Sorafenib use while waiting for liver transplant: We still need to wait

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COMMENTARY ON:


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With its approval in 2007 for advanced hepatocellular carcinoma (HCC), sorafenib became the first systemic agent with proven activity against the disease. To date, two large randomized studies in advanced stage HCC (BCLC C and a subset of BCLC B) have demonstrated its anti-cancer activity and ability to extend survival in patients with Childs A cirrhosis [1,2]. Since then, several studies have been launched to evaluate sorafenib’s potential role in less advanced HCC. Uniquely, sorafenib’s ability to improve survival is not mediated by inducing significant tumor shrinkage, but by its ability to slow progression and prolong the time to tumor progression (TTP). While some data has been presented [3], several ongoing studies including the SPACE (NCT00855218) and STORM (NCT0692770) studies are evaluating sorafenib as an adjuvant (after definitive therapy) to transarterial chemoembolization (TACE) and curative resection or radiofrequency ablation (RFA), respectively. The current study by Vitale and colleagues uses a cost–benefit analysis to determine the potential utility of using sorafenib in the neo-adjuvant setting, prior to liver transplant [4]. The clinical need to ask this question is real, as the authors highlight, drop-out from HCC progression beyond Milan criteria is one of the main reasons why patients awaiting transplant for HCC do not receive an organ.

The Milan criteria was initially described by Mazzaferro and colleagues over a decade ago and has served as the benchmark for prioritizing patients with HCC and otherwise lower MELD scores [5]. However, even with priority, there is still a relative shortage of livers available and HCC patients are competing with those with decompensated liver disease for organs. Though there are regional differences for wait times, the optimal management of patients with tumors within Milan has not been determined from prospective studies and our natural inclination is “to do something” when a patient has a known malignancy. Retrospective analyses do suggest that locoregional therapies such as TACE and RFA may be effective “bridge therapies” to transplant [6,7]; the basic notion being that existing lesions can be kept within size criteria with these approaches. A recent consensus conference on transplant and HCC endorsed this concept, especially when wait times are greater than 6 months [8]. However, these modalities fail as they do not prevent the development of metastases or the development of new, de novo HCC in a cirrhotic liver.

To determine the potential utility of sorafenib while awaiting transplant, the authors of this manuscript develop a Markov model based on the hazard ratio for sorafenib to decrease the risk of progression in the two studies in advanced HCC [1,2]. The model compared the use of sorafenib as a bridging therapy for patients with well-compensated liver disease and HCC to no bridging therapy unless wait times were greater than 6 months, when loco-regional therapies were taken into account. The study assessed sorafenib’s neo-adjuvant use on survival as measured by quality-adjusted life days, transplant probability, costs, willingness to pay, and net health benefit. Using a HR of 0.47 for intermediate stage HCC (BCLC B) derived in a subset analysis of the SHARP study, the authors found that with a monthly drop out probability of 5% and median time to transplant of 3 months, the gain in liver transplant probability due to sorafenib was 5% and increased with length of waiting time and decreasing hazard ratio. These data are shown in Fig. 1 adapted from the manuscript. Additionally, the models demonstrated a median survival benefit of 94 quality adjusted life days (QALDs) for sorafenib, and the net health benefit was 37 QALDs. Net health benefit was sensitive to not only waiting time (>6 months), but also the effectiveness of other (locoregional) therapies. This is an important challenge to the conclusions of the study as in many centers wait times are a year or longer and in that case, patients are surely being treated with a locoregional therapy – the benefit of which (e.g. HR), if any, is unknown. Further, while subset analyses from randomized studies in advanced disease found that the HR for sorafenib in BCLC B patients was less than for BCLC C patients (i.e. those with earlier stage derived a greater benefit), we do not know that this is the case for patients with tumor staged within Milan criteria where the true HR is unknown. Given the challenge of facing a patient with potentially curable HCC and a clear wait time of >6 months, treating physicians offer...
patients locoregional therapy while waiting, so why not offer them sorafenib in addition or even instead?

While the work by Vitale is of interest and highlights an area of unmet medical need, besides the true efficacy (HR) of sorafenib in this setting, the main issues to prevent its routine use is the lack of available safety data in this population. Drugs with anti-angiogenic activity have been associated with surgical complications such as bleeding and delayed wound healing when used in the perioperative setting [9]. In the renal carcinoma literature, neoadjuvant sorafenib specifically has not been associated with surgical complications when stopped at least one day before surgery [10,11]. However, there are concerns unique to liver transplantation such as vascular anastomoses, liver regeneration, and graft rejection. A recent laboratory study evaluated the effects of sorafenib on liver regeneration in a mouse model [12]. Mice were treated in 3 groups; group 1 received sorafenib for 14 days until the day prior to hepatectomy, group 2 received sorafenib as group one and continued after surgery, and group 3 received it only after surgery. The study demonstrated that when sorafenib was stopped one day before surgery there were no effects on liver regeneration, however, there was a decrease in liver regeneration in the other two groups. While these data and the urology literatures are reassuring, at the current time there is a lack of safety data to recommend the use of sorafenib in the pre-transplant setting. Importantly, unlike in the case of elective surgery where the last dose of sorafenib can be controlled, the nature of liver transplant makes this timing difficult and convincing safety data needs to be generated with sorafenib in the pre-transplant setting, specifically in regards to when sorafenib should be stopped. Sorafenib is an oral agent generally given twice daily. In a Phase I study of patients with preserved liver function, the half-life ranged from 24 to 38 h [13] and does not appear to be altered in cases of liver dysfunction [14]. Conceivably, if a patient’s tumor is controlled, sorafenib exposure in the pre-transplant period could be minimized by discontinuing drug at a pre-specified MELD score when the chance of being called for transplant becomes more likely. Based on the available data, a minimum of 24 h would be desired, but longer would be preferred. In addition, pre-clinical models have demonstrated an acceleration in the development of metastasis in mouse models after short-term exposure to VEGF receptor tyrosine kinase inhibitors [15]. This theoretical possibility of actually promoting recurrence is concerning and would need to be assessed prospectively.

In reality, wait times for most patients with HCC are >6 months and many are treated with locoregional therapy despite the lack of prospective randomized data supporting its use in this setting. There is currently a double-blind multi-center Phase III study comparing TACE and placebo versus TACE plus sorafenib in patients with HCC before liver transplant (HeLiVCa) [16]. Results from this study should help clinicians better understand the risk and benefits of using sorafenib in this setting. However, for patients that are not candidates for loco-regional therapy, there should not be a tendency to use sorafenib alone as a bridge therapy at this time.

Ultimately, we hope to move beyond anatomic stage for the selection of patients with HCC for transplant. More molecular studies are needed to identify and validate prognostic markers of favorable clinical behavior. In addition, the identification of predictive markers for those patients that are most likely to benefit from a management strategy that includes sorafenib is needed.

Conflict of interest

R.F. acted as consultant for Bayer, Onyx, and Bristol Myers Squibb.

References


