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Disease Course after Liver Transplantation for Hepatocellular Carcinoma in Patients with Complete Tumor Necrosis in Liver Explants after Performance of Bridging Treatments

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Abstract

Aim: To study the disease course of patients with hepatocellular carcinoma (HCC) showing complete tumor necrosis in their liver explants after undergoing bridging treatments followed by liver transplantation (LTx).

Patients and Methods: We evaluated data corresponding to 10 patients with liver cirrhosis undergoing bridging treatments for HCC prior to LTx. In all cases there was complete tumor necrosis in the explanted livers.

Results: There were 8 men and 2 women. Percutaneous radiofrequency ablation (RFA) was performed under computed tomographic guidance in 4 patients. The remaining 6 patients underwent transarterial chemoembolization (TACE). Five of them received one session of TACE, while the remaining one received a series of 4 sessions prior to LTx. Six patients had solitary nodules with a median diameter of 3.5cm (range 2.5-4.2cm). Four of them underwent RFA. Segmental tumor chemoembolization was performed in 2 patients. The remaining 4 patients had 2 tumors each with a median total diameter of 4.4cm (range 4.2-6.0cm) prior to TACE. They underwent bilobar hepatic chemoembolization, which under staged the tumors prior to live donor liver transplantation (LDLTx). Six patients underwent deceased donor orthotopic liver transplantation. LDLTx was performed in 4 patients. Median waiting time to LTx was 53 days. All patients are alive without recurrence after a median follow-up of 19 months.

Conclusion: Achievement of 100% tumor necrosis by means of bridging treatments followed by LTx for HCC is characterized by a very low recurrence rate and should receive further consideration and study.

Key words: Liver transplantation; hepatocellular carcinoma; bridging treatments; transarterial chemoembolization; radiofrequency ablation; tumor necrosis

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, accounting for about one million deaths annually. Its incidence is estimated to have increased by 75% in the United States over the last decade and reflects in part the increased prevalence of chronic viral hepatitis infection [6]. Liver transplantation (LTx) is considered to be the treatment of choice for early HCC in patients with end-stage liver disease, but is limited by the availability of donor organs. Many patients experience a "dropout" from the waiting list because of tumor progression. Tumor specific bridging treatments such as transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) have arisen as potential bridging treatments to limit tumor progression during the period from listing to LTx.

In this study we evaluated the course of the disease in transplanted patients with HCC and cirrhosis, in whom pathologic examination showed complete tumor necrosis after performance of TACE or RFA during the waiting time to LTx.

Patients and Methods

From April 1998 to April 2005, 703 patients underwent LTx at our centre. Data corresponding to 10 patients with liver cirrhosis who underwent bridging treatments for HCC prior to LTx and showed complete tumor necrosis in the explanted liver were reviewed.

Bridging treatments included computed-tomography guided RFA and segmental or bilobar TACE. Only patients meeting the Milan criteria were offered this therapeutic modality [19]. The decision to perform RFA or TACE was made on an individual basis according to tumor characteristics, anatomical considerations, Child-Pugh Class and the general condition of each patient. All potential candidates were evaluated by means of abdominal ultrasonography, thoraco-abdominal computed tomography and/or magnetic resonance imaging, angiography, and bone scintigraphy. Liver biopsies were performed in all cases to confirm the diagnosis of HCC. Serial levels of alpha fetoprotein (AFP) were obtained prior to and after LTx.

A single pathologist examined (1cm slices) all explanted livers. Tumor classification was made according to the 6th Edition of the Tumor-Node-Metastasis (TNM) System of classification of the Union Interna-

tional Contre le Cancer (UICC) [26]. Of special interest were the extent of tumor necrosis and the viability (if any) of the ablated tumors. Nodules with a preoperative diameter less than 2 cm and no confirmatory biopsy that showed complete necrosis after ablation were not considered tumors as stipulated by the Barcelona criteria [3].

No patient was lost to follow-up. Follow-up studies included CT scans of the abdomen and chest, and measurement of alpha-fetoprotein levels every 3 months during the first 2 years after transplantation, every 6 months during the third year, and yearly thereafter. No patients received adjuvant chemotherapy after LTx.

