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Is it time to recommend low-dose aspirin treatment for the prevention of hepatocellular carcinoma?

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The observational study that Simon *et al*. recently published in the New England Journal of Medicine has significant relevance as it involves a large and selected population of patients with chronic hepatitis B (CHB) or chronic hepatitis C (CHC) who harbor high risk of developing hepatocellular carcinoma (HCC)[1]. The finding that a regular use of low-dose aspirin, particularly long-term, is associated with reduced HCC incidence and reduced mortality but no excess risk of gastrointestinal bleeding strongly reinforces what has been previously suggested by various meta-analyses of the last decade[2-11].

Almost 50 years have passed since the publication of the first preclinical study showing that aspirin holds anticancer potential[12]. The first population-based study in humans on this subject was published in the late 80's and highlighted colorectal cancer as a disease of particular susceptibility to aspirin treatment[13]. Since then, numerous epidemiological studies and even randomized controlled trials have provided findings on aspirin-treated patients at risk of developing and/or progressing varying solid tumors. Again, colorectal malignancies have emerged as the most consistently inversely related diseases[3, 14]. The highly relevant study here summarized[1] may well contribute to add HCC on this list.

Of note, the relationship between strength of anticancer response and dosing or duration of aspirin treatment still remains ill-defined, and this has mechanistic implications as per the mode of action of this nonsteroidal drug possessing anti-platelet, anti-pyretic and anti-

inflammatory properties[15]. Aspirin irreversibly inactivates the cyclooxygenase (COX) 1 and 2 enzymes through selective acetylation of specific side-chain hydroxyl groups[16]. However, because of its short half-life in the bloodstream (less than 20 min) and the capacity of nucleated cells to rapidly re-synthesize Cox isozymes, a single daily low-dose of aspirin - the treatment regimen characterizing the investigation by Simon *et al.*[1] as well as most of the other HCC-related investigations [2-11] - should have negligible effects towards cancer cells or immune and inflammatory cells, apart from anucleate platelets[16].

The involvement of platelets in the mode of action of low-dose aspirin in CHB or CHC patients is noteworthy, as preclinical work starting about 15 years ago linked these cells to the pathogenesis of acute and chronic viral hepatitis. Indeed, using mouse models of HBV infection, it has been shown that the peculiar anatomy and hemodynamics of the liver microcirculation favor the formation of small and transient platelet aggregates within the hepatic sinusoids, and that these aggregates function as docking sites for circulating virus-specific $CD8^+$ T cells, eventually triggering liver disease[17, 18]. Accordingly, the sustained inhibition of platelet function by low doses of aspirin and/or other antiplatelet drugs in models of chronic hepatitis B limits the formation of platelet aggregates and the intrahepatic accumulation of pathogenic HBV-specific $CD8^+$ T cells, secondarily hindering the consequent liver cell injury, the compensatory hepatocellular proliferation, the severity of liver fibrosis and the development of HCC[17, 19]. Ultimately, the unrelenting exposure to aspirin at low doses improves overall survival without causing bleeding side effects[19]. Although the suppression of liver immunopathology provides strong mechanistic evidence for the antitumor effect of low-dose aspirin, the inhibition of other platelet-derived products potentially supporting tumor growth - including different growth factors such as platelet-derived growth factor (PDGF),

vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), hepatocyte growth factor (HGF) and epidermal growth factor (EGF), or small molecules stimulating hepatocellular proliferation like serotonin[20] could also be involved. The notions that aspirin does not prevent HCC onset during chemical hepatocarcinogenesis in mice[19] and that many of the aforementioned platelet-derived products are induced intrahepatically under this experimental condition[21], however, indirectly suggest that the antitumor potential of aspirin in chronic viral hepatitis mainly reflects its capacity to render platelets incapable of supporting liver immunopathology.

