

Letter to Editor

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Systemic treatment for hepatocellular carcinoma beyond milan criteria on the waitlist: is it time for a neoadjuvant therapy?

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Dear Editor,

Liver transplantation (LT) is the best option for the treatment of both cirrhosis and hepatocellular carcinoma (HCC), providing the best long-term outcomes, particularly for patients within the Milan criteria^[1]. Efforts have been made to expand these criteria in order to expand the offer of LT to a higher number of patients with HCC while maintaining an acceptable risk of post-LT HCC recurrence^[2].



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In addition, the efficacy of downstaging approaches, which consist in treating HCC with the aim of reducing tumor burden in order to meet the eligibility criteria for LT, has been explored. Several treatments can be used in downstaging, such as thermal ablation (TA), transarterial chemoembolization (TACE) or transarterial radioembolization (TARE), and systemic treatments, such as inhibitors of immune checkpoint (ICIs) and tyrosine kinase (TKIs). The upper limits of tumor burden after downstaging for LT remain controversial, particularly for HCC patients with macrovascular invasion. In these patients, treatments with an increasingly higher probability of obtaining significant tumor response are now available. In particular, systemic treatments with TKIs or ICI-based combinations have been shown to be effective in achieving stability of disease or even significant radiological response rates.

We present a case series of 5 patients with Milan-out and up-to-seven-out HCC without extrahepatic disease who achieved a successful downstaging after systemic treatment and locoregional treatment (LCRT) and finally received LT in two Italian transplant centers.

All patients were male, with a median age of 60 years. Two patients had macrovascular invasion before downstaging. The median time from the discontinuation of systemic therapy before LT was 90 days, and 2 patients continued systemic therapy until LT. The median time on the waitlist was 87 days. None developed HCC recurrence post-LT. The median post-LT follow-up time was 10±2 months. Clinical features are shown in [Table 1](#).

Patient 1 was affected with autoimmune cirrhosis with multifocal HCC. He received lenvatinib until LT, resulting in the stability of disease. He received basiliximab at day 0 and 4, and tacrolimus plus low doses of steroids as immunosuppressants. He experienced candida esophagitis and cytomegalovirus (CMV) reactivation within the first month after LT. AFP before LT was 8.4 ng/mL and after LT was 1.6 ng/mL.

Patient 2 was affected with HCV-related cirrhosis, with active viral replication and multifocal HCC. He received basiliximab at day 0 and 4, and only tacrolimus as an immunosuppressant. He developed Sars-Cov-2 infection after LT without lung involvement. AFP before LT was 245 ng/mL and after LT was 1.7 ng/mL.

Patient 3 was affected with HCV-related cirrhosis, portal vein thrombosis, and multifocal HCC. He was treated with sorafenib, which was continued until LT. He received basiliximab at day 0 and 4, and only tacrolimus as an immunosuppressant, but his post-surgical recovery was complicated by moderate acute rejection, treated with steroids. AFP before LT was 8.7 ng/mL and after LT was 1.4 ng/mL.

Patient 4 was affected with NASH-related cirrhosis, with multifocal HCC, and had neoplastic portal vein thrombosis. He received sorafenib. As to immunosuppressants, he received steroids and tacrolimus. He developed CMV reactivation during the first month after LT. AFP before LT was 50 ng/mL and after LT was 2 ng/mL.

Patient 5 was affected with alcohol-related cirrhosis and multifocal HCC, and had neoplastic portal vein thrombosis. He received sorafenib followed by regorafenib, because of tumor progression. Post-LT, he developed acute rejection, which was successfully treated with steroids. Immunosuppression included steroids, tacrolimus, and mycophenolate mofetil. AFP before LT was 500 ng/mL and after LT was 2 ng/mL.