RESULTS

Pathological exam showed complete tumor necrosis in all instances. Because of the extension of the necrotic areas, no estimation of grading was possible. There were 8 men and 2 women (Table 1). RFA was performed with percutaneous expandable electrode needles under computed tomographic guidance in 4 patients. Five of the 6 patients undergoing transarterial chemoembolization underwent one session, while the remaining patient received a series of 4 sessions prior to LTx. Five patients underwent deceased donor full-size orthotopic liver transplantation (OLTx). One received a deceased donor split allograft. Live donor liver transplantation (LDLTx) was performed in 4 patients. AFP levels were elevated in all patients at the time of the initial evaluation, with a median value of 76 U/ml prior to bridging treatment (range 58-305 U/ml, normal value <10 U/ml). Median hospital stay associated with the performance of RFA or TACE was 3 days (range 2-5 days).

The etiology of cirrhosis was alcohol in four cases, hepatitis B in two instances, cryptogenic in two other cases, combined hepatitis B and C in one instance, and primary sclerosing cholangitis in the remaining patient. Six patients had solitary nodules with a median diameter of 3.5cm (range 2.5-4.2cm), as determined by radiological evaluation prior to bridging treatments. Four of them underwent RFA, whereas segmental tumor chemoembolization was performed in 2 patients. All these patients fulfilled the Milan criteria (1 tumor ≤5cm, 2-3 tumors all ≤3cm, no vascular invasion) prior to the beginning of the treatment. The remaining 4 patients had 2 tumors each with a median total diameter of 4.4cm (range 4.2-6.0cm) prior to TACE and underwent bilobar chemoembolization with the intent to downstage the HCC. Radiological evaluation after performance of bilobar TACE showed tumor necrosis. LDLTx followed in these 4 patients. Median waiting time to LTx was 53 days (range 0-859 days). Performance of bridging treatments occurred in a median of 25 days after listing for deceased donor LTx (range 2-54 days).

All patients experienced uneventful postoperative courses. No re-transplantation was required. The patient who received the split-liver underwent a second-look laparotomy followed by necrosectomy of the marginal zone of segment IV on postoperative day 13. No bile leakage was detected. Median ICU and hospital lengths of stay were 3 and 28 days, respectively. All patients are alive from 5 to 64 months after LTx. Chronic rejection was not observed in any case. No recurrence has been observed so far after a median follow-up of 19 months.

DISCUSSION

Liver transplantation is now acknowledged as the best therapeutic option for patients with early, unresectable HCC [2, 7]. However, these patients are subject to lengthy waiting times prior to receiving deceased donor organs. As a result of this, attempts are routinely made to treat HCC in transplant candidates in order to prevent disease progression while on the waiting list [9, 10]. TACE and RFA are the therapeutical options most frequently used. The range of indication as well as combination therapies while on the waiting list is becoming wider.

The role of RFA in the treatment of HCC is controversially discussed in the literature [5, 14-15, 18, 22-23, 25]. We were able to find only a limited number of reports addressing the efficacy of bridging treatments as documented by pathological examination of the explanted livers. Harrison et al. analysing the data of 12

Table 1. Patient characteristics. WT: Waiting time; DDLTx: Deceased donor full-size liver transplant; SLTx: Deceased donor split liver transplant. *:total tumor diameter; §: patients undergoing LDLTx were listed in the deceased donor waiting list of "Eurotransplant" after the completion of the evaluation work-up and the performance of bridging treatments.

Patient	Age	sex	BT	AFP	Tumor	WT	LTx	Follow-up
1	61	m	TACE	175 U/ml	2 lesions 6.0cm*	0 days	LDLTx§	5 months
2	31	m	TACE	305 U/ml	2 lesions 4.2cm*	1 days	LDLTx§	64 months
3	59	m	TACE	162 U/ml	2 lesions 4.4cm*	0 days	LDLTx§	51 months
4	59	m	RFA	75 U/ml	solitary 3.5cm	415 days	DDLTx	45 months
5	61	w	RFA	67 U/ml	solitary 4.2cm	40 days	LDLTx§	4 months
6	59	w	RFA	103 U/ml	solitary 2.6cm	859 days	DDLTx	24 months
7	36	m	TACE	64 U/ml	solitary 3.9cm	64 days	DDLTx	30 months
8	68	m	TACE	77 U/ml	solitary 4.1cm	68 days	DDLTx	13 months
9	47	m	RFA	58 U/ml	solitary 3.8cm	343 days	DDLTx	6 months
10	49	m	TACE	62 U/ml	2 lesions 4.7cm*	42 days	SLTx	5 months

Table 2. Review of the literature regarding post-transplant follow-up of HCC patients who underwent bridging treatments prior to LTx. BT: Bridging treatment; N: number of patients; CTN: Complete tumor necrosis; PEI: Percutaneous ethanol injection; n.i.: no corresponding information.

