Reply to: "Sorafenib efficacy for treatment of HCC recurrence after liver transplantation is an open issue"

To the Editor:

We thank Dr. Mancuso *et al.* for their critical comments on our recent paper, in which we sought to demonstrate the efficacy and the safety of sorafenib in a case-control study on transplanted patients affected by HCC recurrence [1]. Rather than being diverted by academic abstractions, we would like to stick to the data and take the opportunity of replying through the explicitation of few points, some of them already expressed in our original article. In brief:

(1) As any cohort study, our original report on consecutive patients presenting with HCC recurrence after LT had some limitations that had been extensively acknowledged both in the text and in the accompanying editorial. However, thanks to a solid statistical analysis, we fail to detect any "strong bias" (namely systematic errors) as those mentioned in the letter.

(2) We acknowledge the note of caution on sorafenib safety, given the Authors' [2] and another group's [3] experience. However, we would like to underline that most of the published studies including ours (Table 1) reported adverse event and drug discontinuation rates that are in line with that of RCTs in non-transplant patients: to be noted, in the majority of these reports more than 50% of patients received sorafenib in association with an mTOR inhibitor. There is a clear heterogeneity in both safety reports and survival outcomes that probably reflects the heterogeneity of patients and of Centers' policies. Overall, the published data confirms that sorafenib does not appear to be associated with a significant toxicity in the transplant setting.

(3) Neither us nor the Editorial comment on our article [4] recommended the use of sorafenib "to be added to the next guidelines" on the management of HCC after transplant. Given the preliminary nature of our investigation both the article and the Editorial were very cautions in that respect, although emphasizing that the signal of effectiveness arising from our comparative cohorts represents one important step towards that may help in the design of guidelines for the management of these patients. It has to be noted, however, that up to now most of the treatments routinely performed for HCC recurrence after LT (such as liver resection, TACE, etc.) and possibly considered in such guidelines would lack the power of evidence grade 1–2 because of the absence of randomized controlled trials (RCTs).

(4) In the present conditions the proposal of Dr. Mancuso *et al.* of a multicenter RCT testing sorafenib *vs.* placebo in recurring HCC after liver transplantation could be rated as unethical, being sorafenib a compound with demonstrated efficacy in advanced HCC irrespective of different patient characteristics and disease presentation [5]. We sincerely think that studies like ours may give the rationale for trial implementation and offer a field practice perspective that helps to unravel the clinical effectiveness and toxicity of a drug when administered in real-life patients. In such perspective probably a single-arm prospective phase 3–4 study would better explore the safety of sorafenib and the possible drug-to-drug interactions that are potentially harmful in the transplant setting.

Table 1. Published series including more than 5 patients that underwent sorafenib for HCC recurrence after LT.

Author (Journal, year)	pts	mTOR*	AE		Discontinuation rate	TTP# (mo)	OS# (mo)
			Grade 3-4	Grade 4-5			
Kim R *et al.* (Oncology, 2010)	9	77.8%	n.r.	n.r.	0%	n.r.	n.r.
Yoon Dh *et al.* (Jpn J Clin Oncol 2010)	13	7.7%	30.7%	0%	0%	2.9	5.4
Gomez Martin *et al.* (Liver Transpl 2012)	31	96.8%	n.r.	6.5%**	0%	6.8	19.3
Sotiropulos GC *et al.* (Transplant Proc 2012)	14	100%	n.r.	n.r.	28.6%	n.r.	12
Staufer K *et al.* (Transplant Int 2012)	13	69.2%	92.3%	n.r.	77%	7	19.4
Vitale A *et al.* (Transplant Proc 2012)	10	70%	n.r.	0%	33%	8	18
Weinmann A *et al.* (Digest Liver Dis 2012)	11	81.8%	n.r.	0%	18%	4.1	20.1
Zavaglia C *et al.* (Eur J Gastroen Hepat 2013)	11	63.6%	n.r.	9.1%**	36%	n.r.	5
Sposito C *et al.* (J Hepatol 2013)	15	46.7%	n.r.	0%	6.7%	8.5	10.6
Pfeiffenberger J *et al.* (Langenbecks Arch Surg 2013)	8	25%	0%	0%	0%	4.5	9

*Percentage of patients undergoing sorafenib + mTOR inhibitors.
#Median, from starting of sorafenib.
**Grade 5 AEs.
pts, patients; mTOR, mammalian target of rapamycin inhibitors; AE, Adverse Event; TTP, Time To Progression; OS, Overall Survival; n.r., not reported.

Conflict of interest

The authors have received lecture fees from Bayer Healthcare for training courses with educational purposes on hepatocellular carcinoma.

References

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