Come what may, the reduced risk of HCC and related mortality that Simon *et al.* reported to be associated with no significant bleeding side effects[1] provides further appealing evidence on the benefit that a long-term use of low-dose aspirin might have in patients with CHB or CHC. A couple of questions then obviously arise: is it time to recommend aspirin treatment initiation in selected CHB or CHC patients or is it still wiser to run randomized clinical trials at first? Answering these questions is not easy, as several arguments come to play, including the intrinsic difficulty of conducting lengthy HCC prevention trials that may require improved methods for predicting HCC risk, frequent monitoring of viral and disease parameters, use of direct acting antivirals when necessary and extended follow-ups, as well as selective aspirin use for the prevention of cardiovascular diseases. Having said that, the full risk of bleeding may have not completely emerged from this or other observational studies. Hence, specific measures to deal with this issue are strongly encouraged even though -as pointed out elsewhere - excessive bleeding that is prevalent in the advanced stage of liver cirrhosis may be a lesser risk than thrombosis in subgroups of patients with chronic viral hepatitis[22]. All in all, the study by Simon *et al.* should motivate a constructive discussion by the international

scientific community on whether or not the preclinical and clinical results gathered thus far can be considered as conclusive background evidence to warrant the use of low-dose aspirin in patients suffering from chronic viral hepatitis.

Comments

Simon *et al* conducted a highly relevant record-linkage cohort study that is based on a nationwide, selected population of CHB or CHC patients with high risk of developing HCC. Despite a young mean age - below 45 years - the cohort had an overall 8.3% incidence of HCC among non-aspirin users after a limited follow-up of 7.9 years[1]. Notably, HCC incidence was only 4% among aspirin users, corresponding to a hazard ratio (HR) of 0.69 (95% confidence interval, CI, 0.62 to 0.76) and an approximately 30% risk reduction of HCC onset[1]. There was also a clear duration-risk relationship, with HRs of 0.90 for 1 to less than 3 years of aspirin use, 0.66 for 3 to less than 5 years, and 0.57 for more than 5 years of use[1]. The 10-year liver related mortality decreased from 17.9% among non-aspirin users to 11.0% among aspirin users[1].

Altogether, these estimates are largely consistent with the results of a comprehensive meta-analysis in which 8 different studies on aspirin and liver cancer were evaluated for a total of 13,556 hepato-biliary cancers, mainly HCC[3]. There, the overall relative risk (RR) for all hepato-biliary cancers among aspirin users was 0.62 (95% CI, 0.44-0.86), and 0.71 (95% CI, 0.46-1.09) for HCC[3]. There was no significant evidence of a publication bias, and the estimates were consistent across different continents (e.g. Asia, Europe and North America)[3]. In addition, that meta-analysis showed a clear duration-risk relationship, with RRs around 0.5 for 6 years of use, and around 0.3 for 10 years, though the CI were very wide[3]. Like in the

case of the study by Simon *et al*[1], the observation that the risk of HCC in CHB or CHC patients is favorably affected by low-dose aspirin like strongly supports the existence of a real inverse association. These findings are also coherent with those of another record-linkage investigation from Taiwan, which included 204, 507 CHB patients of whom only 2,123 patients, i.e. about 1%, regularly used aspirin[5]. Indeed, the HR in that study was 0.71 (95% CI 0.58-0.86) among regular aspirin users and these results are also in agreement with yet another recent investigation from the same database that identified an HR of 0.56 (95% CI 0.43-0.72) among regular aspirin users chronically infected by HCV[4].

Of note, the notion that aspirin is a highly accessible OTC drug opens the possibility that its use may not register in record-linkage studies, which are based on prescriptions only. This would lead to an underestimate of the inverse association, and may at least in part explain the lower RR from case-control studies (which rely on directly collected data from all aspirin uses)[3]. It is also possible that - due to potential bleeding risks - aspirin is less frequently administered to patients with chronic hepatitis and cirrhosis, leading to reverse causation. The study by Simon *et al* considered this possible source of bias, and reported a non-significant difference in the 10-year frequency of gastrointestinal bleeding among patients receiving aspirin (7.8%) versus those not using it (6.9%)[1]. Based on the results of this study, there is now one more piece of relevant evidence justifying a thorough discussion among experts on the regular use of low-dose aspirin in CHB or CHC patients.

References

1. Simon TG, Duberg AS, Aleman S, et al. Association of Aspirin with Hepatocellular Carcinoma and Liver-Related Mortality. N Engl J Med 2020;382:1018-1028.

