Abstract: Growth of tumors can accelerate during the peri-operative period. Accordingly, early relapse of cancer occurs in some patients during the first two postoperative years. Temporal and biologic analyses of cancer pathophysiology suggest a link between peri-operative pathophysiological changes and acceleration of tumor growth. Understanding the role of inflammation and its consequences (i.e., immune response, growth factors, dissemination of tumor cells) could lead to define a role of anesthesiologists in reducing cancer recurrence following surgery. We argue for peri-operative pharmacological interventions to reduce cancer relapse, with a focus on non-steroidal anti-inflammatory drugs.

Key words: inflammation, non-steroidal anti-inflammatory drugs, postoperative cancer recurrence.

1. Introduction

Tumor growth is non-linear, exhibiting alternating periods of dormancy and accelerated growth (1). This growth pattern is changed by surgery. Indeed, analysis of hazard rate of recurrence following resection of a primary tumor has shown an early peak during the first two postoperative years followed by a later peak. The latter represents the progression of initially dormant micro-metastases and does not seem to be due to a direct induction by primary surgery (2-5). Among possible mechanisms of this early peak, the inflammatory reaction triggered by surgery is thought to play a major role. Inflammation accelerates the growth rate of tumor cells and modifies the equilibrium between proliferation and elimination. Inflammation influences cancer cell dedifferentiation and dissemination, and could also inhibit anticancer immunity (6, 7, 8).

Anesthetic techniques and peri-operatively administered drugs can affect postoperative inflammation and, consequently, the associated immune dysfunction. This provides a rationale for supporting a role of the anesthesiologist to fight against postoperative cancer recurrence, as suggested in several retrospective studies (3, -16). Among these interventions, non-steroidal anti-inflammatory drugs may be of particular interest, and need to be investigated in that respect.

2. Increased relapse rate for breast cancer early after primary tumor surgery

2.1. Clinical observation

Over a decade ago, data from the Milan National Cancer Institute suggested that the relapse frequency over time in early stage breast cancer patients treated only by mastectomy could be bimodal (17). Analysis of these data showed an early peak of relapses at 18 months, a nadir at 50 months,
and a broader second peak at 60 months, followed by a plateau lasting for more than 15 years (Fig. 1). Most of relapses (50-80%) occurred during the first peak. This early postoperative peak was also observed by other investigators in large series of patients, regardless of the administration of any adjuvant therapy (18, 19, 20). In some cases, detection of this early peak requires the use of smoothed hazard plots (20). The hazard rate of early recurrence is greater in high risk patients. Risk depends on primary tumor size, grade, lymph node involvement, and estrogen receptor status (20, 21). Demicheli et al. also reported a double peak of recurrence in operated lung cancer patients (22). For other cancers, data of sufficient quality are lacking. As a consequence, this pattern of recurrence may be delayed, modified or even absent in some cancers. For example, it seems to be completely different in prostate cancer patients (5). Regarding breast cancer, for which this pattern was confirmed, two possible mechanisms can explain the high incidence of early relapse after surgery: surgery-induced escape from dormancy and surgery-induced dissemination of tumor cells. Both might be affected by anesthesia and analgesia.

2.2. Surgery and escape from dormancy

The concept of dormancy of tumor cells is not new. It corresponds to a growth arrest and prolonged survival of disseminated single or small groups of tumor cells, and/or to a constant balance between apoptosis and proliferation, keeping the lesion small and undiagnosed (23).

There is a consensus on the existence, in several cancers, of this dormant state of tumors before initiation of overt metastases (24). The escape from dormancy probably involves cell genotype (type of DNA mutation) (1), tumor phenotype (down-regulation of angiogenesis inhibitors and up-regulation of angiogenesis promoters) and tumor environment (including growth factors, inflammatory mediators, and immune cells) (8).

Nonlinear tumor growth has been confirmed clinically in breast cancer. On a series of local recurrences following mastectomy, Demicheli et al. compared the measured diameters of local recurring tumors after mastectomy for breast cancer, with the calculated diameters under the assumption of continuous growth. They noted that their clinical data were violating this assumption, and this confirmed that growth was non-linear (25).

Escape from dormancy explains other observations in breast cancer patients. These include a greater clinical efficacy of adjuvant chemotherapy in premenopausal node positive women (at higher risk of accelerated growth and early relapses), and the greater efficacy of mammographic screening (to diagnose cancer) for women aged between 50 and 59 years than for those aged between 40 and 49 (3). Indeed, these data show that pathophysiology could depend on age, and suggest that surgery may destabilize an equilibrium existing between tumor growth and host defenses, particularly in younger women.

