplanted during the study period. Fifty four had hepatocellular carcinoma 39 confirmed and 15 incidentals. All patients had *postrasplanted* follow up every 6 months using CT or MRI. No differences in survival were found between confirmed and incidental hepatocellular carcinoma. Based on explanted liver pathology findings related to hepatocellular carcinoma recurrences (total tumor diameter > 4 cm, < 3 HCC lesions, microvascular invasion, nuclear grade >II and presence of neural invasion) a recurrence predicting score (RPS) was developed ranging from 0 to 6 points, identifying 2 groups: low risk (6.5% cumulative risk for recurrence) with a ROC curve analysis predicting non-recurrence al 0.75, and intermediated-high risk (14.3 and 66.7% cumulative risk).

Prior to the study the authors hypothesized that incidental tumors would present lower rates of microvascular invasion and smaller undifferentiated nodules, according to previous findings, both tumors had similar levels of microvascular and neural invasion with lower cumulative recurrence for the incidental HCC although not statistically significant.

According to this study aggressiveness of tumor biology is similar in both confirmed and incidental hepatocellular carcinoma, and after applying the recurrence predicting score a similar percentage of patients for low risk for recurrence were detected. These results suggested that HCC monitoring should remain strict for both.

Although the predicting recurrence score seems good for detecting low risk patients for recurrence, further prospective studies with bigger populations are needed to better validate the RPS and to propose a cost-effective follow-up for hepatocellular recurrence after liver transplantation. Also the use of additional explanted liver variables, not yet validated, such as inmunohistochemical biomarkers, molecular cancer pathways as risk factors of recurrence.

Factors affecting screening for hepatocellular carcinoma.

Al Hasani F*, *et al. Surveillance for hepatocellular carcinoma is considered a standard of care for patients with chronic liver disease who are at risk of developing this malignancy.

This recommendation is supported by AASLD and EASL guidelines.[7,8] Unfortunately, many patients at risk are not regularly screened. The aim of the present study was to exploring the characteristics that affect enrollment in a surveillance program. The investigators prospectively studied 82 patients, 48 were in a surveillance program before the diagnosis of HCC and 5% of cirrhotic patients were not screened. The main characteristics analyzed age, sex, level of education, Child-Pugh status and MELD score were similar between the patients who were screened and those who were not screened. Interestingly, patients with a private insurance and patients treated by a liver specialist were more frequently enrolled in a surveillance program. Sixty seven percent of the screened patients were eligible for curative treatment whereas only 15% of the non-screened patients were.

The study of Al Hasani F, *et al* point-out the importance of surveillance program patients with chronic liver disease who are at risk of developing HCC. However, to achieve good results, we have to keep in mind some factors such as the physician

experience, the patient adherence, health system organization, etc play in important role. Finally, hepatocellular carcinoma surveillance could be effective at reducing disease-specific mortality with acceptable cost-effectiveness among selected patient groups, provided it is a well-organized program.

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