Breast Cancer and Anaesthesia

Subjects: Oncology
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Breast cancer is the leading cause of mortality in women. Even when the tumor is completely resected, tumor recurrence occurs in up to one third of patients, with metastatic disease being the direct cause of death. Surgery may generate systemic inflammatory response syndrome, which causes oxidative stress, and in turn impairs the anti-tumor immunologic response. Surgical stress activates a neuroendocrine response in the hypothalamic–pituitary–adrenal axis (HPA axis) and sympathetic nervous system (SNS), which results in the suppression of cell-mediated immunity (CMI); this suppression is induced by the release of neuroendocrine mediators such as catecholamines, cortisol, and cytokines. These mediators, including vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs) and interleukin (IL) 6 and 8, are endogenous regulators that promote tumor growth and angiogenesis, thereby favoring metastasis. Recent studies reveal that the type of anaesthesia administered during cancer surgery may influence the course of the disease.

Keywords: anaesthetic drugs and techniques ; opioids ; propofol ; volatile agent ; breast cancer ; cancer recurrence

1. Anaesthetics and Cancer Relapse

1.1. Hypnotics

Propofol

Propofol may have beneficial effects on survival in cancer patients, including breast cancer patients. This agent inhibits tumor cell migration and proliferation, promotes tumor apoptosis and has anti-inflammatory activity [1][2][3]. This agent acts on the immune system at the level of natural killer lymphocytes (NK), which belong to innate immunity. Cho et al. [4] conducted a prospective study comparing a group of patients who received propofol-ketorolac vs. sevoflurane-fentanyl. The authors observed a reduction in NK activity in the sevoflurane group, whereas this activity was increased in the propofol group. Although evidence consistently shows that propofol has tumor-killing activity, two recent studies associate it with pro-tumor activity in breast and bladder cancer, mediated by the activation of the Nrf2 pathway and the reduction in p53 levels [5][6].

Propofol favors tumor cell apoptosis by affecting matrix metalloproteinase (MMPs) expression, which play a crucial role in extracellular protein degradation and epithelial-mesenchymal transition (EMT), activate vascular endothelial growth factor (VEGF) [7], and inhibit intrinsic apoptosis pathways [8]. Two pathways have been identified to be involved in the inhibition of the synthesis of these proteins: the MAP-kinase pathway (ERK1/2, JNK y p38) in colon cancer [9], and NF-κB in breast cancer [10].

As for the ability to induce tumor apoptosis, several pathways have been investigated, such as the inhibition of anti-apoptosis mechanisms, including Bcl-2, Sox4, Akt/mTOR and Wnt/β-catenin, and the increase in pathways involving tumor suppressor genes such as the Bax, ING3, Fox01 and caspase pathways [11][12][13][14][15][16]. In addition, Wang et al. [17] demonstrated that propofol induces the intrinsic apoptotic signaling pathway by the release of reactive oxygen species (ORS).

Propofol may inhibit surgery-induced systemic inflammatory response syndrome throughout decreasing cell concentrations of hypoxia-inducible factor 1 (HIF1A), which is elevated in the tumor's hypoxic micro-environment and promotes cell migration and invasion [18]. Ecimovic et al. [19] demonstrated in vitro the role of NET-1 (neuroepithelial cell transforming gene-1) overexpression, a gene that is associated with tumor dissemination and which decreases with propofol exposure [20].

1.2. Halogenated

It has been suggested that inhalation agents, for the most part, have a tumorigenic effect since they both inhibit tumor cell apoptosis and stimulate tumor cell proliferation and migration. More specifically, in advanced breast cancer, elevated

caveolin-1 concentrations have been associated with lower survival. This protein has been linked to higher resistance to apoptosis, migration and elevated invasivity in breast cancer cells. Ecimovic et al. [21] analyzed, in vitro, the ability of sevoflurane to stimulate tumor cell proliferation, migration and invasion in patients with positive (ER+) and negative (ER-) estrogen receptor breast cancer (with the latter not having invasive capacity).

However, Kawaraguchi et al. [22] documented that isoflurane confers a protective effect on tumor cells in colon cancer against TNF-mediated apoptosis (TRAIL or TNF-related apoptosis-inducing ligand) by interacting with caveolin-1.

