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Editorial

EDITORIAL

Harnessing the Perioperative Period to Improve Long-term Cancer Outcomes

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The short perioperative period, spanning several days pre- and postsurgery, is now believed to have a nonproportionally large impact on long-term cancer outcomes (1,2). Numerous physiological responses to the newly discovered cancer and to surgical resection trigger pro-metastatic processes that can affect minimal residual disease (MRD; single tumor cells/micrometastases). MRD can potentially seed into new organs, escape from dormancy, and/or accelerate its growth, eventually becoming life threatening. Underlying processes for such surgery-induced deleterious effects include 1) immune suppression, 2) excessive shedding/spreading of tumor cells, 3) systemic release of growth factors (3), and 4) numerous direct pro-metastatic effects of stress and inflammatory mediators on MRD, increasing its proliferation, migration, and invasion capacity, as well as MRD release of pro-angiogenic and pro-growth factors (4,5). These multiple processes occur simultaneously during the perioperative period and act synergistically to facilitate metastatic progression. On the other hand, the removal of the primary tumor diminishes several ongoing metastasis-driving processes (5). Thus, a new and delicate balance between pro- and antimetastatic processes is created perioperatively, which may determine whether MRD will erupt postoperatively or will regress to dormancy—two opposing processes that are each self-perpetuating and bear long-term critical ramifications (5). Therefore, the perioperative period should be exploited therapeutically to achieve an antimetastatic balance, before pro-metastatic processes prevail irreversibly (1).

Nevertheless, there are obstacles to employing common antimetastatic interventions during the perioperative period. Chemo- and radiotherapies prevent tissue healing and cause immune suppression, and immunotherapies often cause adverse and/or pyrogenic effects that are indistinguishable from signs of infection. Thus, these treatments are not given close to surgery. However, in past years, our group and others have found that prominent mediators of the pro-metastatic effects of stress and surgery are catecholamines (epinephrine and norepinephrine) and prostaglandins, secreted perioperatively in response to stress and tissue damage (1,4,6). These responses can be safely and effectively mitigated through simple pharmacological interventions. Indeed, in translational studies, using six tumor models of metastatic progression, we showed that β-adrenergic blockade (using propranolol/nadolol) and/or COX2 inhibition (using nonsteroidal anti-inflammatory drugs [NSAIDs], including etodolac), reduced the metastasis-promoting effects of surgical stress (1,7–10). In studies that involved major surgeries and/or excision of a spontaneously metastasizing primary tumor, only the combined blockade, employing propranolol and etodolac, was robustly effective in reducing metastasis and improving survival rates (7,8).

Recently we concluded two small prospective phase II biomarker clinical trials, treating breast and colorectal cancer patients with propranolol and etodolac for a few weeks, initiating treatment five days before surgery. This therapeutic intervention was proven safe in both studies (11,12). By analyzing biomarkers in the excised primary tumors and in repeated blood samples, we found that the treatment positively affected tumor epithelial-to-mesenchymal transition (EMT) and the composition of tumor-associated leukocytes. In breast cancer, treated patients also demonstrated reduced tumor Ki67 expression, reduced tumor GATA-1, NFkB, and STAT-3 transcriptional activity, and reduced serum levels of IL-6 and CRP and their up- and downstream transcriptional pathways. These are promising multiple indications of the antimetastatic effects of this perioperative drug intervention (11,12). Missing, however, are long-term cancer outcomes, which necessitate larger clinical trials with long-term follow-up.

In this issue of the Journal, Desmedt et al. report an association between intraoperative use of the COX inhibitor ketorolac in breast cancer patients and reduced rates of early metastases (13). This observation corresponds well with animal studies employing various NSAIDs perioperatively (14–16), and with our abovementioned clinical trial in breast cancer patients (12).

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Although only associative, the findings of Desmedt et al. support the clinical benefits demonstrated in the above prospective clinical trials and contribute to the expanding oncologic literature of perioperative NSAID use (17). Intriguing is the equivalence in overall recurrence incidence reached at 96 months postoperatively, which suggests that intra-operative ketorolac induced (or maintained) a state of dormancy in preexisting micrometastases; however, after several years, these foci may escape dormancy. The findings also indicate that although a statistically significant effect of ketorolac was evident in the entire cohort studied (n = 827), it seems that patients with a body mass index (BMI) greater than 25 kg/m^2 (n = 381) are most likely to benefit from this intervention, as it remained statistically significant in these patients alone, but not in those with a BMI lower than 25 kg/m^2 (n = 446). Breast cancer patients with a BMI greater than 25 kg/m^2 were reported to exhibit inflammation of mammary adipose tissue and higher systemic inflammatory status (18), and inflammation is a hallmark of cancer progression (19). Obese women were also found to have more profound stress and inflammatory responses to experimentally induced psychological stress (20). Thus, ketorolac can be expected to have greater efficacy in this susceptible subpopulation. Importantly, prostaglandins have been shown to suppress NK activity in vivo (14) and to modulate the activation of NFkB, STAT3, and CREB, increasing expression of IL6, VEGF, IL8, and MMPs, all known to promote cancer progression (15). Thus, several mechanisms can mediate the beneficial effects of intra-operative use of ketorolac.

The study by Desmedt et al. also reports that intra-operative use of diclofenac, a semiselective COX2 inhibitor, was not associated with reduced recurrence rates (n = 1007) (13). Important to note is that diclofenac and ketorolac were studied in non-comparable settings, including different institutions, patient cohorts, year periods, follow-up modalities, and doses. Additionally, each drug was uniquely associated with the specific characteristics of the patients who consumed it (eg, ketorolac with younger, lower BMI, smaller tumor size). Thus, while it is valid to suggest benefits for ketorolac based on statistical corrections for such known modulating factors, one should be cautious to suggest no effects for diclofenac under noncomparable conditions. Interestingly, the ongoing "Randomized European Celecoxib Trial" (REACT) reported no overall benefits for celecoxib (a selective COX2 inhibitor) at an average 60 months of follow-up, but potential benefits in subpopulations (21). Unfortunately, celecoxib treatment was initiated several weeks after surgery, thus not covering the critical perioperative period.

Overall, perioperative interventions should be prospectively tested in cancer patients (ie, through randomized controlled trials), given that this period has a high impact on long-term cancer outcomes. Future interventions may include some forms of immunotherapies that have minimal adverse effects, systemic pharmacological or dietary anti-inflammatory and/or β-adrenergic inhibiting interventions, stress-reducing behavioral/psychological interventions, or combinations of such interventions, which may be most effective (1). Such approaches may transform the critical perioperative period from a high-risk time frame to an opportunity to arrest cancer progression or to eliminate MRD (1).

Notes

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