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ORIGINAL ARTICLE

Antiviral therapy for recurrent hepatitis C reduces recurrence of hepatocellular carcinoma following liver transplantation

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None.
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Summary

Recurrence of hepatocellular carcinoma (HCC) is one of the major concerns following liver transplantation (LT). With the potential antitumor properties of interferon (IFN), their role in prevention of HCC recurrence is to be defined. We retrospectively reviewed 46 patients who underwent LT for hepatitis C virus (HCV)-related HCC between January 2004 and December 2008. Twenty-four (52.2%) patients with biopsy-proven HCV recurrence received antiviral therapy (IFN group); their outcomes were compared with 22 patients (control group). There was no significant difference for tumor size, number, and type of neo-adjuvant therapy between the two groups. The 1- and 3-year overall patient survival (100% vs. 90.9% and 87.3% vs. 71.8%; $P = 0.150$) and tumor-free survival (100% vs. 72.7% and 83.1% vs. 67.5%; $P = 0.214$) between IFN and control group were comparable. HCC recurrence was the most common cause of death ($n = 6$ of 12, 50%), all in the control group. During follow-up, seven (15.2%) patients developed HCC recurrence: one (4.1%) in the IFN group and six (27.3%) in the control group ($P < 0.05$). In conclusions, HCC recurrence rate and related deaths were significantly lower in patients that received post-transplant antiviral therapy for recurrent HCV.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide, and the third most frequent cause of cancer-related mortality [1]. Cirrhosis resulting from chronic hepatitis C virus (HCV) infection is the most common identifiable risk factor for the development of HCC in North America and Europe. Currently, HCC has an estimated prevalence of 2–3% for HCV infection and the number is likely to increase [2,3].

Liver transplantation (LT) is a definitive treatment in selected patients with HCC. However, recurrence of HCC limits the long-term survival despite refined selection criteria and extensive preoperative staging. The incidence of HCC recurrence in LT recipients has been variably reported ranging from 6.4% to 56.5%, in different patient populations and at diverse follow-up time points [4–13]. A recent meta-analysis concluded that recurrent HCC is the rate-limiting factor for long-term survival in approximately 20% of patients undergoing LT for HCC [14]. In addition, reinfection with HCV is universal in patients undergoing LT with measurable HCV RNA at the time of transplantation [15–20]. Within 5 years, 5–30% of patients with recurrent disease ultimately progress to cirrhosis [15], graft loss occurs in 25–30% of patients [16,17], and survival of transplanted patients with recurrence of HCV disease has been shown to be lower than survival of patients transplanted for

other indications [18–20]. The role of persistent HCV infection after LT in the recurrence of HCC remains unclear [21]. These observations in the presence of donor organ shortage emphasize the need for treatment strategies to prevent allograft and patient loss caused by recurrent HCV and HCC.

Currently, combination antiviral therapy using interferon (IFN) and ribavirin is the only effective treatment to alleviate the course of hepatitis C both before and after LT [22–27]. Newer emerging strategies using protease inhibitors remain to be tested in patients following LT [28,29]. Many studies have shown that antiviral therapy also reduces the incidence of HCC in patients with HCV-related chronic liver disease, especially in patients who achieve sustained virological response (SVR) [30–33]. Furthermore, there seems a potential beneficial effect of antiviral therapy on tumor recurrence and overall survival following resection or ablation of HCC [34–42]. Although antiviral therapy is being recommended and used for treating biopsy-proven HCV recurrence after LT [43–51]; however, there is no data on its effect on HCC recurrence and survival in post-transplant settings.

The aim of this study was to examine the role of post-LT antiviral therapy in prevention of tumor recurrence and survival in patients undergoing LT for HCV-related HCC. We compared the incidence of HCC recurrence and related mortality between patients who received post-LT antiviral therapy for recurrent HCV with those who did not.

Patients and methods

A retrospectively analyses was done for 46 patients who underwent LT for HCV-related cirrhosis and HCC between January 2004 and December 2008. Data were obtained from a prospectively collected transplant database and from a review of the medical records. Preoperative diagnosis of HCC was performed through imaging modalities including computed tomography and magnetic resonance imaging scans, according to the American Association for the Study of Liver Diseases guidelines [52]. The study was approved by the institutional review board (IRB) at the INTEGRIS Baptist Medical Center, Oklahoma City (IRB No. 10-001).

