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Could Sorafenib Disclose New Prospects as Bridging Therapy to Liver Transplantation in Patients with Hepatocellular Carcinoma?

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Abstract

Background-Aim: There are few data on the use of sorafenib as bridging therapy for patients with Hepatocellular Carcinoma (HCC) waiting for Liver Transplantation (LT).

Methods: Six HCC patients were treated with sorafenib before LT at our Institution following the Italian Drug Agency guidelines: they had well compensated cirrhosis (Child-Pugh class A), intermediate stage HCC, good general conditions (performance status 0) and they were not suitable for loco-regional therapies.

Results: Three patients received sorafenib until LT, whereas the other three cases required treatment discontinuation before LT. During the post-surgery period no deaths and anastomotic complications were observed. The four patients receiving Sorafenib for more than 2 months before LT were recurrence-free 27 to 41 months after surgery. Conversely, tumor recurrence leading to patient death was found in the other 2 cases.

Conclusion: We think that these findings justify the start of a phase II study in a larger patient population.

Keywords: Hepatocellular carcinoma; Liver transplantation; Sorafenib; Bridging therapy; Survival

Introduction

Liver Transplantation (LT) for Hepatocellular Carcinoma (HCC) in patients with cirrhosis is recognized as the best therapeutic approach [1]. However, in a considerable proportion of patients listed for LT, long waiting periods may be associated with disease progression so about 23% of these patients are eventually delisted [2]. The so called "bridging therapies" explored, often resulted in rather unsatisfactory and controversial outcomes. A literature survey including level II and III evidences (cohort studies and case series) reports that, in spite of the different therapeutic approaches, the risk of tumor progression and drop-off from the transplantation list still accounts for about 16% [3].

The introduction of sorafenib, has disclosed new opportunities for the management of liver cancer. Following two pivotal multicenter trials, which showed a statistically significant overall survival advantage in patients treated with sorafenib compared to placebo, the product has been acknowledged as the only treatment presently effective in this setting of patients [4,5].

In this stimulating scenario we have centred particular attention to the possibility to evaluate the role of sorafenib in patients with HCC in the waiting list for LT [6]. Using a simulation Markov model for the assessment of a cost-benefit analysis taking as reference cases a patient population with early stage HCC and compensated cirrhosis, sorafenib as neo-adjuvant treatment before LT was compared against no bridging therapy in the first six months [6]. Results, freshly published, indicated that neo-adjuvant treatment with sorafenib is cost-effective, particularly during the first six month of the waiting period [6].

These evidences strongly call for the execution of a confirmatory clinical study: however, before designing it and starting patients' accrual an evaluation of the safety of sorafenib in patients' candidate for LT was mandatory. Here, we reported our preliminary experience with the clinical use of sorafenib in six HCC patients undergoing to LT.

Case Series

Six patients were treated with 400 mg b.i.d. sorafenib. Their characteristics are depicted in Table 1. All enrolled patients were male and sorafenib therapy was indicated since they had tumor progression or recurrence after previous loco-regional therapies. All enrolled patients had an intermediate HCC unresponsive to at least two procedures of trans-arterial chemoembolization. At the moment of Sorafenib indication all enrolled patients were therefore judged not suitable for further loco-regional therapies. Results after sorafenib therapy are highlighted in Table 2. Three cases required treatment discontinuation before LT: the first due to poor patient compliance (case 4), the second due to gastro-intestinal bleeding (case 5) and the third due to severe hand-foot skin reaction (case 6). Another patient (case 3) had dose-drug reduction to 200 mg/day because of onset of severe hypertension.

Modified RECIST criteria [7] were used to assess the response to Sorafenib therapy. Globally, three patients received sorafenib until LT (cases 1, 2, and 3) and four patients had more than 2 months of treatment (cases 1, 2, 3, and 6): pre-LT imaging displayed two cases of partial radiological responses and two stable diseases. Case 4 had a partial response to sorafenib at the moment of treatment refusal. The

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Case	1	2	3	4	5	6
Sex	Male	Male	Male	Male	Male	Male
Age (years)	61	64	57	63	47	59
Cirrhosis etiology	Alcol	HCV	HCV	HCV	HCV	Alcol
Radiologic tumor characteristics Number of nodules	4	6	3	2	8	5
Size of the largest nodule (cm)	3,5	2	5	4,5	4	6
Previousanticancertherapy	Resection; Ablation; TACE	Resection; Ablation; TACE	Laparotomic Ablation; TACE	Resection; Ablation; TACE	TACE	TACE; Ablation
Alphafetoprotein > 200 ng/ml	No	Yes	No	No	Yes	No

HCV, hepatitis C virus; TACE, trans-arterialchemoembolization

Table 1: Characteristics of the enrolled patients.

