Editorial

Aspirin: a new old anticancer drug

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A positive effect of aspirin against colorectal cancer (CRC) was suggested for the first time by Kune *et al.* in 1988, who noticed a significant lower rate of aspirin users among new cases of colon and rectal cancer in Melbourne (Australia) metropolitan area [relative risk (RR), 0.49; 95% CI: 0.40–0.71] (1). Since then, the chemo-preventive potential of aspirin has been confirmed by different large cohort studies, in particular through analysis of data from large cardiovascular prevention trials (2).

After becoming the most used and useful drug in the prevention of cardiovascular events, despite its more than 100 years of history, aspirin still surprises. In their recent work, Bains *et al.* (3) point strongly to a role of this old and cheap drug as an efficient therapeutic agent for CRC. Among 23,162 Norwegian patients diagnosed with CRC between 2004 and 2011, 6,102 were defined as aspirin chronic users based on data from a national population-based prescription registry that list all prescriptions dispensed to individuals in ambulatory care by pharmacies. At cox regression survival analysis, patients under aspirin after CRC diagnosis experienced a significant improved specific (CSS) (HR, 0.85; 95% CI: 0.79–0.92) as well as overall survival (OS) (HR, 0.95; 95% CI: 0.90–1.01). This confirms observations by previously published studies. The first of these, by Chan *et al.* (4), found that in their entire cohort the overall 5-year survival was 88% for those participants who used aspirin compared with 83% for those who did not. In that study, the advantage was limited to those who started aspirin after CRC diagnosis. This is an important point, as the main question to be answered is whether the observed effects on survival is secondary to a better biologic behavior, given by long time aspirin use before diagnosis, rather than on a therapeutic effect on established cancer. The largest population data published until now on the argument, presented by Bains *et al.*, may give new insights on this, as well as other open questions. In this study, the survival advantage in aspirin user with CRC was present also in those patients already taking aspirin before diagnosis, where the effect seemed even enhanced in terms of CSS (HR, 0.77; 95% CI: 0.71–0.84) and OS (HR, 0.86; 95% CI: 0.81–0.92). Aspirin users before diagnosis were also more likely to have CRC in a less advanced stage (American Joint Committee on Cancer stage I to II) and to have a tumor with less aggressive properties (well to moderate tumor differentiation). This suggests that aspirin could actually work in different tumor development phases, by inhibiting progression on one side and interfere with distant relapse on the other. Although the molecular mechanism by which aspirin could act as an anticancer agent is still unclear, some authors enlighten a prominent role of COX-2 inhibition, following observations that survival was improved just in patients where COX-2 was overexpressed (4). However, aspirin could act also in different ways, with its known inhibitory effect on platelet activity playing probably an important role, especially in established cancers, by interfering with metastatic spread. Platelets could facilitate metastatic dissemination by sort of 'shield' mechanism, protecting circulating tumor cells from immune system attack (5).

The amazing survival advantage shown by these studies

is thrilling for different reasons. The most obvious is that we could have found an unexpected efficient therapeutic agent that could further improve OS in that subgroup of patients in which adjuvant therapies are already a mainstream, as with patients in stage III disease. Although very notable, however, this might not be the most important consequence. Aspirin is a relative safe drug and even considering the known augmented risk of bleedings, which represent the prominent adverse events during long term use, its toxicity profile is not comparable to that of other chemotherapeutics agents. This suggests a role of aspirin also as a single agent for those patients at lower risk of recurrence that nowadays have no indication to any adjuvant therapy, but still present a not negligible risk of distant relapse. Again, Bains *et al.* give important new elements on this argument, showing that patients in stage II disease were the ones having the largest benefit from aspirin use in terms of CSS (HR, 0.71; 95% CI: 0.60–0.83). Another particular subgroup of patients is that affected by rectal cancer. Locally advanced rectal cancer is usually treated with both neoadjuvant treatment plans, for local control, and adjuvant therapies after surgical resection with the idea of lowering metastatic spread chances. Unfortunately, the results of these strategies in terms of distant disease recurrence don't seem to match those of colon cancer. Data from different trials show, in fact, that DSF remain mostly unchanged whatever neoadjuvant and/or adjuvant therapy is implemented (6). Interesting, in this study, when the analysis was stratified according to tumor localization, patients with tumors located in the transverse and left colon experienced no significant effect of aspirin use on CSS, whereas tumors located in the rectum had the most improved CSS (HR, 0.79; 95% CI: 0.69–0.90). This important analysis, confirm our recent data on patients with rectal cancer undergoing neoadjuvant chemoradiotherapy, where chronic low dose aspirin was associated with a significantly higher rate of good pathological response (46% *vs.* 19%) and less chance of metastatic spread that reflected in a significant better prognosis (7). To ultimately test the use of aspirin in CRC adjuvant setting, different prospective randomized trials are already ongoing. The increasingly available evidences, however, arises more than one question on whether or not aspirin should be already given as an adjuvant agent in CRC. If on one side, in fact, evidences come from observational studies, it is also true that the magnitude of available data is impressive, and almost all point to just one, evident, direction.

The prospected benefits of this "old/innovative" anticancer drug in terms of morbidity and mortality seem already to outweigh concerns about GI bleeding, which is rarely life threatening, and cerebral bleeding, which is extremely rare.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Kune GA, Kune S, Watson LF. Colorectal cancer risk, chronic illnesses, operations, and medications: case control results from the Melbourne Colorectal Cancer Study. Cancer Res 1988;48:4399-404.
2. Flossmann E, Rothwell PM, British Doctors Aspirin Trial and the UK-TIA Aspirin Trial. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet 2007;369:1603-13.
3. Bains SJ, Mahic M, Myklebust TÅ, et al. Aspirin as secondary prevention in patients with colorectal cancer: an unselected Population-Based study. J Clin Oncol 2016;34:2501-8.
4. Chan AT, Meyerhardt JA, Giovannucci EL, et al. Aspirin use and survival after diagnosis of colorectal cancer. Gastroenterology 2006;130:A468.
5. Palumbo JS, Talmage KE, Massari JV, et al. Platelets and fibrin(ogen) increase metastatic potential by impeding natural killer cell-mediated elimination of tumor cells. Blood 2005;105:178-85.
6. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006;93:1215-23.
7. Restivo A, Cocco IM, Casula G, et al. Aspirin as a neoadjuvant agent during preoperative chemoradiation for rectal cancer. Br J Cancer 2015;113:1133-9.

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