Fig. 1. — Data from Milan are shown in raw form as number of relapse events in 10-month wide bins. Also indicated are the various modes of relapse that are predicted by the computer simulation. From (13), with permission.
The question then arise to know whether surgery is able to induce an escape from dormancy. Epidemiological arguments suggest such an effect in humans, supported by observations in animal models. In humans, the analysis of the efficacy of mammographic screening allowed determining the influence of surgery on the tumor growth rate. Indeed, the timing of the early peak of postoperative recurrences appears to be more influenced by the time of surgery than by the stage of the disease (12, 20). The timings of recurrences are super-imposable, whatever the metastatic sites (viscera, bones, or soft tissues) (4, 16, 26). The time to recurrence and the time to death may be influenced by the time of surgery. An initial excessive mortality has been suspected in women aged between 40 and 49 years, when surgery was proposed earlier and following mammographic screening (3, 27). Taken together, these data suggest that surgery can promote growth of metastases. However, it might be possible to interfere with this postoperative accelerated growth of residual tumor. In the randomized clinical trial ATAC, the aromatase inhibitor anastrozole reduced early relapses in postmenopausal patients with hormone receptor positive breast cancer, as compared to tamoxifen (5). The peaks of recurrences were still present, but delayed.

In animal models, several results support an impact of surgery on the biology of tumor cells. In rats, we and others have observed surgery-induced tumor progression of metastases of a syngeneic mammary adenocarcinoma (28, 29, 30). A similar influence of surgery has been observed in other cancers. Through an analysis of growth rate of liver metastases in patients with colorectal carcinomas, Pieters et al. have reported a similar observation, showing that tumor growth rate is significantly higher after resection of the primary tumor (31). This suggests that surgery can modulate tumor growth by decreasing the levels of soluble inhibitory factors and/or increase those of growth factors, with a greatest impact during the immediate postoperative period (32). Growth factors such as VEGF, as well as inflammatory mediators such as PGE2, have been proposed as tumor growth promoting factors after tissue injury and during postoperative wound healing (33, 34). These mediators could influence postoperative disease progression, depending on cancer type.

2.3. Surgery and dissemination of tumor cells

If surgery induces an accelerated growth of residual tumor cells, it may concern intra-operatively disseminated tumor cells in addition to previously dormant micro-metastases. Despite surgeons’ efforts to anatomically isolate the primary tumor during resection, it has been shown that many patients present tumorous markers in the systemic circulation during and following surgery. As an example, data from Pachmann show a surge in circulating epithelial cells after primary breast cancer surgery. Intriguingly, this surge occurs 3 to 7 days after surgery (35). A delayed increase of circulating like tumor cells (CTCs) after breast cancer surgery has also been reported by Daskalakis et al. Nevertheless, the origin of CTCs is not yet clarified, and even their surgery-induced increase in incidence is debated (36, 37). CTCs have been shown to be present in many cancer patients with apparent non-disseminated tumors (33). It implies that CTCs circulate in many cases, but with a low probability of finding a niche to survive, transmigrate out of the vessels, and grow as metastases (24). Moreover, CTCs may originate from the primary tumor, or from already disseminated cancer cells (in bone marrow or other tissues) (39). Surgery could promote recurrence either through an intra-operative dissemination or through the release of systemic factors that would influence previously disseminated tumor cells (8). Whatever their origin, CTCs have a prognostic value. Breast cancer patients with CTCs were shown to have earlier recurrences (40). In metastatic breast cancer, CTCs have been correlated with disease progression and mortality (41). Similar observations have been made in other cancers, such as colorectal carcinomas (34).

3. The central role of inflammation

Whatever the moment of tumor cell dissemination, before, during, or after surgery, the mechanisms are similar. Before dissemination, cytokines, particularly pro-inflammatory ones, play a central role in carcinogenesis, dedifferentiation and tumor growth (8, 43). After the dissemination step, inflammation promotes proliferation of tumor cells by inhibiting apoptosis and increasing mitosis rate (8). However, inflammation also contributes to the initiation of antitumor immune responses, mainly through a cell-mediated immunity (CMI). Sensors of the innate immune system appear capable of detecting tumors at an early stage, for example through the recognition of soluble nucleic acids released from tumor cells. They trigger the local production of inflammatory cytokines that recruit immune cells such as lymphocytes, macrophages and dendritic...
3.1. Inflammation promotes tumor cell dissemination and proliferation