2. Lee TY, Hsu YC, Tseng HC, et al. Association of Daily Aspirin Therapy with Hepatocellular Carcinoma Risk in Patients with Chronic Hepatitis C Virus Infection. Clin Gastroenterol Hepatol 2020.

3. Bosetti C, Santucci C, Gallus S, et al. Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis through 2019. Ann Oncol 2020;31:558-568.

4. Liao YH, Hsu RJ, Wang TH, et al. Aspirin decreases hepatocellular carcinoma risk in hepatitis C virus carriers: a nationwide cohort study. BMC Gastroenterol 2020;20:6.

5. Lee TY, Hsu YC, Tseng HC, et al. Association of Daily Aspirin Therapy With Risk of Hepatocellular Carcinoma in Patients With Chronic Hepatitis B. JAMA Intern Med 2019;179:633-640.

6. Simon TG, Ma Y, Ludvigsson JF, et al. Association Between Aspirin Use and Risk of Hepatocellular Carcinoma. JAMA Oncol 2018;4:1683-1690.

7. Tao Y, Li Y, Liu X, et al. Nonsteroidal anti-inflammatory drugs, especially aspirin, are linked to lower risk and better survival of hepatocellular carcinoma: a meta-analysis. Cancer Manag Res 2018;10:2695-2709.

8. Hwang IC, Chang J, Kim K, et al. Aspirin Use and Risk of Hepatocellular Carcinoma in a National Cohort Study of Korean Adults. Sci Rep 2018;8:4968.

9. Pang Q, Jin H, Qu K, et al. The effects of nonsteroidal anti-inflammatory drugs in the incident and recurrent risk of hepatocellular carcinoma: a meta-analysis. Onco Targets Ther 2017;10:4645-4656.

10. Lee PC, Yeh CM, Hu YW, et al. Antiplatelet Therapy is Associated with a Better Prognosis for Patients with Hepatitis B Virus-Related Hepatocellular Carcinoma after Liver Resection. Ann Surg Oncol 2016;23:874-883.

11. Sahasrabuddhe VV, Gunja MZ, Graubard BI, et al. Nonsteroidal anti-inflammatory drug use, chronic liver disease, and hepatocellular carcinoma. J Natl Cancer Inst 2012;104:1808-14.

12. Gasic GJ, Gasic TB, Murphy S. Anti-metastatic effect of aspirin. Lancet 1972;2:932-3.

13. Langley RE. Clinical evidence for the use of aspirin in the treatment of cancer. Ecancermedicalscience 2013;7:297.

14. Chan AT, Cook NR. Are we ready to recommend aspirin for cancer prevention? Lancet 2012;379:1569-71.

15. Cattaneo M. Aspirin and clopidogrel: efficacy, safety, and the issue of drug resistance. Arterioscler Thromb Vasc Biol 2004;24:1980-7.

16. Ornelas A, Zacharias-Millward N, Menter DG, et al. Beyond COX-1: the effects of aspirin on platelet biology and potential mechanisms of chemoprevention. Cancer Metastasis Rev 2017;36:289-303.

17. Guidotti LG, Inverso D, Sironi L, et al. Immunosurveillance of the liver by intravascular effector CD8+ T cells. Cell 2015;161:486-500.

18. Iannacone M, Sitia G, Isogawa M, et al. Platelets mediate cytotoxic T lymphocyte-induced liver damage. Nature Medicine 2005;11:1167-1169.

19. Sitia G, Aiolfi R, Di Lucia P, et al. Antiplatelet therapy prevents hepatocellular carcinoma and improves survival in a mouse model of chronic hepatitis B. Proceedings of the National Academy of Sciences of the United States of America 2012;109.

20. Haemmerle M, Stone RL, Menter DG, et al. The Platelet Lifeline to Cancer: Challenges and Opportunities. Cancer Cell 2018;33:965-983.

21. Santos NP, Colaco AA, Oliveira PA. Animal models as a tool in hepatocellular carcinoma research: A Review. Tumour Biol 2017;39:1010428317695923.

22. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med 2011;365:147-56.