Sevoflurane reduces NK activity, thereby reducing immunosurveillance and favoring progression of micrometastases. In contrast, a range of studies have been conducted to compare immunosuppression induced by halogenated anaesthetics vs. general intravenous anaesthesia, with inconsistent results [23][24][25][26][27][28]. Enlund et al. [23] found no significant differences in 1-year and 5-year survival in a sample of 1837 breast cancer patients. Kim et al. [25] compared propofol with a variety of halogenated agents (sevoflurane, desflurane, isoflurane and enflurane), without significant differences. Recent retrospective studies [26][27][28] provide cumulative evidence of the absence of significant differences between intravenous and inhalation anaesthetics in terms of recurrence or survival.

2. Analgesics

2.1. Opioids

Opioids have an immunosuppressive effect that influences cellular and humoral immunity, as they reduce NK lymphocyte activity and proliferation, citokine production, phagocytic activity, and antibody release [29]. The type and degree of immunosuppression depends on the type, dose and time of exposure to the opioid. All synthetic opioids reduce NK activity [30][31].

Morphine inhibits T and NK lymphocyte activity, promotes lymphocyte apoptosis, reduces toll-like 4 factor in macrophages [32] and has angiogenic activity [33]. In addition, the tumorigenic activity of morphine is mediated by two independent mechanisms, namely: by direct stimulation of mu receptors in tumor cells, the overexpression of which has been associated with poor prognosis, and indirectly by promoting neo-angiogenesis through metabolic signaling pathways similar to those used by VEGF factor [34][35].

In breast tumor cells, fentanyl exhibits an antitumoral effect by reducing levels of proteins involved in cell apoptosis and differentiation mechanisms (Bax, Bcl2, Oct4, Sox2, and Nanog) [36]. Although tramadol is a μ-receptor agonist, its analgesic effect is prevailingly mediated by the inhibition of noradrenaline and serotonin reuptake. Sacerdote et al. [37] assessed the relationship between tramadol and immune response in patients with uterine carcinoma. The authors found that tramadol not only inhibits but also stimulates NK lymphocyte activity. Thereupon, Xia et al. [38] demonstrated, in vitro, in breast tumor cells that tramadol reduces tumor cell proliferation, migration and invasion by up to 28 days through the inhibition of the α2-adrenergic receptor. In a retrospective study, Kim et al. [39] observed lower rates of mortality and tumor recurrence in the group of breast cancer patients treated surgically who received tramadol. This effect is conferred by the inhibition of tumor cell proliferation, induction of apoptosis, and action on serotonergic receptors and transient receptor potential channel V1 or TRPV1.

2.2. Regional Anaesthesia and Local Anaesthetics

There is a variety of locoregional anaesthesia techniques in breast cancer surgery that have good analgesic outcomes. Paravertebral block (PVB) is the most widely used technique, although it is associated with a higher risk of severe complications. New techniques have been developed, with pectoral block type II having shown good effectiveness, and having been employed in a similar context as PVB [40]. Several studies have been published comparing general anaesthesia and combined anaesthesia: five retrospective studies, two prospective studies and a systematic review. These studies provide evidence of the beneficial effects of not using opioids and/or local anaesthetics per se [41][42][43][44][45][46][47][48].

Exadaktylos et al. [41] published the first retrospective study assessing the outcomes of 129 patients with breast cancer treated surgically, of whom 50 received combined anaesthesia (PVB+Propofol) and 79 balanced general anaesthesia. The rate of recurrence was lower in the group that received combined anaesthesia. In contrast, a recent systematic review conducted by Pérez-González et al. [48] did not show statistically significant differences between combined and general anaesthesia.

Local anaesthetics block afferent and efferent nerve response and effectively suppress sympathic stimulation through the inhibition of hypothalamic–pituitary–adrenal (HPA) stimulation induced by surgical stress, thereby reducing HPA activity [48].

Lidocaine has been proven to exert beneficial effects in vivo and in vitro, and it is associated with a reduction in tumor cell proliferation, migration and invasion in breast, liver and lung cancer [49][50][51]. Lidocaine inhibits the proto-oncogen that releases Src, an intracellular non- tyrosine kinase protein that is involved in cell proliferation and migration processes through ICAM-1 phosphorylation, which enables neutrophils to cross the endothelium and increase immune response [51]. It has been reported to have effects on other signaling pathways such as TRPV-6 inhibition [52] or DNA demethylation in breast cancer cells [53]. Chang et al. [54] demonstrated in vitro that both lidocaine and bupivacaine induce breast cancer cell apopotosis through the activation of caspases 7, 8 and 9. In the same line, D'Agositino et al. showed that lidocaine inhibits cytoskeletal modification in breast cancer cells [55].

