Serum Cholesterol and mTOR inhibitors: Surrogate Biomarker or Epiphenomenon?

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Summary

Lee et al report that rise in serum cholesterol is associated with improved clinical outcomes in patients with renal cell carcinoma treated with temsirolimus. While these findings must be validated prospectively, it should also be determined if this marker is a true mechanism-based toxicity or an epiphenomenon associated with therapy.
In this issue of Clinical Cancer Research, Lee and colleagues report through a retrospective analysis that increased levels of serum cholesterol is a potential predictor of clinical efficacy of temsirolimus in patients with advanced renal cell carcinoma (RCC) (1).

Two rapalogues, temsirolimus and everolimus, are now approved by the U.S. Food and Drug Administration for the treatment of patients with advanced RCC. Treatment with rapalogues, allosteric inhibitors of the kinase mammalian target of rapamycin (mTOR), has been associated with several metabolic abnormalities including hypercholesterolemia (2). The exact mechanism by which the rapalogues induce hypercholesterolemia is unknown. As Lee et al discuss, the mTOR pathway has been implicated in the regulation of sterol regulatory element binding protein (SREBP) – 1 and -2, which in turn are master transcriptional regulators of fatty acid and cholesterol biosynthesis, respectively (Figure 1). The authors propose that attenuation SREBP activity may underlie the hypercholesterolemia associated with temsirolimus. However, it has recently been shown that many functions of SREBP-2, in particular the regulation of cholesterol biosynthesis genes, are dependent upon mTOR complex 1 (TORC1) but resistant to rapamycin (3). It is perhaps more likely that the recent finding that low density lipoprotein (LDL) receptor gene expression is dependent upon TORC1 and sensitive to rapamycin more directly contributes to rapalogue-induced hypercholesterolemia (4). Regardless, this toxicity appears characteristic of mTOR inhibitors and its correlation to clinical outcomes has previously been unstudied.
In this issue, Lee et al present the results of a retrospective analysis of the correlation between changes in fasting serum cholesterol, triglycerides, and glucose during treatment with clinical outcome measures in patients treated with temsirolimus and interferon-α (IFN) as part of the Global Advanced RCC Trial (1). In their analysis, the authors show that larger increases in serum cholesterol from baseline in patients treated with temsirolimus were associated with both reduced risk of disease progression and prolonged overall survival. Strikingly, when the effect of cholesterol change was accounted for through multivariate analysis, there was no additional advantage to temsirolimus over IFN. Moreover, both greater baseline serum cholesterol and larger increase in serum cholesterol during treatment were associated with improved clinical outcomes regardless of treatment arm. The authors therefore conclude that change in serum cholesterol may be a promising predictive biomarker of response to mTOR inhibitors.

Lee et al stress that this retrospective analysis is meant to be hypothesis generating and indeed many questions come to mind. First, why is greater baseline serum cholesterol associated with better clinical outcomes regardless of treatment arm? This finding is curious given that some studies have linked obesity and high cholesterol diets with risk of RCC development (5, 6). RCC have been shown to contain elevated levels of cholesterol esters (7), leading some to speculate that both the enzyme responsible for cholesterol ester formation, acyl-coenzyme-A:cholesterol acyl transferase (ACAT), and LDL-mediated uptake may be critical for RCC progression (8), implying that RCC with less LDL import may simply be less aggressive or metabolically active. It is also possible that
baseline serum cholesterol may be more representative of nutritional status, perhaps even more relevant in the poor-risk population studied in the Global Advanced RCC Trial. In this light, baseline serum cholesterol may be more of a prognostic marker independent of treatment rather than predictive. One might also speculate if this marker would continue to be prognostic or predictive in patients who have favorable risk features.

The most provocative finding of this analysis, however, remains that greater increase in serum cholesterol during treatment was associated with improved clinical outcomes across the study. While the authors focus on the predictive value with respect to temsirolimus, the fact that this finding was independent of treatment arm raises an important question: Is the increase in serum cholesterol during treatment a true mechanism based-toxicity or an epiphenomenon? One might speculate that tumor cells which are proliferating less rapidly would require less lipid and cholesterol for generation of new cell membrane. While it is likely that the majority of lipid and cholesterol required for cell membrane is generated through de novo biosynthesis, rapid proliferation may require enhanced cholesterol import. Therefore, increase in serum cholesterol might be an epiphenomenon indicative of slowed tumor growth rather than as a marker of the degree of mTOR inhibition.

On the other hand, the most current understanding of the biology of the mTOR pathway supports the belief that the observed increase in serum cholesterol may be a pharmacodynamic marker. In addition to the mechanistic rationale that rapalogues have been shown to induce changes in gene expression which would be expected to reduce
cholesterol uptake, this belief is further supported by the fact that in the current analysis, serum cholesterol was not observed to change significantly in patients treated with IFN. The correlation of mechanism-based toxicities with improved clinical outcomes is a familiar paradigm with other molecularly targeted agents. Examples include skin rash with epidermal growth factor (EGF)-pathway inhibitors in patient with non-small cell lung cancer and hypertension with vascular endothelial growth factor receptor-2 (VEGFR2) antagonists in patient with RCC (9, 10).

The distinction between epiphenomenon versus true mechanism-based toxicity is critical as with the later the failure to observe a rise in serum cholesterol would suggest inadequate suppression of the biologic target in normal tissue and could serve as a surrogate for the same in tumor cells. In this case, the dose of temsirolimus might be escalated until an increase in serum cholesterol is observed. This approach might be even more feasible with temsirolimus than with other molecularly targeted agents as phase I trials identified a recommended phase II dose of up to 250mg IV once weekly, significantly in excess of the standard 25mg IV once weekly dose approved in RCC (11). On the other hand, in a large phase II trial in which patients with advanced RCC were randomized to receive temsirolimus at doses of 25mg, 75mg, and 250mg IV once weekly, no differences in efficacy were noted between the treatment arms (12). As intra-patient dose-escalation of temsirolimus has not been studied, however, further retrospective analysis to confirm a correlation between plasma concentrations of temsirolimus with serum cholesterol levels in these trials would be helpful in supporting the feasibility of and rationale for this concept.
In summary, the work presented by Lee et al provides many avenues for future research. As with any retrospective analysis, these findings must be validated prospectively and independently. Should rise in serum cholesterol be validated as a predictive biomarker of temsirolimus efficacy, this measure could be used to more rapidly identify patients who would not be expected to benefit from treatment. Given the unique biology of RCC, it would be interesting to determine if serum cholesterol is similarly predictive of benefit of mTOR inhibitors in different cancer types. If changes in serum cholesterol levels in RCC are more of an epiphenomenon associated with therapy, would this marker be similarly predictive of benefit with VEGFR inhibitors? Finally, perhaps the most enticing possibility is that rise in serum cholesterol may be a true mechanism-based toxicity that can be used as a pharmacodynamic surrogate. Should this prove to be the case, consideration might be given to the prospective study of intra-patient dose-escalation of mTOR inhibitors in patients with RCC.
References


Figure Legend:

Figure 1: Regulation of fatty acid and cholesterol biosynthesis and LDL-receptor gene expression by mTOR.

Akt = Protein Kinase C; TSC1 = Tuberous Sclerosis Complex 1; TSC2 = Tuberous Sclerosis Complex 2; RHEB = Ras Homolog Enriched in Brain; mTOR = Mammalian Target of Rapamycin; Raptor = Regulatory protein associated of mTOR; SREBP-1 = sterol regulatory element binding protein-1; SREBP-2 = sterol regulatory element binding protein-2
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