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Statins: a panacea to reduce mortality in patients undergoing liver transplantation for hepatocellular carcinoma?

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In Greek mythology *Panacea* was the goddess of universal remedy or health. In literary terms a panacea represents a solution to solve all ills and there are few drugs that can claim such an accolade. One drug class that has claimed to be a panacea in adults at increased risk of cardiovascular disease are statins. Since their FDA approval in the late 1980s, statins have revolutionised the management of hypercholesterolemia. Statins

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have unequivocally been associated with reduced risk of all-cause and cardiovascular mortality and cardiovascular events, with absolute benefits in patients at greater baseline risk in 19 trials enrolling over 71,344 patients. (1) Benefits appear consistent across demographic and clinical subgroups, including populations without marked hyperlipidemia. Statins inhibit hepatic conversion of HMG-CoA to mevalonate by inhibiting the rate-limiting enzyme of the mevalonate pathway HMG-CoA reductase depleting intracellular cholesterol triggering. Cholesterol has multifaceted roles in tumorigenesis eliciting anti-cancer effects through cholesterol depletion and tumour-specific apoptosis. Despite these observations statins have yet to be repurposed and integrated into oncology treatment regimens. (2)

Liver cancer is the third leading cause of cancer-related deaths globally. Liver transplantation (LT) provides the best chance for long-term survival in highly selected patients with early-stage hepatocellular carcinoma (HCC), but is *not* a panacea. Aside from the morbidity and mortality resulting from the surgery and long-term immunosuppressant medication, recurrent HCC post-transplant occurs in approximately 15% of recipients no matter how rigorous the selection criteria utilised. Recurrent HCC is associated with a significant decrease in recipient survival. (3) Statins have been shown to contribute to HCC prevention in patients with hepatitis B and C, patients who underwent initial liver resection for HCC, and the general population. (4) A number of studies have also suggested statins improve short and long-term outcomes in solid organ transplantation. It is therefore highly topical to read the study by Lee and colleagues published in this issue which retrospectively analyzed 430 consecutive patients undergoing LT for HCC between 1995 and 2019. (5) Utilising inverse probability of treatment weighting methods to balance any confounders and the landmark method to avoid immortal time bias they showed a consistent anticancer effect of statins on HCC recurrence; 25% of the cohort were statin users. Statin use was a predictor of lower HCC recurrence, all-cause mortality and HCC-related mortality in a dose-dependent fashion. This effect was independent of known factors associated with HCC recurrence; such as morphologic staging of tumour at diagnosis, alfa fetoprotein levels and explant histology; and other potentially cancer protective medication such as aspirin. Mean trough calcineurin inhibitor levels are reported, but not wait-list time.

A potential weakness of this study is that it represents a single-centre retrospective analysis, however well the 2 patient cohorts were matched. Somewhat surprisingly the median time between LT and commencing the statin was close to 3-years (range 7-months to 5-years) raising concerns other factors could be influencing outcomes here. This also makes it harder to comprehend how statin use led to the impressive reduction in 2-year and 5-year cumulative incidences of all-cause mortality translating to an astounding 20% improved survival.

Whilst observational studies suggest statins may have protective anti-cancer effects data pertaining to their use as treatment for HCC is less promising. PRODIGE-11 compared the combination of sorafenib and pravastatin versus sorafenib alone in patients with Child Pugh A cirrhosis and advanced HCC and did not demonstrate any survival benefit with pravastatin although the median survival was just 10-months. (6) PRODIGE-21 compared sorafenib versus pravastatin versus combination versus best supportive care, with no survival benefit from pravastatin. (7)

Whether statins have an independent favourable impact on post-LT outcomes merits debate. We know patients undergoing renal transplantation have better graft function on statins. (8) Statins elicit immunomodulatory effects. A tumour microenvironment rich in cholesterol with tumour-infiltrating CD8+ T cells promotes enhanced expression of immune checkpoint proteins and T-cell exhaustion allowing tumour cells to escape immune surveillance. Therefore, statins could augment cytotoxic T-cell activity. (9)

As statins are generally well tolerated in solid organ post-transplant settings and are indicated for cardiovascular disease primary prevention applicable to the growing cohort of patients developing HCC in the context of metabolic-associated liver disease (with and without cirrhosis), routine use could be argued to be evidence-based. However, whether statins will offer an independent survival advantage for patients transplanted for HCC by reducing HCC recurrence, remains to be determined. A randomised-controlled trial with an appropriately powered primary mortality outcome is required. Whilst interesting, this study has not provided the panacea.

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- Accepted Article
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