To disseminate and grow, tumor cells have to survive, proliferate and be fed by a blood supply.
after migration to peripheral tissues. Inflammatory pathways promote all these mechanisms in both established tumors and disseminating CTCs. First, survival is facilitated by PGE2 secretion, inducing Bel-2/nuclear factor-kappa (NFκB) via Toll-like Receptors (TLR) and peroxisome proliferator activated receptor-delta (PPARδ) activation. NFκB and TLR increase cell motility and migration by the induction of cytokines such as high mitotity group B1 molecules (HMGB1). Second, a modified extracellular environment (reflected by the level of matrix metalloproteinase type 2 - MMP2), in the periphery and at a systemic level, is linked to facilitated migration of tumor cells. Finally, inflammation promotes proliferation through the induction of phosphorylation of ERK and activity of the aromatase enzyme, and it promotes angiogenesis through VEGF and bFGF secretion and an IL-1beta-mediated NFκB-dependent expression of COX-2 (8, 43, 44).

There is a possible role for platelets, as well. Initially, platelets could promote the survival of CTCs, possibly through a protection from NK cells and resistance to shear stress. After adhesion to endothelial cells and extravasation, platelet-derived factors such as platelet-derived lysosphatidic acid (LPA) enhance metastasis, angiogenesis and tumor growth in an animal model of bone metastasis (45).

Tumors produce a multitude of growth factors. For example, over-expression of COX-2 by colon or breast adenocarcinomas leads to PGE2 secretion and stimulation of epithelial cell proliferation, inhibition of apoptosis, stimulation of angiogenesis and production of mutagens (46).

3.2. Inflammation suppresses immune defenses

3.2.1. NK cells, cytotoxic T lymphocytes and dendritic cells

Natural Killer cells (NK), cytotoxic T lymphocytes (CTL) and dendritic cells are crucial effectors against infection and are also involved in controlling tumor development (8, 43, 47).

NK cells have caught attention of many investigators and have been extensively studied in animal models. Considered as major effector cells, but particularly vulnerable during surgery, NK are already active at the early stages of tumor growth, before the activation of adaptive immunity by T cells (47, 48). In animal models, NK activity is positively correlated with resistance to metastasis (28, 29, 30). Interestingly, these models have shown that the negative impact of surgery on NK activity can be prevented by analgesic techniques (49, 50). In humans, a decrease of NK cytotoxicity during the perioperative period is well documented (48, 51). However, there is no firm evidence of an effective role of NK activity yet, although a few reports suggest its role during the development of metastases (52).

Cytolytic CD8+ T lymphocytes can specifically recognize and kill tumor cells. Quantitative and qualitative markers of tumor infiltration by T lymphocytes have been identified as strong prognostic factors, even if the causative link to outcome is still debated (53). PGE2 inhibits cytokine production and cell survival. It can alter lymphocyte function through G protein-coupled E-prostanoid receptors and synthesis of cyclic adenosine monophosphate (cAMP) (54). Dendritic cells (DCs) play an important role in the development of anti-tumor T-cell responses. They present tumor-associated antigens to naive T-cells and stimulate their differentiation into cytolytic effectors. Their functions are inhibited by PGE2, which can be produced by tumor cells or by monocytes and DCs to regulate the inflammatory cascade (55, 60).

Noteworthy for the anesthesiologist, lymphocyte function is influenced by local or systemic inflammation, as well as by the central nervous system. This has been well described for NK cells (47, 56). Concurrent with the inflammatory response to trauma (or surgery), the active pain regulatory mechanisms act through the midbrain periaqueductal gray matter, as well as through β-endorphin and adrenergic pathways. Norepinephrine inhibits NK activity through a direct effect on β-2 receptors, whereas the cholinergic system and the vagus nerve often counteract the sympathetic system (56, 57). In turn, the brain influences prostaglandin secretion and the inflammatory cascade (56).

3.2.2. Tumor-associated immune cells

Immune cells play a major role in carcinogenesis (8). Tumor-associated neutrophils can “feed the tumor”. They produce reactive oxygen species (ROS), as well as bFGF, PGE2 and VEGF (58). These factors lead to the development of more aggressive tumors, with accelerated growth. As described above, PGE2 is produced either by immune cells, such as monocytes, macrophages and DCs, and by the tumor itself (59, 60, 61). COX-2, which is over-expressed in many tumor cells, and particularly in carcinomas, stimulates a direct PGE2-induced increase of tumor growth and angiogenesis.
In addition to a direct immunosuppressive effect on lymphocytes, tumor-associated macrophages (TAM) are attracted, as well as myeloid-derived suppressor cells (MDSC). TAMs have both pro- and anti-tumor effects, depending, at least partially, on PGE2 secretion (43). In so far as COX-2 is over-expressed in many tumor cells, as well as in TAM, a potential vicious circle may be initiated. It involves TAM attraction, pro-tumor activity and PGE2 secretion. The granulocyte/neutrophil-like MDSC are a group of myeloid cells that accumulate in many cancer patients. They are morphologically similar to neutrophils, and their number and activity are rapidly and greatly increased by inflammation, notably by the cytokines IL1-beta and IL-6. These cells inhibit CTL and NK cell activities, blunting the antitumor immune responses (62) (Fig. 2).