Author	Year	BT	N	CTN	Recurrences	Post-LTx follow-up
Venook	1995	TACE	10	40%	0/10	40 m (median)
Harnois	1999	TACE	24	n.i.	0/24	29 m (mean)
Yamakodo	2002	TACE+RFA	64	100%	2/64	12.5 m (mean)
Graziadei	2003	TACE	41	29%	1/41	n.i.
Fisher	2004	TACE/RFA/PEI	28	n.i.	1/28	n.i.
Hajashi	2004	TACE	12	n.i.	0/12	35 m (mean)
Moreno	2005	TACE/RFA/PEI	13	n.i.	0/13	15 m (median)
Actual series	2005	TACE/RFA	10	100%	0/10	19 m (median)

patients with HCC who underwent LTx after RFA, showed that 5 of them (42%) demonstrated no viable tumor in the explanted liver [12]. Maluf et al., investigating the efficacy of different noresective techniques in HCC patients undergoing LTx, found no viable tumor after bridging treatment in 5 of 11 patients (46%) [17]. Even better results were reported by Coad et al. and by Yamashiki et al. with complete necrosis of the HCC in 4/5 patients after RFA (80%) and in 16/18 lesions after microwave coagulation therapy (89%) respectively [4, 30]. Mazzaferro et al. in a prospective study of the histological response rate to RFA in 60 cirrhotic patients with small HCCs awaiting liver transplantation, found a complete response rate of 55%. Size of tumor >3cm and time from treatment >1year were associated with a high risk of tumor persistence in the targeted nodule. Although found to be a safe and effective bridging treatment in patients awaiting LTx, the authors concluded that RFA "should not be considered an independent therapy for HCC" [18].

Similar to the few reports about the efficacy of bridging treatments as documented in pathology, there are only sporadic studies referring to the post-transplant course of HCC patients who had received bridging treatments prior to transplantation. In a literature review [8, 10-11, 13, 20, 28-29], only 4 recurrences were found out of a total of 192 HCC patients treated with TACE alone or in combination with RFA or percutaneous ethanol injection (PEI) prior to transplantation (Table 2). The median post-transplant follow up ranged from 15 to 40 months. Unfortunately, there was great disparity in the extent of tumor necrosis documented by pathologic exam. Venook et al. reported a median post-transplant recurrence free survival of 25 months in 4 patients with 100% tumor necrosis after TACE. Graziadei et al. reported complete tumor necrosis in 29% of the patients treated (14/41 patients). Yakamodo et al., on the other hand, reported 100% complete tumor necrosis in their series, regardless of tumor size or morphology, after performing TACE in combination with adjuvant RFA prior to LTx. There were no reported local recurrences in nodular lesions during a mean follow-up of 12.5 months. To the best of our knowledge, apart from the present study, this has been the only current study addressing outcome after complete tumor necrosis.

Although the aim of all bridging treatments before LTx is to achieve 100% necrosis of the nodules, this was reported in less than 30% of cases when the histological evaluation of removed livers was performed [10, 16, 21, 27]. In a series of liver resections, Adachi et al. [1] showed that TACE improved patient survival when it produced complete necrosis, whereas in cases of partial necrosis, it increased the risk of HCC recurrence. In a similar series of LTx for HCCs, Ravaioli et al. confirmed that, as reported for liver resections, the presence of partial necrosis increased the tumor recurrence rate, reduced recurrence free-survival, and was a risk factor for tumor recurrence after liver transplantation by both univariate and multivariate analyses [24].

In our series of biopsy-proven HCC patients with complete tumor necrosis after bridging treatments followed by LTx, no recurrence was observed after a median follow-up of 19 months. Although our series is small in number of patients, the "rarity" of similar reports in the literature coupled with the encouraging results achieved could lead to further discussion and consideration.

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