OMICS International
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J Cancer Sci Ther 2014, 7:10
http://dx.doi.org/10.4172/1948-5956.C1.061

8th Euro Global Summit on Cancer Therapy

November 03-05, 2015 Valencia, Spain

Can peri-operative NSAID reduce early relapses in breast cancer?

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In 1997, our group was examining a breast cancer database from Milan using computer simulation and came to the conclusion that most relapses in breast cancer were in the initial 1-3 years post surgery and were triggered somehow or other by something that happened at or about the time of surgery. We were unsure of what the mechanism was that caused sudden tumor growth just post surgery but this was apparently the dominant effect resulting in mortality from breast cancer. We suggested some possible mechanisms and some therapies that might prevent or disrupt this process but nothing was convincing enough to result in clinical or experimental investigations. However in 2010 a report was published by a Brussels anesthesiology group that an NSAID given peri-operatively resulted in 5-fold reduction in early relapses. The NSAID cost $2 and has been one of several analgesics used for decades. This was a retrospective analysis but it was remarkable and caused us to propose a dramatic process and also a dramatic non-toxic and inexpensive intervention that could prevent the induced relapses. With the Brussels group, we suggested that surgery to remove the primary tumor caused transient systemic inflammation which could by a number of mechanisms induce angiogenesis of dormant avascular micro metastases and also induce division of dormant single cells. This fit both Brussels and Milan data as well as our theoretical model of tumor growth. The dramatic conclusion is that by just using the right analgesic drug, it may be possible to prevent most relapses in breast cancer. This could cut the breast cancer problem by perhaps half at no cost or toxicity. We are suggesting that in breast cancer, a disease that runs its course in over a decade, most of the biological events that lead to relapse occur in the few days after primary surgery. Also these events can be prevented by the proper choice of analgesic interventions and thus the anesthesiologist without knowing it may be among the most important persons in the efforts to prevent relapse and mortality from breast cancer.

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Harnessing the immune microenvironment of gastrointestinal cancers using combined modalities

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Immunotherapy has recently emerged as a promising modality in cancer treatment leading to the approval of immune checkpoint inhibitors in few malignancies including melanoma and lung cancer. Tumor-infiltrating lymphocytes (TILs) play a major role in anti-tumor immune responses and their presence is correlated with survival in a variety of tumors. However, these TILs do not reach the pancreatic cancer (PC) cells in significant numbers due to the presence of stroma and suppressive microenvironment. In addition, some colorectal cancers (CRC) have low immune score, a score that was recently described by Galon et al to assess the presence of TILs in CRC. Furthermore, one of the leading causes for immune suppression is elevated expression of PD-L1 either by the tumor cells or the surrounding regulatory cells, resulting in dysfunction of TILs. There is recent evidence to suggest that chemo-radiation therapy (CRT) can increase the presence of TILs in the PC and CRC microenvironment, leading to production of interferon-γ (IFN-γ), which could increase the expression of PD-L1 through a negative feedback loop. We are currently investigating the combination of anti-PD-1 inhibitor and CRT in patients with pancreatic cancer and rectal cancer. Testing this combined modality in the neo-adjuvant setting will allow us to study the safety of this approach and its effect on the tumor microenvironment by comparing TILs and other effector (NK, macrophages) and suppressor immune cells (T-regs, MDSCs) and receptors (PD-L1, CTLA-4) pre- and post- treatment. Finally, we will study the correlation between these immune biomarkers and clinical outcomes.

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