Transplant International

LETTER TO THE EDITORS

Response to Di Benedetto: ''sorafenib before liver transplantation for hepatocellular carcinoma: risk or give up?''

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Dear Sirs,

We read with interest the letter from Dr. Di Benedetto, *et al.* [1], regarding our article ''Sorafenib therapy for hepatocellular carcinoma prior to liver transplant is associated with increased complications after transplant'' published in the July 21, 2011 edition of *Transplant International* [2]. We have also read the Letter to the Editor referenced by Dr. Di Benedetto in another journal that outlines a case report of successful neoadjuvant use of sorafenib in a single patient with a Milan stage T2 lesion and high alpha-fetoprotein prior to transplant [3]. We agree that the role of sorafenib in the pretransplant setting is not fully defined and that more study is needed.

As we stated in the publication, our study was not randomized and patients received sorafenib based on the transplant physician's preference in the setting of informed consent by the patient. There were a few patients during the study period that declined the use of sorafenib in the pretransplant setting and they were included in the control group of the study. Additionally, there were some physicians who did not choose to use sorafenib in this patient population in the pretransplant setting. Despite these very subjective differences in cases and controls, Table 1 in the publication showed that the demographics and tumor characteristics were both clinically and statistically similar between cases and controls. This study was not meant to replace a randomized, double blind, placebo controlled trial but merely to raise questions and associations between the drug and post-transplant complications.

In regard to number of locoregional therapies, Table 1 of the article also outlines the different locoregional therapies offered to the patients prior to transplantation; 90% of sorafenib patients underwent transarterial chemoembolization (TACE) of the primary tumor(s) while one patient underwent no pretransplant locoregional therapy (T1 stage). Twenty percent of sorafenib patients also had either radiofrequency ablation (RFA) or external radiotherapy to the primary lesion in addition to TACE. No patient had more than one TACE. In the control group, 69% of patients had a TACE as the primary therapy for the tumor and 13% had no locoregional therapy because of either rapid transplant or T1 lesion; 17% of controls had only RFA as the primary treatment and 21% of control patients had a combination of TACE and another modality of treatment in the pretransplant phase. Also stated in Table 1, 44% of the sorafenib patients and 52% of controls had residual viable tumor in the explant.

We also agree that it is ideal to stop the sorafenib 2–3 weeks before major surgical procedures as suggested in the Nexavar package insert in the United States. However, the current organ allocation system in the U.S. does not allow us the luxury of knowing the exact date or time of transplantation for the vast majority of recipients. Therefore, it was the decision of the transplant team that we would continue the drug up until an organ offer was accepted for each recipient. If a live donor was available for the patient, it would allow the optimal situation of a fixed date for the transplantation and would allow the transplant team the ability to adhere to a schedule of discontinuation of the sorafenib. In this series, there were no living donor transplants performed. Despite the short time frame for stopping the drug in the pretransplant setting, we experienced no extra wound complications in the sorafenib group versus the controls.

Dr. De Benedetto, *et al.*, in their letter, state that sorafenib ''should not be reserved to patients with advanced HCC to whom no [sic] other curative treatment is possible but it should be offered also to a different setting of patients such as young patients outside standard criteria to LT.'' While this was the original thought process bringing our transplant physicians to the use of sorafenib in the pretransplant setting, at the time of this response, there are no data published to support the statement in the transplant population other than single patient case reports or theoretical cost-effectiveness simulations [4]. The post-transplant complications in our patient cohort have raised new questions about the safety of this practice. While our data do not carry the strength of a randomized controlled trial, our article should at least raise questions about the safety of this drug in the pretransplant setting and need to be added to the conversation held with transplant candidates on the waiting list

regarding the use of this medication until more definitive data are published.

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