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Mini Review

Should We Use Statins During the Therapy of Metastatic Renal Cancer?

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Abstract

Statins are a class of drugs which primarily funcion as competitive inhibitors of HMG-CoA reductase. There are numerous studies investigating the effect of statins on cancer patients with contradictory and controversial results. Regarding renal cancer, current research show that the effect of adjuvant statin therapy during the treatment of metastatic renal cancer differs greatly based on targeted treatment drug. Using available research, we propose that the elevation of cholesterol levels during the targeted treatment of renal cancer patients with sunitinib, might originate from the destruction of cancer cells and thus not necessarily requiring introduction of statin therapy without additional investigation. The study which we hope will shed some light on the issue is currently undergoing in our Clinic.

ABBREVIATIONS

Mrcc: Metastatic Renal Cell Carcinoma; HMG-Coa: 3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A; VEGF: Vascular Endothelial Growth Factor

INTRODUCTION

Statins are a class of drugs which primarily function as competitive inhibitors of HMG-CoA reductase, an enzyme anchored in endoplasmatic reticulum of the cells, paramount in biosynthesis of cholesterol. Blocking the enzyme, statins induce a reduction of cholesterol levels, hence reducing cardiovascular morbidity and mortality. It was recently shown that statins also exhibit a nonenzymatic mechanism in modulating cholesterol particles [1].

STATINS AND CANCER

There are numerous studies investigating the effect of statins on cancer patients with contradictory and controversial results. For example, Boegemann et al., proved in 2016. that use of statins as a concomitant medication does not improve survival outcomes or best clinical benefit in men with metastatic castration resistant prostate cancer treated with abirateron acetate during the 5-year investigation of 108 men [2]. Little benefit was also found in a large cohort study of patients with invasive breast cancer [3]. On the other hand, Lin et al., reported an improved survival among patients with stage IV non-small cell lung cancers on statins [4], while dose-dependently chemopreventive effect of statins were noticed in colon cancer patients [5,6].

Even regarding only kidney cancer patients, results are uneven. Nayan et al., showed in 2016. that there is no significant association between statin use and outcomes of non-metastatic kidney cancer patients [7]. McKay et al., on the other hand, reported in 2016. that an increase in overall survival (OS) was found in metastatic renal cancer (mRCC) undergoing targeted terapy. However, the mentioned study primarily evaluated patients who were already on statins during the cancer therapy. Also, it is necessary to note that the effect differed based on treatment drug. The most significant effect was unsurprisingly noted in patients treated with vascular endothelial growth factor (VEGF) inhibitors, whilst no effect on OS was found in those treated with interferon alpha [8]. Treatment of statins along with VEGF inhibitors might be a plausible idea since VEGF inhibitors lead to net reduction of capillary density, loss of contractile function and exhibit severe cardiotoxic effects [9]; on the other hand, statins also have an effect in lowering VEGF levels [10].

In 2015, Taissi et al., noted an increase in total cholesterol levels and triglycerides in mRCC patients treated with sunitinib, one of the most common first-line targeted therapy drugs [11]. The cholesterol levels however did not respond to introduction of statin therapy, unlike a reduction of sunitinib dose which effectively lowered cholesterol levels. In our work, we hypothesized that elevation of cholesterol levels during the targeted treatment of mRCC patients might actually indicate efficacy of the targeted treatment. We explained how elevation of cholesterol might also correlate with elevation of ferritin levels during mRCC treatment, since both of these pathways are affected by mTOR inhibition [12]. As Kell and Pretorius postulated, elevation of serum ferritin mainly originates from

damaged cells and could be a marker of inflammation [13]. Similarly, elevation of serum cholesterol might also originate from destruction of cancer cells. This hypothesis is reinforced by the fact that application of statins during the mRCC therapy resulted in no significant effect, unlike a reduction of dose of the targeted drug.

CONCLUSION

Statins are a controversial issue in oncology, partly due to many side effects, such as statin-induced diabetes [14] and miopathy [15], which are especially problematic in cancer patients who are already burdened with many comorbidities. Statins are primarily blockers of a cellular enzyme, with proven efficacy in reduction of cholesterol levels [16]. A clinical study proved however, that in treatment of hypercholesterolemia during the mRCC treatment with sunitinib, statins have almost no effect, unlike a reduction of targeted therapy dose. This could mean that elevation of cholesterol during the mRCC treatment with sunitinib does not come from HMG-CoA reductase activity, which is a primary target for statins, but perhaps, as Kell elaborates, from damaged cells. If this is the case, statin drugs should not necessarily be introduced during the treatment of metastatic kidney cancer with sunitinib, even with notable hypercholesterolemia, unless, of course, patient requires statins for cardiovascular reasons. The drug-induced hypercholesterolemia has an actual potential to be a positive prognostic factor and might be caused by a different mechanisms than those statins affect. A notable exception might be the treatment of mRCC with VEGF inhibitors, where statins have a potential as adjuvant therapy due to mechanism of VEGF inhibitors, but more quality research is needed. As mentioned before, the rise of triglycerides as shown by Tassi, might be the main target for antilipemic drugs during mRCC treatment with sunitinib.

We are currently undergoing a study trying to shed additional light on the need for statin therapy and cholesterolemia as prognostic factors in mRCC treatment.

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