Acetylsalicylic Acid is Unlikely to Beneficially Interfere with Radiation-induced Vasculopathy

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To the Editor:

In a recent letter (1) the author suggested that coronary artery disease associated with radiotherapy for Hodgkin's disease and breast cancer is preventable by salicylates. The risk of radiation-induced atherosclerosis after radiotherapy is well known (2, 3). Irradiation of vascular tissue results in a temporary increase of vascular prostaglandin I_2 (PGI_2)-production (4) apparently in order to restore disturbed haemostatic balancing. Exhaustion of this defense mechanism, an increased mitotic activity of endothelial and smooth muscle cells, monocyte entry into the arterial wall, smooth muscle cell proliferation and increased extracellular matrix production are additional events which may finally result in severe arterial damage. As the balance between thromboxane (TXA_2) and prostacyclin (PGI_2) is unfavorably affected (4, 5) persisting for a long period of time (6), the administration of acetylsalicylic acid (ASA)—not salicylate—on a preventive base has been discussed. In our opinion, this approach is unlikely to beneficially interfere. First, during in-vivo experimental perfusion it has been shown that the vessel wall and not the platelets are the key determinant for thrombogenicity (7) as has been found for other pathophysiological conditions as well.

The platelet-derived growth factor(PDGF)-liberation from the platelets is enhanced during their activation as occurs during irradiation. In turn, the temporarily increased PGI_2-formation by the vessel wall, especially in the early phase, is able to selectively counterbalance the PDGF-release from the platelets. Subsequently, as PGI_2-production is decreased, proliferative and mitotic stimuli become dominant. The capacity of the vessel wall to respond to certain stimuli with an enhanced PGI_2-synthesis seems to be one of the key mechanisms.

Second, ASA-therapy at doses above 50 mg/day may not only lower TXA_2 but even further impair the vascular defense mechanism of PGI_2-productions and synergism with other mediators (NO-EDRF, tPA). However, ASA at doses below 50 mg/day affecting platelet TXA_2 might be as helpful as other antiplatelet agents like prostaglandins (I_2, E_1, stable analogues) for example, but it is very unlikely to result in a significant benefit, as the key target, the vessel wall, is not affected. Third, intracellular cholesterol-accumulation and a decreased degradation is favoured by diminished local PGI_2-levels. Malondialdehyde derived from activated platelets together with LDL resulting in malonyl-LDL formation also increases the intracellular cholesterol accumulation. The fact that radiation is associated with an oxidative injury and induces also oxidation of LDL explains macrophage accumulation and (via the scavenger receptor) foam cell formation. An enhanced degradation of PGI_2 due to radiation has also been claimed to reduce the actual biologically active amount of this antiatherosclerotic mediator.

The future approach for effectively preventing radiation-induced vasculopathy should be directed to enhance vascular thromboresistance.

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