Editorial

Chemoprevention for hepatocellular carcinoma: the role of statins

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In oncology, cancer prevention may be categorized as primary, secondary and tertiary. Primary prevention refers to the identification of genetic, biologic, and environmental factors that play an etiologic or pathogenetic role, in order to impair their effects on tumor development and halt progression of cancer and ultimately death. The objective of primary prevention is to prohibit or to halt effective contact of a carcinogenic agent with a susceptible target in the human body. Secondary prevention refers to identification of existing pre-neoplastic and early neoplastic lesions in order to treat them thoroughly and expeditiously. Since the stage of cancer dictates the therapeutic choice, early detection is a primary objective. The goal of cancer screening is to reduce mortality through a reduction in incidence of advanced disease. Tertiary prevention refers to preventing recurrence in patients cured of an initial cancer (1).

Recent, even if contrasting evidences (2-4) suggested that a potential role in cancer primary prevention should be provided by statins, or hydroxyl-3-methylglutaril coenzyme A (HMG-CoA) reductase inhibitors, that are the second most prescribed drug in the United States. In this line in fact, statins have been suggested to decrease risk of cancer in preclinical studies by inhibiting Ras- and Rho-mediated cell proliferation, up-regulation of cell-cycle inhibitors (e.g., p21 and p27), induction of apoptosis of transformed cells and inhibition of angiogenesis. On the other hand several large trials of statins on cardiovascular disease risk, having cancer prevention as secondary end-points, and two meta-analyses of randomized trials, have shown no benefit to cancer risk with follow-ups between 18 months to 4 years (5,6). However these trials were non adequately powered to examine cancer end point.

In this complex picture, the role of statins in prevention of hepatocellular carcinoma (HCC) is unknown. HCC is a challenging malignancy of global importance. It is the sixth most common cancer, and the third cause of cancer-related death worldwide. Cirrhosis is the strongest and the most common known risk factor for HCC, usually due to hepatitis C virus (HCV) and hepatitis B virus (HBV) infections. However, different lines of evidence identify in non-alcoholic fatty liver disease (NAFLD) a possible relevant risk factor for occurrence of HCC. The geographic distribution of HCC is highly uneven: three areas with different incidence rates (low, intermediate, and high) have been recognized (7). HCC is associated with a high rate of mortality and its prognosis remains dismal, in particular when diagnosis is made at an advanced stage, when patients are symptomatic with a variable degree of liver function impairment (8). Although early diagnosis and effective treatments (secondary prevention) are paramount in controlling the death rate of patients with HCC (9), the importance of cancer prevention (primary prevention) has gradually emerged because advanced (i.e., large or locally invasive) HCC is difficult to cure. Therefore, HCC (chemo)-prevention remains a major issue in the long-term management of cirrhotic patients, especially where chronic HCV or hepatitis B virus (HBV) infection is the leading cause of chronic liver disease (up to 80% of cases in the Mediterranean area). Vaccination against HBV is the most efficient primary prevention measure currently available to reduce the HCC incidence and mortality in high-incidence areas, while data on the role of interferon (IFN) and nucleos(t)ide analogues (NUC) are still controversial. The pooling of data from the literature suggests a slight preventive effect of antiviral therapy on HCC development in patients with HCV-related cirrhosis, but the preventive effect is limited to sustained virological responders (7).

In their interesting paper, Tsan *et al.* (10) performed a

methodologically sound population-based cohort study from the Taiwan National Health Insurance Research Database aiming to evaluate the association between the use of statins in HBV-infected patients and the risk of HCC. Authors included a wide cohort [33,413] of patients and found 1,021 HCCs in the HBV cohort during the follow-up period of 328,946 person-years. A number of potential confounders such as anti-HBV treatment (interferon, lamivudine, entecavir, adefovir dipivoxil, and telbivudine), aspirin, angiotensin-converting enzyme (ACE) inhibitors (captopril, enalapril, lisinopril, perindopril, ramipril, quinapril, benazepril, cilazapril, and fosinopril), triglyceride-lowering medications (bezafibrate, clofibrate, etofibrate, fenofibrate, gemfibrozil, and simfibrate) and sociodemographic characteristics (age, sex, income, and level of urbanization) were evaluated in the model. The analysis showed that there was a dose-response relationship between statin use and the risk of HCC in the HBV cohort. With all the caveats of a retrospective analysis and the lack of pretreatment patient stratification, analysis in this study indicated that statin use of 28 to 90 cumulative defined daily dose (cDDD) was associated with a 34% risk reduction in HCC compared with nonuse. Moreover, lack of a randomized control group lead to existence of several unmeasured (such as body mass index, smoking, alcohol intake, and other over-the-counter drug use) and unknown confounders.

These data, needing to be validated in randomized controlled studies, add further evidence on the potential protective effect of statins in patients with chronic liver diseases (CLD). In fact, in the last years the scenario of statin use in patients with CLD progressively changed from the fear to use statins, to the evidence, also stated by Food and Drug Administration (FDA), that an elevated ALT after initiating a statin is not a sign of hepatotoxicity (11,12), being severe liver reactions to statins rare (11), and further to data showing that statin use in patients with CLD could provide benefits. In this line in fact: (I) data from a Greek randomized trial on the efficacy and safety of statins in patients with coronary artery disease, baseline increases of alanine transaminase (ALT), and steatosis, showed that statin use was associated with ALT improvement (13); (II) statin use was not associated with ALT elevation in cohorts of HCV patients (14-16), subjects at higher cardiovascolar risk (17) and where statin could exert their protective endothelial effect; (III) statins showed HCV antiviral activity *in vitro* (14), being this data supported by evidences in RCTs that statin use is an independent positive predictor of sustained virological response in CHC patients underwent interferon-based dual (18) and triple (19) therapy.

In conclusion, even if the nice study of Tsan and colleagues (10) suggests that statin use may reduce the risk for HCC in HBV-infected patients in a dose-dependent manner, we think that large RCTs should be performed to confirm the efficacy of this therapy. Furthermore, when mechanistic role of statin in prevention of HCC will be clarified, this therapy could be evaluated compared to placebo with or without sorafenib, for tertiary prevention of HCC after resection or local ablation.

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