Inclusion criteria were (i) HCV-related cirrhosis with HCC as indication for LT, (ii) post-LT survival for at least 6 months, and (iii) absence of human immunodeficiency virus/hepatitis B virus (HBV) infection before and after LT. Patients who died within the first 6 months after LT for various reasons (including HCC recurrence) were excluded. Patients were also excluded if they received any other form of adjuvant systemic chemotherapy.

Pretransplant data points coded for analysis included recipient demographics, body mass index (BMI), presence of diabetes, HCV genotype, pretransplant HCV therapy, alpha-fetoprotein (AFP), radiologic characteristics of HCC (number and size), pretransplant neo-adjuvant therapy, model for end-stage liver disease (MELD) score (both true and upgraded for HCC), and waiting-list period with upgraded MELD score for HCC. The explanted native livers were examined for the presence of HCC and histopathologic tumor characteristics including number, size, presence of vascular invasion, and tumor viability. Explanted livers were analyzed and tumors were staged using the American Joint Cancer Committee (AJCC) classification. All recipients received a triple-drug-based immunosuppression regimen consisting of tacrolimus, mycophenolate mofetil, and tapering dose of corticosteroid (discontinuation at 3–6 months after liver transplant).

With an intention to treat recurrent HCV following LT, all patients with biopsy-proven HCV recurrence (HAI $\geq$5 or fibrosis score $\geq$2) and serum-positive HCV determined by polymerase chain reaction irrespective of biochemical liver function parameters were offered 48 weeks of IFN-based antiviral therapy. Prophylactic antiviral treatment was not used. Twenty-four (52.1%) patients received antiviral treatment using PegIFNa 180 μg/week and ribavirin 800 mg/day. Twenty-two patients did not receive antiviral therapy for the following reasons: (i) asymptomatic with stable graft functions, (ii) liver biopsy showing HAI <5 or fibrosis score <2, (iii) nonresponders to pretransplant antiviral therapy, (iv) side-effects of pretransplant antiviral therapy, and (v) poor compliance during pretransplant antiviral therapy because of social reasons. Based on post-LT antiviral therapy, the studied patients (n = 46) were divided into two groups: IFN group (n = 24) and control group (n = 22). The primary outcome was HCC recurrence after LT. The secondary outcomes were overall and HCC-related mortality.

Follow-up

All patients were followed up till February 2011. In patients on the antiviral therapy, the clinical course was followed prospectively for the end of therapy response, SVR, toxicity, and withdrawal rate. SVR, defined as the absence of detectable HCV RNA in serum (using HCV RNA assay with a lower limit of detection of 50 IU/ml) 24 weeks after the end of treatment. Blood counts and liver function tests were performed every 2 weeks for the first month and at 4 week intervals thereafter. Serum samples were collected once every 4 weeks for quantitative HCV RNA detection (ViraCor Labs, MO, USA; sensitivity

5 IU/ml). Flexible dose adjustments were made to avoid serious adverse events and to prevent a lapse in treatment.

Surveillance for HCC recurrence was done with AFP (every 3 months for next 5 years after liver transplant) and computed tomography of the abdomen (every 3 months for the first 2 years, then every 6 months for the next 3 years, and annually thereafter). None of the patient in the present cohort received post-transplant adjuvant chemotherapy. Post-LT HCC recurrence was examined. In addition, overall patient and tumor-free survivals at 1, 3, and 5 years following LT were determined.

Statistical analysis

Categorical data was compared using the Fisher's exact test. When a normal distribution could not be assumed, continuous variables were summarized as mean and ranges and compared by the two-way ANOVA test. Kaplan–Meier analysis (SPSS Window version 18; SPSS Inc., Chicago, IL) was used to estimate the 1, 3, and 5 year overall patient and tumor-free survival rates. Log-rank test was used to compare the difference in survival by Kaplan–Meier analysis. For all analysis, a P value of 0.05 or less was considered significant. Cumulative probability for HCC recurrence was not calculated because of the small number of patients with HCC recurrence.

Results

Table 1 illustrates the patient demographics, clinical details, and tumor characteristics for the study cohort. There was no significant difference for age, sex, ethnicity, and body BMI between the two groups. Fifteen (68%) patients in the control group had pretransplant diabetes compared with nine (37.5%) patients in the IFN group ($P = 0.045$). Except for HCV genotype 1a, the distribution of HCV genotype did not differed significantly. HCV genotype was not known in three patients in the control group.

