Potential role of everolimus in inducing cholestasis

Everolimus, an orally administered mammalian target of rapamycin (mTOR) inhibitor, is currently the first and only agent to show benefit in patients who had progressed on vascular endothelial growth factor receptor tyrosine kinase inhibitor (TKI) therapy [1].

We report two cases of progressive cholestatic changes anticipated by serum lipidic asset modifications clearly related to everolimus treatment in metastatic renal clear cell cancer patients.

Both patients started everolimus as third-line therapy after failure of two lines of TKIs. No hypercholesterolemia or hypertriglyceridemia was found during and before the treatment with these two therapeutic agents; moreover, they had no history of liver function test abnormalities or history of radiologically detectable cholestasis. In addition, they were not treated previously or at the same time with drugs potentially causing cholestasis including ampicillin and other penicillin-based antibiotics, anabolic steroids, chlorpromazine, cimetidine, erythromycin or others.

We also excluded the presence of Stauffer's syndrome in consideration of the absence of systemic symptoms such hepatosplenomegaly, fever and weight loss or specific laboratory abnormalities (erythrocyte sedimentation rate and a2-globulin elevation, thrombocytosis and prolongation of prothrombin time) and moreover, both patients were previously nefrectomized.

Twenty days after everolimus start, biochemical blood tests showed an initial alteration of serum cholesterolemia (more than two times in both cases) and hepatic cholestasis indicators (γ-glutamyltransferase more than 3 times and alkaline phosphatase more than 1.5 times).

Approximately 60 days from everolimus start, cholesterolemia raised up to three times in both cases and at the same time, computed tomography scan showed dilatation of extra- and intrahepatic biliary tract with presence of biliary sludge and gall-bladder distention associated with a further upraise of hepatic cholestasis indices (γ-glutamyltransferase more than 10 times and alkaline phosphatase more than 3 times in both cases). These biliary modifications were confirmed in both cases by magnetic resonance imaging cholangiography.

At the discontinuation of the treatment, we observed a progressive reduction of hepatic cholestasis indices even if we did not observe a complete normalization.

We can speculate that these cholestatic changes may be explained by an indirect and a direct everolimus-related mechanism. It is well known that high cholesterol level can cause the secretion of an 'abnormal bile' which leads to precipitation of cholesterol from micellar solution [2] and it is equally well known that mTOR inhibitor treatment is correlated to modifications of lipidic metabolism leading to an increase of cholesterolemia and triglyceridemia [3] and this correlation has been confirmed also for everolimus in phase I, II and III trials [1].

In fact, in a preclinical model, mTOR inhibition demonstrated to reduce low-density lipoprotein (LDL) receptor-mediated cholesterol ester accumulation in hepatocytes resulting in a delay of LDL-cholesterol clearance from circulation and consequently in an increase of plasma cholesterol concentration [4].

As for direct mechanism, in rat model, this inhibition demonstrated to cause cholestatic change in liver enzymes through a down-regulation of messenger RNA levels of canalicular transport proteins (Mrp2) and an increase of sinusoidal transport proteins (Oatp2) leading to accumulation of toxic metabolites in the hepatocytes [5].

In conclusion, oncologists must be aware of this newly observed side-effect occurring during mTOR inhibitor-based treatment.

F. Pantano*, D. Santini, F. Guida, B. Vincenzi & G. Tonini

Department of Medical Oncology, University Campus Bio-Medico, Rome, Italy
(*E-mail: f.pantano@unicampus.it)

references

1. Motzer RJ, Escudier B, Oudard S et al. on behalf of the RECORD-1 Study Group. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008; 372: 449–456.
2. Wang HH, Portincasa P, Wang DQ. Molecular pathophysiology and physical chemistry of cholesterol gallstones. Front Biosci 2008; 13: 401–423.
3. Ma KL, Ruan XZ, Powis SH et al. Sirolimus modifies cholesterol homeostasis in hepatic cells: a potential molecular mechanism for sirolimus-associated dyslipidemia. Transplantation 2007; 84(8): 1029–1036.
4. Bhojani N, Jeldres C, Patard JJ et al. Toxicities associated with the administration of sorafenib, sunitinib, and temsirolimus and their management in patients with metastatic renal cell carcinoma. Eur Urol 2008; 53(5): 917–930.
5. Bramow S, Ott P, Thomsen Nielsen F et al. Cholestasis and regulation of genes related to drug metabolism and biliary transport in rat liver following treatment with cyclosporine A and sirolimus (Rapamycin). Pharmacol Toxicol 2001; 89: 133–139.

doi:10.1093/annonc/mdp558
Published online 2 December 2009