Reducing Injury Response to Surgery With Repurposed Drugs: An Evolving Approach to Prevention of Cancer Metastases

Michael Lowe, MD [1]; Vidula V. Sukhatme, MS[1,2]; and Vikas P. Sukhatme, MD, ScD[1]

Despite dramatic improvements in survival for most cancers over the past decade, outcomes for cancer patients with metastatic disease continue to be dismal; for instance, 5-year survival for patients with stage IV colorectal cancer (CRC) is only 14%.[1] Considerable research and development efforts have expanded the number of available therapeutic options, but these efforts have resulted in marginal improvements in survival and are associated with exorbitant costs to the health care system. In addition, although inexpensive, US Food and Drug Administration (FDA)-approved medications for noncancer indications that may augment current cancer therapies are readily available, they have lain fallow, largely because of a lack of economic incentive. Momentum is building nationally—with both philanthropic and federal support—to introduce some of these drugs (which we have referred to as "financial orphans"[2]) into human clinical trials when sufficient preclinical data exist. Ben-Eliyahu and colleagues have made significant contributions to drug repurposing[3]; in this issue of *Cancer*, they follow their preclinical observations with a randomized trial of the perioperative combination of COX2 and β-adrenergic blockade in patients with resectable CRC.[4]

The concept of perioperative interventions to alter the deleterious effects of surgery is not a new one, and the evidence to support the use of medications in the perioperative setting is abundant.[3,5-7] Cancer surgery and events surrounding the surgery result in a cascade of events that may enhance the metastatic potential of the tumors being resected. These events include removal of the tumor, which may also remove anti-angiogenic factors made by the tumor; creation of the wound required to remove the tumor, which leads to a fairly stereotyped wound-healing/injury response; anesthetic techniques and agents utilized; blood transfusions required during or after the operation; and variations in temperature throughout the perioperative period. In particular, the injury response events—characterized by hemostasis, tissue repair through inflammatory and immune mechanisms, and tissue remodeling through angiogenesis and epithelial/stromal cell proliferation—is an inevitable consequence of surgery and may exert detrimental effects on micrometastatic deposits existing at the time of surgery or on potentiating spread during surgery. Specifically, the influx of neutrophils, macrophages, mast cells, and platelets leads to local and systemic increase in cytokines skewing the immune response toward a repair-oriented/immunosuppressive environment through expansion of regulatory T cells, myeloid-derived suppressor cells, and M2 macrophages. The resultant promotion of stem cell proliferation and epithelial-to-mesenchymal transition (EMT) may awake dormant micrometastases and/or increase the likelihood of residual disease to become aggressive recurrences. In summary, the injury response leads to the development of a tumor microenvironment conducive to proliferation and spread. It follows that medications that inhibit or at least minimize the injury response may prevent tumor progression locoregionally and/or distantly. The goal of these perioperative interventions is to reduce chemokines and growth factors, mitigate immune suppression, inhibit EMT, and reduce stem cell populations.

Beta-blockers and COX2 inhibitors are 2 classes of drugs known to suppress these pathways; in preclinical models, blockade with propranolol and etodolac reduced postoperative metastases and/or mortality rates in animal models, including CRC. However, retrospective data have produced conflicting results.[8,9] Thus, there is a need to conduct prospective studies. In the accompanying study, Haldar et al[4] performed a double-blind randomized placebo-controlled trial of propranolol and etodolac in patients undergoing resection for CRC to test the hypothesis that this drug combination would alter the transcription profile away from prometastatic factors. Patients were given drug or placebo for a total of 20 days: 5 days before surgery, and 15 days after surgery. Compliance was measured but was dependent on patient reporting. The primary endpoint was the change in progression-related transcriptome profiles in the tumors measured using genome-wide transcriptional profiling and based on a priori hypotheses about CRC-related pathways thought to be affected by β-adrenergic or COX2 inhibition. Secondary endpoints included compliance, disease-free survival, and safety.

Corresponding Author: Vikas P. Sukhatme, James B. Williams Medical Education Building, 100 Woodruff Circle, Suite 423, Atlanta, GA 30322 (vsukhatme@emory.edu).

[1]Morningside Center for Innovative and Affordable Medicine, Emory University, Atlanta, Georgia; [2]GlobalCures, Newton, Massachusetts

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Of the 34 patients who were randomly assigned, tumors from only 20 patients (9 who received drug treatment and 11 who received placebo) were available for assessment of the primary endpoint. Six patients were not compliant with the protocol and were therefore excluded from analysis, and the remaining 8 patients had no tumor available. Using preselected gene sets, the authors found that treatment with propranolol and etodolac resulted in downregulation of genes characteristic of mesenchymal polarization, monocytes, and B cells, and upregulation of genes associated with NK cells. Of 19 transcription factors known to be associated with prometastatic factors, treatment with propranolol and etodolac had a positive impact on 12. Compliance was higher in the placebo group, and there was no difference in adverse events or surgical complications. Although not powered to detect a difference, there was a trend toward higher 3-year disease-free survival in the treatment group when including only the protocol-compliant patients ($P = .054$).

