



Metronomic Nab-Paclitaxel and Topotecan Inhibit Angiogenesis

Previs, Armaiz-Pena, and Lin *et al.* _____ Page 2677

Metronomic chemotherapy, or the frequent administration of low, minimally toxic doses, inhibits the proliferation of endothelial cells. Previs, Armaiz-Pena, Lin, and colleagues tested the efficacy of nab-paclitaxel and topotecan (increases TSP-1 and suppresses carbonic anhydrase IX) at metronomic doses on multiple orthotopic ovarian cancer models and demonstrated decreased angiogenesis and increased apoptosis. Additionally, metronomic treatment suppresses hypoxia in the tumor microenvironment. Treatment with both agents led to a significantly prolonged overall survival compared to vehicle and other monotherapy groups ($P < 0.001$). These findings support further clinical development of this combination, which has potent antiangiogenic effects.

Recombinant Immunotoxin with Low Immunogenicity

Mazor *et al.* _____ Page 2789

SS1P is a recombinant immunotoxin (RIT) that targets mesothelin. In clinical studies, it has produced dramatic responses in patients with advanced mesothelioma when combined with immunosuppressive therapy so that several treatment cycles could be given. Otherwise its activity is limited by its immunogenicity. To overcome this impediment, a RIT with low immunogenicity was developed by removal of eight T-cell epitopes. LMB-T20 is more active than SS1P *in vitro*. It also has potent antitumor activity in mice, and has reduced immunogenicity as measured by cytokine secretion assays. LMB-T20 is a favorable candidate for evaluation in clinical trials.

Mdm2 Modulation Potentiates Carboplatin-Mediated DNA Damage in TNBC

Tonsing-Carter *et al.* _____ Page 2850

The murine double minute 2 (Mdm2) protein is elevated in many therapy-refractive breast cancers, making it an attractive therapeutic target. In triple-negative breast cancer (TNBC) cells, Nutlin-3a modulation of Mdm2 protein-protein interactions sensitized mutant p53 TNBC cells to carboplatin. Combination Nutlin-3a/carboplatin was synergistic in promoting p73a-dependent cell death. This correlated with persistence of DNA damage as assessed by increased γ H2AX and association of Mdm2 with chromatin. Moreover, in a human breast-to-lung metastatic TNBC model, combination Nutlin-3a/carboplatin resulted in decreased tumor growth at primary and metastatic sites. This investigation provides rationale for developing novel combination therapies that target Mdm2 in TNBC.

Acute Tumor Lactate Changes Reflect Tumor Genotoxic Stress

Sandulache and Chen *et al.* _____ Page 2901

Continued refinements in the delivery of ionizing radiation to solid tumors and development of novel radiosensitizing agents have great potential to improve patient treatment. However, identifying reliable, predictive markers of genotoxic stress and radiation response remains elusive. Sandulache, Chen, and colleagues demonstrate that irradiation triggers quantifiable, transient, and reversible perturbations in tumor lactate levels, which correlate with intrinsic and acquired radioresistance. These findings provide a critical biochemical foundation for using noninvasive imaging techniques to assess tumor lactate levels. Incorporation of lactate as a real-time biomarker of radiation effectiveness in the treatment of solid tumors could revolutionize current clinical paradigms.

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