The number of effective systemic treatments for HCC has been rapidly increasing over recent years^[3,4], as well as the likelihood of achieving clinical/radiological response. In particular, the advent of ICIs represents a breakthrough in this field, with objective response rates never before seen with TKIs, and with survival

Table 1. Clinical features fo patients uderwent systemic treatment before liver transplantation

	Age	Etiology	Type of systemic treatment	Duration (months)	RECIST pre-LT	Time from the last administration to LT (months)	Loco-regional treatment	Size largest nodule (mm)	Number of nodules	AFP At LT (ng/ml)	RECIST at LT	Necrosis at explant	Number of nodules at explant	Size of the largest nodules at explant (mm)	Grading	Vascular invasion
Case 1	55	AIH	Lenvatinib	5	PD	0	TAE	30	5	8.7	PD	60%	2	23	G2	Yes
Case 2	60	HCV	Atezolizumab/Bevacizumab	4	PR	2	TAE	45	2	120	SD	80%	2	29	G2	No
Case 3	49	HCV	Sorafenib	12	PR	0	-	50	3	8.5	SD	70%	2	26	G2	Yes
Case 4	62	NASH	Sorafenib	9	PR	2	2 TACEs, RFTA	40	3	32	SD	90%	1	14	G3	Yes
Case 5	64	ALD	Regorafenib	5	PR	2	RFTA, TACE, TARE	40	4	43	CR	NA	0	-	-	No

AIH: autoimmune hepatitis; NASH: non-alcoholic steatohepatitis; ALD: alcoholic liver disease; TACE: transarterial chemo-embolization; TAE: transarterial embolization; RFTA: radiofrequency thermoablation; TARE: transarterial radioembolization; AFP: alpha-fetoprotein, LT: liver transplantation; PD: Progression disease, PR: partial responders; CR: complete response, SD: stable disease.

outcomes that appear to be comparable to those of LCRT. Systemic treatment is usually considered the last treatment option in the patient's journey and is usually reserved for advanced stage with vascular invasion and/or metastases after the failure of locoregional treatments. These patients have an extremely poor prognosis and are generally excluded from the transplant program due to the high risk of post-transplant HCC recurrence.

However, in recent years, given the increasing indication for liver transplantation for HCC, there is a growing demand to consider transplant programs for patients who were initially excluded due to disease extension, but subsequently presented a good response to downstaging therapies and therefore met the transplant criteria.

Though downstaging with LCRT has proved to be effective and to allow access to LT for patients otherwise destined for poor survival^[5], data on the effectiveness of systemic agents in downstaging or as bridge therapy in patients with HCC who could potentially receive LT are scant^[6].

Systemic treatment with ICIs deserves careful evaluation. Since programmed cell death protein 1 (PD-1) is expressed on liver allograft-infiltrating T cells, the risk of using checkpoint inhibitors blocking PD-1 ligand is the overproliferation of T cells in transplanted patients, resulting in graft loss, ranging from 36% to 54%^[8]. Tabrizian et al described only one case of mild acute rejection in a case series of nine patients treated with nivolumab for advanced HCC and

transplanted at Mount Sinai Medical Center^[9]. Schawacha-Eipper *et al.*^[10] also reported the case of a patient with HCC who experienced disease progression after sorafenib and regorafenib, but achieved a partial response to nivolumab, meeting the Milan criteria. According to the four-week half-life of nivolumab, the authors stopped treatment with nivolumab six weeks prior to activation on the waiting list for LT, and the patient was transplanted without rejection or recurrence of HCC after one year of follow-up.

Our small series is one of the few examples in the literature on patients with advanced HCC, who underwent different systemic therapies and locoregional therapy, resulting in downstaging, and subsequently had access to LT, and also patients with a previous macrovascular invasion. We observed that systemic treatments administered before LT were associated with good outcomes after transplantation and had an acceptable safety profile. Moreover, graft and patient's survival at 1 year after LT is 100% and we had no HCC recurrence. These data could open a new scenario in terms of neoadjuvant therapy for patients out of Milan Criteria at high risk of HCC recurrence after LT.

Given the paucity of available data, properly designed clinical trials and prospective real-world data are needed in order to substantiate the usefulness of systemic treatment for HCC before LT, and to identify an increasingly large number of patients otherwise certainly destined to have a poor prognosis.

DECLARATIONS

Authors' contributions

Collected data and wrote the manuscript: Magro B, Triolo M

Wrote the manuscript: Celsa C, Cabibbo G, Pagano D

Revised the paper: Cammà C, Faggiuoli S, Gruttadauria S

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