There was no significant difference between the two groups for pretransplant HCV status, pretransplant antiviral therapy, Milan criteria, neo-adjuvant therapy for HCC, and MELD score (true and upgraded). Eight of 22 (36.3%) patients in the control group and nine (37.5%) patients in the IFN group received pretransplant antiviral therapy. Only one patient demonstrated pretransplant SVR in the control group and none in the IFN group. In the control group, 19 (86.3%) patients had HCC within the Milan criteria compared with 20 (83.3%) patients in the IFN group ($P > 0.05$). Overall, 7 (15.2%) patients were transplanted beyond the Milan criteria. This was in accordance to the listing criteria for HCC in the United Network for Organ Sharing region 4 (single lesion ≤6 cm, two or three lesions with the largest tumor <5 cm and the total tumor diameter <9 cm). Fifteen patients in the control group (68%) and 12 (50%) patients in the IFN group received neo-adjuvant therapy for HCC; (radio-frequency ablation in 12, trans-arterial chemoembolization in two, and percutaneous

Table 1. Patient, clinical, and tumor characteristics.

	Control group ($N = 22$)	Interferon group ($N = 24$)	P value
Age, mean ± SD (range) years	57.4 ± 5.6 (51–67)	55.7 ± 6.1 (47–69)	NS
Gender, M:F	18:4	17:7	NS
Ethnicity			
Caucasian	21	20	NS
African-American	–	3	NS
Asian	1	1	NS
BMI, mean ± SD (range) kg/m^2	28.5 ± 4.2 (19–38)	28.7 ± 5.9 (22–39)	NS
Diabetes mellitus	15/22	9/24	0.04
HCV genotype			
1a	6	14	0.04
1b	8	5	NS
2b	4	1	NS
3a	1	4	NS
Unknown	3	–	
Pretransplant antiviral therapy	8/22	9/24	NS
Pretransplant HCV status			
Positive	21	24	NS
Negative	1	–	
HCC-Milan criteria			
Within	19	20	NS
Beyond	3	4	NS
AFP, mean ± SD (range) IU/ml	366.1 ± 801.3 (4.8–2828)	699.7 ± 1896 (4.8–8452)	<0.05
Neoadjuvant therapy	15/22	12/24	NS
RFA/PEI/TACE	12/2/2	11/1/1	
Waiting period (days)			
Mean ± SD (range)	38.4 ± 25.1 (3–88)	24.2 ± 19.1 (1–68)	<0.05
MELD score			
True	11 (6–35)	13 (7–19)	NS
Upgraded for HCC	22 (22–36)	22 (19–24)	NS
AJCC staging			
I	13	12	NS
II	7	9	NS
III	2	3	NS
Vascular invasion	1/22	4/24	NS
Viable tumor cells	16/22	17/24	NS

M, male; F, female; BMI, body mass index; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; RFA, radio-frequency ablation; PEI, percutaneous ethanol injection; TACE, trans-arterial chemoembolization; MELD, model for end-stage liver disease; AJCC, American Joint Cancer Committee.

ethanol injection in two of the control group and radiofrequency ablation in 11, trans-arterial chemoembolization in one, and percutaneous ethanol injection in one of the IFN group).

Patients in the IFN group had significantly higher pretransplant serum AFP levels (699.7 ± 1896 vs. 366.1 ± 801.3; $P < 0.05$), while a shorter wait-list time (24.2 ± 19.1 vs. 38.4 ± 25; $P < 0.05$) compared with the control group. On histological evaluation of the explanted liver, 13 of 22 (60%) patients in the control group had stage I HCC (per AJCC Classification) and one patient had vascular invasion. In contrast, four patients in the IFN group had vascular invasion ($P = 0.348$).

Details of post-transplant antiviral treatment

Antiviral therapy was started once patient had stable immunosuppression for a minimum of 8–12 weeks. The mean ± SD time to start the antiviral therapy was 15.1 ± 10.9 (range: 5.1–48.8) months. Fourteen of 24 (58.3%) patients required early withdrawal of antiviral therapy. Ten patients (41.6%) received antiviral therapy for ≤24 weeks, of which one (4.16%) received for only 12 weeks. Another four patients (16.6%) discontinued therapy between 24 and 48 weeks. Although most of the patients had multiple reasons for discontinuation of therapy, myelosuppression was the commonest reason for early withdrawal of therapy in ten patients. Overall, 14 patients (58.3%) received erythropoietin and 15 (62.5%) received granulocyte colony stimulating factor (G-CSF) for anemia and leucopenia, respectively. Other reasons included severe fatigue in six, intractable diarrhea in two, failure to thrive in two, renal dysfunction in one, pneumonia in one, and rejection in one.