Case	1	2	3	4	5	6
Lenght of therapy (months)	5	7	4	1.5	0.5	6
Maintenance of maximum dosage (800 mg/die)	Yes	Yes	No (reduction to 200mg/die)	Yes	No	Yes
Sorafenibtherapyinterruptionbefore LT	No	No	No	Yes (patientrefusal)	Yes (bleeding)	Yes (HFS)
Months between therapy interruption and LT	0	0	0	4	6	1
Serious adverse events before LT	No	No	Hypertensivecrises	No	Gastro-intestinalbleeding	HFS
Response to therapy	Partial	Stable	Stable	Partial	Notevaluable	Stable
Pathologic tumor features						
Size of the largest nodule (cm)	3.4	0.8	4	3.5	3.6	7
Number of nodules	3	7	2	2	9	5
Vascular invasion	No	No	No	Yes	Yes	No
Poorly differentiated grade	No	No	No	Yes	No	No
Serious adverse events after LT						
Anastomotic	No	No	No	No	No	No
Non anastomotic	No	Yes (Intestinalperforation)	Yes (hemoperitoneous)	Yes (biliaryleak)	No	No
Postoperative day	-	3 and 7	7	20	-	-
Hospital stay (days)	10	40	40	17	10	12
Length of follow-up after LT (months)	41	40	39	8	32	27
Patientdeath / HCC recurrence	No / No	No / No	No / No	Yes / Yes	Yes / Yes	No/No

Table 2: Outcome of sorafenib therapy in the enrolled patients.

short treatment period with sorafenib in case 5, didn't allow evaluating its therapeutic effect on HCC growth.

Size and number of nodules were not considered as absolute selection criteria both for liver transplantation as previously reported [8].

During the post-surgery period no deaths were observed. Moreover, we did not record any case of anastomotic complication in the first postoperative month. Non anastomotic early complications were: intestinal perforation (case 2) andhemoperitoneous (case 3) both resolved surgically. Case 4 had a biliary leak after T-tube removal and this complication was treated radiologically. All four patients receiving Sorafenib for more than 2 months before LT had not aggressive tumor features (poorly differentiated grade, vascular invasion) at explant patology and were recurrence-free 41, 40, 39 and 27 months after surgery, respectively.

The two patients discontinuing sorafenib after less than 2 months of therapy, conversely, had both aggressive HCC features at pathology (Table 2). Case 5 had HCC multifocal hepatic recurrence diagnosed 8 months after LT. Interestingly; he underwent 2 procedures of trans-arterial chemoembolization obtaining a partial response and a left surrenectomy surgical procedure. He died 32 months after LT.

Finally, case 4 developed a multifocal pulmonaryrecurrence of HCC, and died at 8 months from LT.

Discussion

To the best of our knowledge, this is the first reported series of HCC patients treated with sorafenib as bridging therapy before LT. In our study, sorafenib was not used to downstage HCC from the intermediate to the early stage as in other experiences [9]. The rational of sorafenib neo-adjuvant therapy in our centre, conversely, is to reduce the risk of tumor progression before LT and thus the probability of patient dropout from the waiting list. In a recent Markov model, in fact, we have shown that the use of sorafenib in this setting is potentially cost-effective [6].

This issue is of particular relevance when intermediate stage HCC patients like those in the present series are considered for LT, because in these kind of patients the risk to develop aggressive tumor features like vascular invasion, extra-hepatic metastases and poorly differentiated tumor is higher.

The powerful antiangiogenic effect of Sorafenib has the potential to interfere with vessel repair and thus give rise to a potentially higher risk of post-surgical complications, however. This potentially toxic

effect may also be more relevant in transplant candidates due to the unscheduled nature of LT (making it impossible to prudently suspend Sorafenib some days before surgery) and to the presence of arterial, venous and biliary anastomoses at risk of leakage or thrombosis. There are not data, however, to demonstrate and measure this potential toxicity of Sorafenib in surgical patients.

Our preliminary experience showed the absence of early postoperative mortality in the enrolled patients. Moreover, we had no cases of early anastomotic complications. We recorded three severe complications (cases 2, 3, and 4) in the early post-LT period. However, it has to be underlined that all these patients had previous abdominal surgery (Table 1) that is a well known negative prognostic factor in patients undergoing to LT [10]. More importantly, we did not observe anastomotic leaks or thromboses in the first month after LT in the 3 patients continuing sorafenib therapy until the day of transplantation.

As second point, we observed sorafenib side effects in cirrhotic patients during the waiting period. In the Sharp study [4], dose reductions due to adverse events occurred in 26% of the patients in the sorafenib group, whereas dose interruptions due to adverse events occurred in 44%. These proportions were similar to that occurred in our experience where 1 patient (20%) had dose reduction, whereas 3 patients (50%) had dose interruption.

The very low number of enrolled patients doesn't allow any conclusion on sorafenib efficacy when used as bridging therapy before LT. However, some preclinical mouse models have recently shown that anti-VEGF therapy promotes invasion and increases the metastatic potential of tumours [11,12]. These preclinical data argue that neo-adjuvant treatment with sorafenib may, rather than slowing disease progression, increase tumour invasiveness and metastatic potential during therapy and recurrence of HCC after liver transplant. This potential "toxic" effect of sorafenib on tumor growth was not apparently observed in our small experience: patients treated with sorafenib more than 2 months before LT (cases 1-3 and 6), in fact, had not apparently pathologic progression (Table 2) with respect to their initial radiological staging (Table 1) and, more importantly, they had not aggressive tumor features (vascular invasion or poorly differentiated tumor) at pathology and they did not experience HCC recurrence after 41, 40, 39 and 27 months from LT respectively. On the contrary, patients discontinuing sorafenib therapy 4 and 6 months before LT respectively (cases 4 and 5) had a suspect increase in tumor invasiveness at pathology, and they had both post-LT HCC recurrence. On a pure speculative basis, this preliminary case series suggests a potential effect of sorafenib therapy on delaying tumor progression before LT rather than a potential promoting effect of sorafenib on HCC invasiveness. We think that these findings justify the start of a phase II study in a larger patient population, since sorafenib could represent a new interesting alternative for patients waiting for LT.

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