In general, these data add to the growing body of literature supporting the use of β-blockers and anti-inflammatory drugs in the treatment of cancer. More specifically, this study demonstrates a legitimate signal that justifies a larger trial evaluating the efficacy of the combination of propranolol and etodolac. This is based mainly on the apparent safety of the combination and the extensive amount of supporting preclinical data in addition to the pilot biomarker data presented here. However, demonstration of significant changes in the transcription profiles of treated tumors compared with untreated ones does not necessarily prove a change in the actual immune profile in the tumor or the blood. Analyses such as immunohistochemistry could prove that the alteration of the prometastatic genetic profile in treated tumors actually results in a decrease in regulatory T cells and/or myeloid-derived suppressor cells or a change in macrophage phenotype and an increase in CD8+ cytotoxic T cells in the tumor microenvironment. More sophisticated analyses such as single-cell sequencing would provide an even greater wealth of data that are not dependent on a priori assumptions of transcription profiles. Given recent advancements in bioinformatics, the ability to collate data into meaningful conclusions without predetermined biases may uncover associations or even causations that have yet to be discovered. This is particularly important when multiple mechanisms could explain outcomes. Propranolol and etodolac both have numerous mechanisms of action, and the combination likely increases the potential interactions. The use of drugs with multiple mechanisms of action that affect complicated inflammatory and immunologic pathways requires the use of as many sophisticated analyses as possible to provide a mechanistic understanding of the drugs' impact.

Several other factors need to be considered when weighing the evidence presented by Haldar et al. First, this study is essentially an analysis of 20 patient samples. The authors highlight this limitation and appropriately make no assumptions about efficacy because of it. However, a more robust, biomarker-driven analysis of these 20 tumors may provide even greater evidence to use this combination in a larger study. Second, compliance was assessed by patient reporting, although the requirement to return pill packs augments this reporting. Compliance is and will continue to be a criticism of trials using repurposed drugs, particularly ones that are readily available over the counter or are already in patients' possession (eg, metformin). Investigators are obligated to strictly document compliance to ensure that outcomes are related to the drug and not to chance. In addition, a compliance rate of 60% likely underestimates the impact of this combination. Making the compliance rate too high understandably undermines the ability to perform analyses on protocol-compliant patients and their samples, but trials investigating repurposed drugs must demand protocol adherence to minimize the number of patients enrolled and increase time to protocol completion. Legitimate patient motivation to participate should be an unwritten inclusion criterion to maximize resource utilization and minimize trial cost, given that most of these trials are being funded by sources with far fewer resources than the pharmaceutical industry has at its disposal. Finally, the authors fail to account for the use of chemotherapy in their study. It appears that the majority of patients received chemoradiation before or after surgery, but there is no mention of timing or treatment doses in relation to surgery. There are accumulating data to support the notion that chemotherapy may impact the effects of perioperative inflammatory/immune blockade both positively and negatively.[10,11] Thus, the timing of perioperative chemotherapy should be considered when designing larger randomized clinical trials evaluating these and other repurposed drugs in the perioperative period.

Where do we go from here? A unifying hypothesis to pursue is a focus on the full-fledged injury response by countering the effects of each of the major events involved[3,5-7] as follows: blockade of the adenosine A2A receptor; inhibition of mast cell release of histamine or its downstream effects especially on the H2 receptor;

antiplatelet agent use; catecholamine release or action; and the administration of a pathogen-associated molecular pattern to skew the immune system into attack mode rather than repair mode. Drugs exist to accomplish each of these, including etodolac and propranolol; istradefylline (an A2A receptor blocker approved in Japan), H2 blockers such as cimetidine or famotidine, and nonselective COX inhibitors that would inhibit both COX1 and COX2, since there may be distinct advantages of COX1 blockade.[11] The main disadvantage of the latter is that nonsteroidal anti-inflammatory drugs with COX-1 activity could result in bleeding complications in the postoperative period. There is evidence that these interventions can enhance T cell antitumor immunity. These drug combinations might have multiple antitumor effects, but we expect that the unleashing of an adaptive antitumor response would be a key mechanism. There is also likely to be an impact on the innate response that is often depressed postoperatively.[12] Thus, we would posit that surgery (by virtue of debulking) relieves tumor-induced immunosuppression, but that the subsequent injury response is immunosuppressive. A combination of drugs that tempers or counters the injury response can be expected to unleash antitumor immunity to eliminate micrometastatic disease that exists at the time of surgery or decrease tumor spread at the time of surgery.

Haldar et al should be applauded for their steadfast pursuit of repurposed drugs for the treatment of cancer. This study is another example of how preclinical data can be used to rationally bring a combination of safe, readily available, inexpensive, FDA-approved medications to patients with cancer. The application of these drugs in the perioperative period is of paramount importance and may have long-lasting antitumoral effects. It is our hope that larger trials focusing on these and other agents will soon prove that to be true.

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