Based on their response to therapy, patients were divided into three groups: Group I patients who achieved end of treatment response but relapsed, group II patients achieved end of treatment response and maintained SVR, and group III patients who did not respond to treatment (Table 2). Five (20.8%) patients had rejection while on antiviral treatment compared with two (9.1%, $P = 0.417$) patients in the control group.

HCC recurrence

During the follow-up, seven patients (15.2%) had HCC recurrence, six (27.3%) in the control group and one (4%) in the IFN group ($P < 0.05$). Among the control group, the mean ± SD time to diagnosis of HCC recurrence was 12.4 ± 9.1 (range: 6.2–30.6) months, and all of them died. The only recurrence in the IFN group was diagnosed at 25.4 months and the patient was alive at the last follow-up (Table 3).

Table 3. Details of HCC recurrence.

	Control group ($n = 6$)	Interferon group ($n = 1$)
HCC – Milan criteria		
Within	4	0
Beyond	2	1
AJCC staging		
I	1	0
II	4	0
III	1	1
Vascular invasion	1/6	1/1
Viable tumor cells	6/6	1/1
Time-to-HCC recurrence		
Mean ± SD, months	12.4 ± 9.1	25.4
Site of HCC recurrence*		
Spine	3	0
Lungs	3	0
Pancreas	1	0
Adrenal gland	1	1

HCC, hepatocellular carcinoma; AJCC, American Joint Cancer Committee.

*Three patients had recurrence at multiple sites.

Table 2. Details of antiviral therapy.

	Responders ($n = 12$)		
	Group I ($n = 6$)	Group II ($n = 6$)	Nonresponders ($n = 12$)
Age, mean (years)	53.3	56.3	57.1
HCV genotype (*n*)	1a (2), 1b (1), 3a (3)	1a (3), 1b (1), 2b (1), 3a (1)	1a (9), 1b (3)
Time interval between LT and IFN initiation, mean (weeks)	51.3	51.1	78.2
Duration of IFN, mean (weeks)	26	34.6	39.6
Required GM-CSF	Yes (3), no (3)	Yes (3), no (3)	Yes (8), no (4)
Required erythropoietin	Yes (4), no (2)	Yes (4), no (2)	Yes (7), no (5)
Early withdrawal of therapy	5	3	6

LT, liver transplantation; IFN, interferon; GM-CSF, granulocyte-macrophage colony stimulating factor.

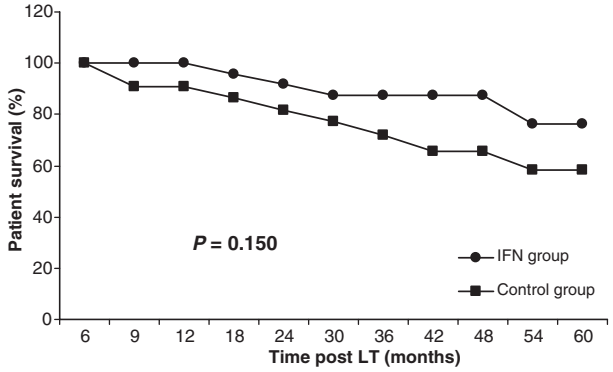

Figure 1 Kaplan–Meier overall patient survivals.

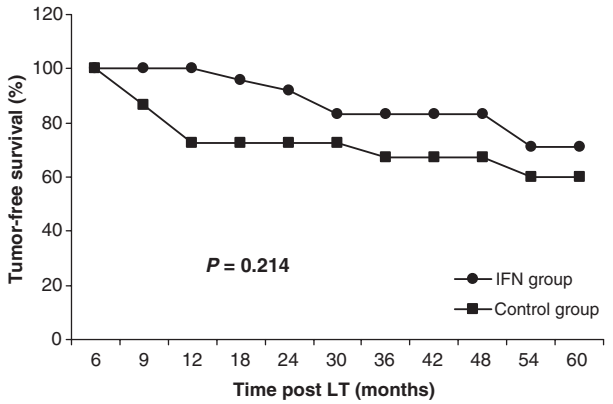

Figure 2 Kaplan–Meier tumor-free survivals.

Survivals

Overall, 12 (26.1%) patients died during the follow-up period. The most common cause of death was HCC recurrence ($n = 6$) followed by graft failure caused by recurrent HCV ($n = 3$), cardiomyopathy ($n = 1$), renal failure ($n = 1$), and severe rejection ($n = 1$). Notably, all deaths resulting from tumor recurrence occurred in the control group ($P < 0.05$).