3.2.3. The paradox of inflammation and immune response

The paradox of inflammation, which induces both pro-tumor and anti-tumor mechanisms, has been clearly summarized by Dinarello (39). Cytokine production, production of ROS and PGE2, or the influx of macrophages and neutrophils are initially needed to induce immunity but can also contribute to its inhibition. Cytokines such IL1-beta and IL-8 contribute to an increase in the release of vascular adhesion molecules, production of VEGF and other growth factors, therefore promoting angiogenesis and metastasis. These same cytokines also recruit cells of the innate and adaptive immune system into the tumors.

The Society for Immunotherapy of Cancer, supported by the National Institute of Health (NIH), recently confirmed the importance of inflammation in cancer (8). The panel of experts recognized the importance of inflammatory and immune monitoring in cancer, and the need for specific interventions targeting, among others factors, IL-1beta, TNF-alpha and PGE2. Increased levels of these mediators have been shown to be deleterious in terms of tumor progression (8). It is therefore possible that surgery-induced rise of these cytokines, of growth factors and of PGE2, at a time when CTCs are peaking in the bloodstream, has a long-term impact on patients overall survival.

For the anesthesiologist, the important message is that the inflammatory mediators produced by the tumor or by the host play a role in cancer and in relapses after surgery, and that there might be practical means to interfere with these mechanisms.

4. THE PLACE FOR PERIOPERATIVE INTERVENTIONS TO LOWER CANCER RECURRENCE RATE

4.1. Rationale sustaining pharmacological interventions

Since surgery has been suspected to accelerate tumor growth, anesthesiologists have tried to control the consequences of surgical trauma and avoid negative consequences of their interventions (63). As a consequence, there is a rationale supporting the development of perioperative techniques to lower cancer recurrence rate associated with surgery.

First, opiates, and their avoidance with loco-regional analgesia, have been studied in this context, with discrepant results (10-16, 64). Immunosuppressive effect of pain and opiates has been observed in animals and in humans. Cell-mediated immunity, and particularly NK activity, has been shown to be vulnerable to opiates. This effect is more pronounced when opiates are given at high doses. On the other hand, the largest immune suppression has been shown in operated animals where pain was not treated (30, 49-52). In addition, morphinergic pathways have been suspected to directly increase tumor growth rate (65), possibly through an epidermal growth factor activation (66). Therefore, avoiding opiates could favorably impact cancer recurrence when an alternative pain management is possible and adequate. Loco-regional analgesia is one possibility, which could have a direct effect on the inflammatory response (67).

Moreover, there is a large core of animal studies arguing for a positive influence of loco-regional analgesia on anticancer immunity (mostly NK activity, again) and metastasis occurrence (29, 30, 49-52). These results are in accordance with the possible influence of loco-regional analgesia (e.g. epidural) on several cytokines expressed during the perioperative period (67). Some of these cytokines could have a direct and/or indirect effect on the rapid progression of the disease after cancer surgery. Possible mechanisms include an influence on immune cells (both limiting and promoting tumor growth), tumor cell metabolism and capacity to increase mitosis rate, extracellular matrix and capacity to disseminate and migrate and, finally, angiogenesis mechanisms (Fig. 1). All these mechanisms, favored by surgery, are suspected to be responsible for the magnitude of the first peak of relapse. Unfortunately, there are no specific studies focusing on the influence of opiates (or their avoidance) with loco-regional techniques on the first peak of relapse compared with the second peak. Most of studies
analyzed the disease-free survival and/or the overall survival without highlighting a specific period. Moreover, several discrepancies, possibly methodology-related, appear in outcome studies. Briefly, there are problems with endpoint choices (e.g. definition of disease-free survival), over-fitting in multivariate analyses (16, 68), as well as absence of an assessment of the patients’ peri-operative inflammatory status, which is a major prognostic determinant (69). Apart from opiates and loco-regional analgesia, another pharmacological intervention could be the use of non-steroidal anti-inflammatory drugs (NSAIDs). While largely under-investigated, there is a strong argument for a possible role of NSAIDs in the prevention of cancer recurrence after surgery.

