Integrating sorafenib into an algorithm for the management of post-transplant hepatocellular carcinoma recurrence

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Since the introduction of the Milan criteria in 1996, liver transplantation has become the best treatment option for many patients with early non-resectable hepatocellular carcinoma (HCC), with expected five-year patient survivals in excess of 70% [1]. Despite strict candidate selection, some 10–15% of patients still develop a post-transplant recurrence. While the liver transplant community is endeavouring to lower these figures, refining selection criteria and exploring (neo-)adjuvant cancer treatments, the treatment of the patients with recurrence has received little systematic attention and is still in its infancy, mainly due to the limited number of patients.

Contributions, such as the one of Sposito et al. [2], shed some new light on the issue: the investigators show that the tenet that recurrences always lead to rapid death is no longer true, as some 15% (5/35) of the patients remain free of cancer after resection of the recurrence. These findings provide evidence in favour of diligent post-transplant protocols to detect recurrences early and allow suggesting a management algorithm (Fig. 1).

From a theoretical point of view, patients can experience two types of recurrences. Early recurrences may be the link to remaining (previously un-detected) extrahepatic HCC left at the time of transplantation, or result from the post-transplant engraftment of aggressive circulating HCC clones. Conversely, late recurrences are linked to the engraftment of more indolent and potentially less numerous circulating HCC cells [3]. These two types of recurrences have differing expected outcomes, with better survivals for patients with late recurrences [4]. These expected outcomes should be kept in mind when offering a treatment, as more side-effects can be accepted when decent chances of cure or at least of prolonged survival can be foreseen. As an example, some early intrahepatic HCC recurrences may be better “tested” by a locoregional treatment, prior to performing a resection, pending that no further disease appeared in the mean time.

At the time of a diagnosis of recurrence, a decision should be made whether to change the immunosuppression. Calcineurin inhibitors have been associated with an increased risk of post-transplant HCC recurrence [5], while mammalian target-of-rapamycin (mTOR) inhibitors are considered as protecting from de novo cancers and HCC recurrence [6]. Based on these (limited) data, many groups, including ours, switch patients to mTOR inhibitors at the time of recurrence (between 2007 and 2011, seven patients managed by Sposito et al. were or had been put on mTOR inhibitors at the time of recurrence). Overall, it appears sensible to keep the immunosuppression as low as possible in order to spare the anti-cancer immune activity.

Resection is the best treatment for both hepatic and extrahepatic single and oligonodular HCC recurrences [7], and this option should always be explored first. Unlike habitual HCCs, most post-OLT HCC recurrences develop in non-cirrhotic livers without portal hypertension, thus qualifying most patients for surgery. In the report by Sposito et al., 57% (25/44) of patients underwent a resection, and four were alive and free of HCC at a median of 35.6 months after recurrence [2]. Other investigators described improved outcomes after resection of lung HCC recurrences [8]. Of note, small (<3 cm) oligonodular hepatic recurrences can also be managed by radio-frequency ablation.

Sorafenib is a multi-tyrosine kinase and angiogenesis inhibitor. It is a treatment option for patients with HCC recurrences not amenable to surgery or locoregional treatment (n = 9), or in case of progression after first-line local (most often surgical) treatment (n = 35), and the contribution of Sposito et al. provides new data regarding the use of this drug for these specific indications.

Fortunately, patients with post-transplant recurrences are rare, imposing one of the limitations of the study, namely the inclusion of “only” 39 patients over 17 years. In addition, patients on sorafenib (n = 15) were different from controls (n = 24), as they presented more factors previously associated with better survival than patients on best supportive care. Sorafenib patients were managed in the most recent years (2007–2011), when the investigators were likely better in selecting good transplant candidates and more aggressive in the treatment of recurrence, and sorafenib patients were more often on mTOR inhibitors and had...
longer intervals between transplant and recurrence (38.1 vs. 15.7 months). Taking this into account, the uni-institutional design was a strength, considering the consistent policies in place, and the study’s main achievement was to provide an updated and transparent summary on the state-of-the-art management of recurrence, whether the improved survival was linked solely to sorafenib or not. The non-covariate-adjusted median survival from the time of recurrence nearly doubled in the sorafenib group compared to patients with best supportive care (21.3 vs. 11.8 months, \( p = 0.0009 \)). While this effect was likely amplified by the previously mentioned variables, its significance remained after correction for covariates.

The synergistic effect of sorafenib and mTOR inhibitors remains to be explored further, but Sposito et al. showed a trend towards a better tumour response according to modified RECIST criteria with the use of the combination (\( p = 0.0699 \)). This observation is in line with previous reports [9–11], and further supports the revision of the immunosuppression protocol at the time of HCC recurrence, favouring mTOR inhibitors. Of note, the combined use of sorafenib and sirolimus does not lead to a drug-drug interaction, and starting one drug should not require any dose adjustment of the other [12].

The post-transplant side-effect profile of sorafenib (especially in combination to mTOR inhibitors) is a point of concern [13–18]. The reported adverse events included hand-foot skin reaction (60%), diarrhea (40%) and fatigue (17%). They led to a dose reduction to 400 mg/day in more than half of the patients (target dose: 800 mg/day), only half of them recovering and being able to continue treatment at full dose. In addition, sorafenib was withdrawn in a patient with renal and hepatic insufficiency. It is difficult to predict the occurrence of these effects, but one would expect more adverse events in more fragile patients, especially early after transplantation. Yet the management of recurrence did not appear to be as gloomy as we thought in the past, and overall, patients in the sorafenib group accumulated almost 5 years of survival from the time of transplantation (38.1 month until recurrence and 21.3 months after recurrence).

A further advantage of the study is to draw attention to the lengthening interval between transplantation and detection of recurrence: in more recent years, the median time to recurrence increased from 15.7 months to 38.1 months. Studies exploring the safe expansion of selection criteria should take this into account, increasing the length of follow-up necessary for meaningful statistics.

Finally, the study by Sposito et al. also demonstrated that 61.7% of the recurring recipients had more advanced HCCs (beyond Milan) on the explant pathology [2]. This observation should promote a careful pathological review of the explants, and potentially the use of adjuvant post-transplant treatment in patients with signs of HCC aggressiveness (i.e., microvascular invasion, poorly differentiated HCC). Based on recent preliminary animal and clinical data, sorafenib may also have an interest in this setting, but this point remains to be confirmed by more studies [19,20].

Managing post-transplant HCC recurrence is a challenging field due to the low incidence of the disease, and a prospective
randomized (or even a case-control matched) study would be difficult to design. Only multi-centric efforts would be possible, but they would, by nature, bring more heterogeneity between cases. The contribution of Sposito et al. represents one important step towards the design of guidelines for the management of these patients, and suggests that sorafenib has a reasonable benefit/side-effect balance in patients with non-resectable recurrences.

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Conflict of interest

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References