The overall patient survival was 73.9%; 63.6% in the control group and 83.3% in the IFN group. The 1, 3, and 5 year patient survivals among the IFN group compared with the control group were 100% vs. 90.9%; 87.3% vs. 71.8%; and 76.4% vs. 58.5%, respectively ($P = 0.15$, Fig. 1). The overall tumor-free survival was 71.7%; 63.6% in the control group and 79.2% in the IFN group. The 1-, 3-, and 5-year tumor-free survivals among the IFN group compared with the control group were 100% vs. 72.7%; 83.1% vs. 67.5%; and 71.3% vs. 60%, respectively ($P = 0.21$, Fig. 2).

Discussion

This study showed that post-transplant antiviral therapy could significantly reduce the risk of HCC recurrence and related mortality in patients undergoing LT for HCV-related HCC. To our knowledge, this is the first study that provided comprehensive assessment on HCC recurrence and patient outcomes including mortality and tumor-free survival after antiviral therapy in LT recipients.

Several clinical variables have been identified that independently influence tumor recurrence and patient survival after LT. Well-known risk factors for HCC recurrence include tumor size, number, bilobar disease, Edmondson's grade, vascular invasion, and serum AFP levels [9–14]. In our study, there were no significant differences in baseline patient characteristics except for lower prevalence of diabetes, higher prevalence of HCV genotype 1a, and shorter waiting period from listing to transplant in the IFN group compared with control group. There was no difference for tumor size, number, and neo-adjuvant therapy. In fact, patients in the IFN group had more patients with poor prognostic factor: high serum AFP levels (699.7 ± 1896 vs. 366.1 ± 801.3; $P < 0.05$) and vascular invasion (4/24 vs. 1/22; $P < 0.05$) compared with the control group. Although, overall patient and tumor-free survivals were comparable, we noted a significantly higher incidence of tumor recurrence in the control group compared with the IFN group (6/22 vs. 1/24; $P < 0.05$).

IFN is a multifunctional cytokine and is being used in the treatment of solid tumors and hematologic malignancies including renal cell carcinoma, melanoma, and myeloproliferative disorders [53]. In patients with HCV-related chronic liver disease, the anticarcinogenic activity of IFN and its potential for chemoprevention is based on different mechanisms: antiproliferative – suppression of replication of HCV; tumoricidal [54–56]; antifibrotic – reduces hepatic inflammation, which may retard or induce remission of hepatic fibrosis even in non-SVR patients [57]; and reduction of the expression of the c-*myc* oncogene and induction of antiproliferative factors and tumor suppressor genes [58]. Human lymphoblastoid IFN-a has shown an antiproliferative effect on the human hepatoma cell line PLC/PRF/5 in a dose-dependent manner, both *in vitro* and *in vivo*, after implantation in nude mice [59]. A recent study demonstrated the integration of IFN-α/β signaling to p53 responses in tumor suppression, which resulted in enhancement of cancer cell apoptosis by IFN [60]. Romerio and Zella reported the mechanism by which IFN inhibits carcinogenesis through the regulation of the MEK/ERK pathway [61,62]. IFN has been shown to inhibit MEK/ERK function without affecting Ras and Raf-1 activity. IFN regulates MEK phosphorylation by interference with *de novo* protein synthesis and/or regulation of a specific gene(s). Analysis of downstream events controlled by the MEK/ERK pathway showed reduced activity of Cdk2 and Cdk4, high levels of

mitogenic inhibitors (p21*Waf1* and p27*Kip1*), and decreased cyclin D and E expression. Interestingly, inhibition of Raf serine-threonine kinase (MEK/ERK signal transduction pathway) is one of the mechanisms for antitumor effect of Sorafenib [63,64].

