Extended Abstract
Volume 6:2, 2020

Journal of Oncology Translational Research

Open Access

Perioperative use of NSAID Might Prevent Early Relapses in Breast and Other Cancers: An Upstream Approach

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Keywords: Biomembrane, CC-pVTZ, Hartree-Fock Method, nano-molecule Kurumi, Raman Spectroscopy, 6-311G** (3df, 3pd)

Abstract

A bimodal pattern of hazard of relapse among early stage breast cancer patients has been identified in multiple databases from US, Europe and Asia. We are studying these data to determine if this can lead to new ideas on how to prevent relapse in breast cancer. Using computer simulation and access to a very high quality database from Milan for patients treated with mastectomy only, we proposed that relapses within 3 years of surgery are stimulated somehow by the surgical procedure. Most relapses in breast cancer are in this early category. Retrospective data from a Brussels anesthesiology group suggests a plausible mechanism. Use of ketorolac, a common NSAID analgesic used in surgery was associated with far superior disease-free survival in the first five years after surgery. The expected prominent early relapse events in months 9-18 are reduced 5-fold. Transient systemic inflammation accompanying surgery (identified by IL-6 in serum) could facilitate angiogenesis of dormant micro metastases, proliferation of dormant single cells, and seeding of circulating cancer stem cells (perhaps in part released from bone marrow) resulting in early relapse and could have been effectively blocked by the perioperative anti-inflammatory agent. If this observation holds up to further scrutiny, it could mean that the simple use of this safe, inexpensive and effective anti-inflammatory agent at surgery might eliminate early relapses. We suggest this would be most effective for triple negative breast cancer and be especially valuable in low and middle income countries. Similar bimodal patterns have been identified in other cancers suggesting a general effect.

Introduction: Cancer treatment is a double-edged sword, as surgery (including biopsy), chemotherapy, or radiation can induce tumor-dormancy escape and subsequent metastatic outgrowth by impairing tumor-specific immunity through inflammation-mediated growth signals and loss of resolution of inflammation. Even anesthetics can impair inflammation resolution. Recent results show that chemotherapy-generated cell death can paradoxically promote tumor growth via the release of proinflammatory and proangiogenic cytokines. Moreover, a preoperative cycle of chemotherapy can stimulate proinflammatory cytokines after cancer surgery, and surgical wounding may impair the efficacy of chemotherapy.

In the treatment of loco regional disease, the perioperative period offers a unique window for curbing the risk of metastatic growth and relapse. For instance, a bimodal pattern of recurrence for early stage breast and lung cancers suggests that surgery potentiates the metastatic process by inducing tumor-dormancy escape of micro metastatic lesions. Micro metastases present in cancer patients at the time of surgery are associated with reduced survival. Moreover, surgery can promote metastasis, not simply by mechanical dissemination of cancer cells, but also by stimulation of systemic inflammation and surgery-associated immunosuppression, resulting in outgrowth of dormant cancer cells at distant sites.

Over 30% of healthy individuals harbor microscopic dormant cancers, and non-cancer surgery and anesthesia may promote the growth of such occult micro tumors. Importantly, retrospective analyses of tumor recurrence in patients undergoing breast cancer surgery revealed that preoperative administration of ketorolac was associated with a marked reduction of recurrence and mortality after surgery. However, ketorolac did not exhibit cancer-preventive activity when administered postoperatively, which is when NSAIDs are routinely administered for pain management. Preoperative ketorolac increased blood CD4+ T cells in patients undergoing tumor resection, potentially reversing surgery-induced immunosuppression during the perioperative period.

Chronic inflammation has been associated with tumor-promoting activity, in part due to a deficit in the resolution of inflammation. Cancer therapies have focused on blocking the production of COX-2–derived eicosanoids to suppress tumor-promoting inflammation. However, COX-2 is also host protective, as its metabolite, prostaglandin E2 (PGE2), plays a role in the resolution of inflammation in the chronic phase. Specifically, tight regulation of the temporal pattern of PGE2 release is critical for activating the class switching of lipid mediators from production of inflammatory mediators to that

of irresolution signals through specialized proresolving mediators (SPMs). PGE2 released by dead cells negatively regulates an inflammatory response activated by damage-associated molecular patterns, which may also contribute to the irresolution activity of PGE2. Other COX-2–derived prostaglandins of the D2 and J2 series generate lipid mediators that accelerate resolution of inflammation and control endogenous inflammation. Thus, COX-2 inhibitors may be “resolution toxic,” as they suppress the production of these prostaglandins and may worsen therapy-induced cancer progression.

Here, we utilize a well-established animal model in which dormancy escape and outgrowth of lung metastases are triggered by primary tumor resection to study therapeutic approaches to overcoming the tumor-promoting capability of surgery. We show that a single preoperative, but not postoperative, dose of ketorolac suppresses lung micro metastases present at the time of primary tumor resection, an outcome dependent on COX-2 activity and host antitumor immunity as well as inhibition of COX-1–derived thromboxane A2 (TXA2). Moreover, preoperative acceleration of inflammation resolution with resolvins inhibited micro metastases and prevented tumor-dormancy escape. Our results indicate that preoperative and peri chemo therapeutic interventions can control tumor recurrence via inflammation resolution and promotion of host antitumor immunity.

Biography: Michael Retsky (PhD in Physics from University of Chicago) made a career change to cancer research 30 years ago. He is on Staff Member at Harvard TH Chan School of Public Health and Faculty at University College London. He was on Judah Folkman’s Staff at Harvard Medical School for 12 years. He is Editor of a Nature/Springer book on the breast cancer project published July 2017. He was the first person to use what is now called metronomic adjuvant chemotherapy and is a founder and for 10 years was on the Board of Directors of the Colon Cancer Alliance. He has published more than 60 papers in physics and cancer.