Evidence has been provided that lidocaine infiltration in the peritumoral region inhibits tumor growth by binding EGFR [56]. As for the immune system, lidocaine, at clinically relevant concentrations, stimulates the cytotoxic effect of NK lymphocytes [57]. A prospective, randomized trial conducted by Galoș et al. revealed that lidocaine reduced neutrophil extracellular traps, a phenomenon that has been associated with tumor recurrence [58].

2.3. NSAIDs

The enzyme cyclooxygenase (COX-2) causes an increase in prostaglandins, which are involved in immune system control and angiogenesis. Ketorolac is the most extensively studied NSAID in relation to cancer. It is a COX-1 and COX-2 inhibitor that is commonly used in the perioperative period. Evidence from retrospective studies demonstrates that perioperative administration of ketorolac reduces breast cancer recurrence by diminishing the production of prostaglandins and VEGF. Forget et al. attempted to replicate these results in patients with breast cancer at high risk of recurrence (triple negative, neutrophil/lymphocyte ratio ≥ 4) [59] in a prospective study [60] of 203 patients, without differences having been found between treatment groups.

3. Dexmedetomidine

Dexmedetomidine is a selective α2 agonist with sympatholytic and anti-inflammatory activity that reduces IL-6, IL-8 and TNF-α concentrations and increases anti-inflammatory cytokine IL-10 levels [61].

Despite its anti-inflammatory effect, a pro-tumoral activity is attributed to dexmedetomidine. Lavon et al. [62] demonstrated in animal models that it promotes metastasis in breast, lung and colon cancer. This effect is credited to the transient immunosuppression induced by dexmedetomidine, added to the effects of surgical stress and changes in vascular patency.

In the same line, Xia et al. [63] investigated the effect of dexmedetomidine in breast cancer cells, in vitro and in vivo, in mice and concluded that dexmedetomidine promotes tumor cell proliferation, migration and invasion through the inhibition of the α2/ERK adrenergic receptor pathway [38].

Cata et al. [64] performed a retrospective study involving 1404 patients with non-small lung cancer (NSCLC) treated surgically to investigate a potential relationship between tumor recurrence and the use of dexmedetomidine. This relationship was not confirmed. Indeed, the results showed a significant relationship between dexmedetomidine and lower survival.

Beta-blockers and lipid lowering drugs are two of the main groups of drugs among patients undergoing a surgical procedure.

4. Beta-Blockers

Beta-adrenergic receptors are found both in tumor cells and the immune system [65], and seem to play a key role in carcinogenesis [66]. Beta-blockers have been proven to be involved in angiogenesis and cellular neoproliferation [67]. Exposure to beta-agonists inhibits lymphocyte NK activity [68][69] and induces an increase in T-regulator lymphocytes [70], leading to immunosuppression. Kang et al. documented that adrenergic stimulation activated the MAP-kinase cascade and, more specifically, the DUSP1 cascade, which causes resistance to chemotherapy and apoptosis [71]. Recently, Zhou et al. [72] observed that propranolol prevented T-regulator lymphocyte elevation. Another potential cellular signaling pathway is adrenergic activation of PI3K/AKT and HIF-1 α, which is also inhibited by propranolol [73].

Contradictory results were obtained in five retrospective [74][75][76][77][78] and two cohort studies [79][80] assessing recurrence in breast cancer patients after surgery due to the lack of a standard treatment administration protocol [81][82][83][84].

5. Lipid Lowering Drugs

The increased prevalence of cardiovascular disease in the recent years has resulted in an increase in the use of lipid lowering drugs, with statins being the most common pharmaceutical group. As a component of the cellular membrane, cholesterol plays an essential role in cellular division; therefore, a reduction in extracellular cholesterol should cause an inhibition of tumor cell proliferation. Cholesterol metabolites such as 27-hydroxycholesterol and 25-hydroxycholesterol may stimulate estrogen receptors (ERs) [85][86]. Alikhani et al. [87] reported an increase in breast tumor growth mediated by the PI3K/AKT pathway in hyperlipidemic mice.

Cholesterol favors a pro-inflammatory environment by the activation of macrophage toll-like receptors [88] and the inhibition of CCR7 expression in dendritic cells, which explains their antigenic effects [89]. On the other hand, cholesterol modulates lymphocyte T activity through the liver X receptor (LXR) [90].

As for the use of statins, inconsistent results were obtained in six retrospective [76][91][92][93][94][95] and five prospective studies [81][96][97][98][99] (four supporting its use and the remaining seven having not provided clinically relevant results). In contrast, the three meta-analyses retrieved [99][100][101][102] provide consistent evidence that statins reduce breast cancer recurrence. However, these studies were conducted using non-standard methods, and prospective randomized studies are needed.

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