4.2. Non-steroidal anti-inflammatory drugs (NSAIDs)

In addition to their opiate-sparing effect, NSAIDs present a promising anticancer profile with respect to the pathophysiological steps of tumor proliferation and dissemination. Most, but not all, of these effects may be mediated by the inhibition of PGE2 synthesis, described above as a major mediator in cancer. The inhibition of PGE2 synthesis could occur directly in tumor cells, impairing their capacity to survive, dedifferentiate and proliferate. This inhibition could increase the cytotoxic activity of NK and T lymphocytes, which is normally inhibited by PGE2. It could also decrease the influx and activity of tumor-associated immunocytes. Prior to the dissemination steps, NSAIDs could protect the integrity of the extracellular matrix, thereby reducing the liberation of tumor cells in the blood stream. During the dissemination process, NSAIDs may directly interfere with the survival capacity of CTCs, and their capacity to adhere to endothelial cells. This could also occur indirectly through the inhibition of platelet function, which is involved in all the following steps, including the angiogenesis processes. Finally, the growth of metastases disseminated before surgery or not, may be reduced through the same pathways, including inflammatory-related angiogenesis, immunocytes- and platelet-related release of growth factors, and survival and proliferation of tumor cells. All these mechanisms were described above and summarized in Figure 2 (for a review, see reference 43). These therapeutic effects of NSAIDs in cancer have been described for various carcinomas, with a great concordance between studies. While the role of NSAIDs in cancer prevention remains unclear, this is not related to a lack of data on their anticancer effect but, rather, to side effects associated with chronic administration (61, 70, 71, 72).

In June 2010, we reported data from a retrospective study of 327 consecutive breast cancer patients treated by one surgeon in one Belgian hospital, comparing various perioperative analgesic and anesthetic regimens (3). Patients were treated by a mastectomy and conventional adjuvant therapy, and did or did not receive the NSAID ketorolac intraoperatively. The average follow-up was 27.3 months with range of 13-44 months. Intra-operative ketorolac administration was associated with a significantly higher disease-free survival during the first 5 years after surgery. With Retsky and our collaborative group, we have recently reanalyzed this database, focusing on the differential impact of ketorolac on early and late recurrence peaks (73). Using hazard smoothed plots analysis, we confirmed that the expected prominent early relapse peak is all but absent in the ketorolac group. The few events in the ketorolac group show a small bump during the first 10 months, and then a slow rise until the fourth year. We observed an approximately six fold decrease of the early peak hazard. If this observation holds up in a larger and randomized trial, it would mean that using this safe and effective anti-inflammatory agent at the time of surgery could prevent most early relapses.

Similar retrospective analyses could be conducted on other cohorts, focusing on the impact of perioperative interventions in oncological surgery. Noteworthy, in a series of patients, we compared loco-regional anesthesia and systemic opiates. We observed that, if present, the impact of a perioperative technique affects primarily the early recurrence peak (4, 10-14). We cannot firmly conclude to a causal relationship, but a better understanding of the pathophysiology of cancer during the perioperative period is urgently needed.

Conclusions and future

The anesthesiologist takes care of cancer patients at a critical time of their life. In addition to inflammation and immune disorders caused by the neoplastic disease, surgery is an additional source of disequilibrium for factors influencing tumor growth. There is a need for a more profound understanding of tumor biology during the perioperative period, and for an analysis of the impact of various anesthetic maneuvers on tumor recurrences. Assessments of perioperative inflammation and immunity could identify several groups requiring distinct
anesthetic managements, in order to minimize their risk of relapse. The anesthesiologist’s role in the oncology ‘medical team’ could substantially increase.

Acknowledgements

The authors would like to acknowledge Karen Retsky for her contribution to the quality of the manuscript.

References


after 11 to 16 years of follow-up. A randomized screening trial of mammography in women age 40 to 49 years, ANN. INTERN. MED., 157 (5 Part 1), 305-12, 2002.


44. Jung Y. J., Isaacs J. S., Lee S., Trepel J., Neckers L., IL-1β-mediated up-regulation of HIF-1α via an NFκB/IFN-γ/COX-2 pathway identifies HIF-1 as a critical link between inflammation and oncogenesis, FASEB JOURNAL, 17, 2115-7, 2003.


57. Panerai A. E., Sacerdoti P., Beta-endorphin in the immune system, a role at last?, IMMUNOL. TODAY, 18, 317-9, 1997.

58. Di Carlo E., Forni G., Neutrophils in the antitumoral...


68. Forget P., Leonard D., Kartheuser A., De Kock M., Choice of Endpoint and Not Reporting All the Analgesics Used May Render Inconclusive Studies on Oncological Outcome, Anesthesiology, 114 (3), 717, 2011.