Based on the above mentioned mechanisms of IFN, three randomized controlled trials studying a total of 154 patients have shown a significant beneficial effect of IFN therapy on tumor recurrence and overall survival following resection or ablation of HCC [34–38]. In another randomized controlled trial, IFN induced objective tumor regression in a significant number of patients with inoperable HCC [65]. The beneficial effects of IFN in patients with HCC may be different in patients with HBV as compared with patients with HCV as the underlying etiology. Sun *et al*. demonstrated a significant overall survival effect of IFN after 2 years, but disease-free survival and recurrence rates were not statistically different [39]. However, their study evaluated only HBV patients, which has a different oncogenic potential compared with HCV infection [66]. In their study, the improvement in survival may be related to improvement of inflammation from HBV. A retrospective analysis evaluating 913 Caucasian patients suggested that IFN-related HCC prevention might appear only in HCV pure infections as opposed to HBV with HCV co-infected patients [67]. Another trial involving predominantly HBV infections also failed to show significant benefit of IFN [40]. In contrast, four trials demonstrated a significantly improved survival and tumor recurrence rates exclusively for patients with HCV and HCC [34,36,38,41].

As in most centers, antiviral therapy in our patients was considered when significant or progressive HCV disease develops following transplantation. The International Liver Transplantation Society Expert Panel on LT and hepatitis C suggested that antiviral therapy should be initiated when abnormality in liver allograft function was noted along with histological evidence of moderate to severe necroinflammatory activity (grade 3 or 4) or fibrosis stage 2 or greater (scale of 4) [68]. In our cohort, the median time to start the therapy was 64.5 weeks following liver transplant. We noted severe adverse effects of the antiviral therapy leading to either treatment disruption or dose reduction in up to 60% of the patients. Side-effects were dose dependent and often hinder full-dose treatment. In a recent study, the dose reduction in IFN and ribavirin was required in 35% and 26.7% of cases, respectively, with an overall withdrawal rate of 40% before completion of therapy [26]. Despite erythropoietin and G-CSF use in more than half of the treated patients, myelosuppression was the commonest cause for early withdrawal of therapy.

The present study demonstrated a response rate of 50% including six patients who achieved SVR. Response rates to antiviral therapy in post-transplant patients are lower compared with immunocompetent patients [46]. SVR rates of 30–48% have been reported in the literature [43–51]. As in the nontransplant setting, SVR rates were higher with genotype 2/3 than with genotype 1/4 infection. Lower SVR rates in the present study might be due to higher prevalence of genotype 1 in our cohort. Thirty-three (68.7%) patients including 19 of 24 (79.1%) patients in the IFN group were infected with HCV genotype 1. Interestingly, all patients in the nonresponder group were infected with HCV genotype 1. HCV genotype 1b is associated with higher risk (almost double) to develop HCC than those infected with other genotypes [69]. However, neither genotype nor viral load of HCV affects prognosis after development of HCC [70]. We did not observe any significant difference for tumor recurrence or survival between the responders and nonresponders on subgroup analysis. Previous studies indicated that HCC incidence was reduced by IFN treatment, especially in sustained responders including sustained virological responders and sustained biochemical responders [33,71–73]. But, recent studies have demonstrated that IFN treatment reduces HCC development even in nonsustained responders including transient responders [74,75] and nonresponders [75,76]. This preventive effect may be speculated to be the result of the anti-inflammatory effect on persistent necro-inflammation and blocking progression of fibrosis in liver.

There are some limitations to this single-center study. The limitations are a small size and retrospective analysis. Selection bias always remains a concern for a retrospective study involving complexity to draw conclusions about potential benefits of the study. We acknowledge that some patients in the control group had stable graft functions with biopsy showing HAI <5 or fibrosis score <2, which did not indicate the need for antiviral therapy. However, it is possible that some of these patients might have developed the HCC recurrence before the significant HCV recurrence. This demonstrates the need for prospective, observational, and preferentially randomized controlled trials. The duration of follow-up was not a major limitation, as most tumors recur within the first 2 years after LT [9,11,22]. Studies such as these remain important as HCV-related cirrhosis and HCC are the most important indications for LT. The results of our study support the findings of previous studies showing efficacy of antiviral therapy in prevention of recurrence after curative treatment (surgical/ablation) in patients with HCV-related HCC. Correspondingly, IFN-based antiviral therapy directed for HCV recurrence in LT recipients may alter the course of tumor recurrence.

In conclusion, findings of our study suggested that IFN-based antiviral therapy directed for HCV recurrence

after LT may decrease tumor recurrence and trend toward better survival even if an SVR is not attained. There may be a potential role for early initiation of antiviral therapy in patients undergoing transplantation for HCC associated with HCV. Furthermore, randomized, prospective, and larger studies must be initiated to evaluate the potential benefits of post-transplant IFN-based antiviral therapy on HCC.

Authorship

VK and AS: participated in research design, writing of paper, performance of research, and data analysis. LE: participated in performance of research and data analysis. SJ: participated in performance of research.

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