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REVIEW

The effects of local anesthetics on cancer cells

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ABSTRACT
During cancer surgery, the perioperative period is characterized by stress response and immunosuppression that can lead to further worsening of the disease and metastatic spread. Local anesthetics have antiproliferative, cytotoxic and antimetastatic effects on cancer cells *in vitro*. There is scientific evidence that local anesthetics possess anti-inflammatory effects, help to preserve normal immune function and reduce the possibility of metastatic spread. Anesthetic care affects pain, inflammation, and immunosuppression, which may have a great impact on the outcome of oncological patients. The use of local anesthetics during the perioperative period in oncological patients may have a beneficial effect on their survival and cancer recurrence. This article summarizes the effects of local anesthetics *in vitro (Tab. 1, Fig. 1, Ref. 36).* Text in PDF *www.elis.sk*
KEY WORDS: local anesthetics, cancer cells.

Introduction

According to the WHO, cancer caused almost 10 million deaths in 2020, and the most common types were breast, lung, colon/rectal, prostate, skin, and stomach cancers (1). Surgery is still the standard treatment for most solid tumors although there is a tendency to implement new treatment strategies, especially those related to immune response (2). However, there is always a risk of metastatic spread during surgery. The perioperative period along with stress response, inflammation process, pain, and immunosuppression can contribute to the survival of cancer cells and the progression of the disease. Anesthetic care may play an important role in the outcome of oncological patients. The term "onco-anesthesia" or "anesthesia in oncosurgery" keeps emerging in literature with great frequency. Local anesthetics, especially amides such as bupivacaine, levobupivacaine, lidocaine, ropivacaine, and mepivacaine, are widely used in daily practice in regional anesthesia (spinal, epidural, peripheral nerve blocks). Recently, a growing body of scientific evidence suggests their cytotoxic, antiproliferative and antimetastatic effects on cancer cells *in vitro* (3). The effect of nerve block is explained by a temporary inhibition of the propagation of action potential due to the blockade of voltage-gated sodium channels in the nerve fibers while causing the sensation of numbness. In addition to the voltage-gated sodium channels, local anesthetics act on different receptors and channels and modulate various molecular pathways explaining their anti-inflammatory, analgesic, and antitumor effects (4). After infiltration of local anesthetics in clinical concentrations, they act locally but upon absorption into the blood stream, they may also exert systemic effects. The concentrations of local anesthetics in the blood after infiltration are illustrated in Table 1. The use of local anesthetics during the perioperative period in oncological patients may have potential benefits on survival and recurrence-free days. There is scientific evidence that inhalation agents and opiates may promote the proliferation or even metastatic spread of cancer cells *in vitro* (5). The use of local anesthetics as anticancer drugs is very promising but still controversial although the body of evidence from clinical randomized control trials (RCTs) is growing (6).

Cancer pathogenesis

At present, cancer theory is constantly shifting from the "cancer cell" view to a more complex concept that involves a network of stromal cells such as fibroblasts, vascular endothelial cells and immune cells that all together form the tumor microenvironment (TME). Moreover, the tumor cells release soluble factors into their microenvironments to block the cell-mediated immunity (7). Cancer arises from two diverse processes as follows: genetic and epigenetic instability of cells when tumor suppressor genes are inhibited and oncogenes are activated (1) and loss of immune surveillance (2). The tumor cell must liberate itself from other cells and move through the extracellular matrix with the help of matrix metalloproteases (MMPs) which can degrade the matrix, cross the basement membrane, enter the bloodstream or lymphatic circulation, escape the immune system, survive as a circulating cancer cell (CTC), invade the new microenvironment and proliferate as metastasis (8). Moreover, there is a link between the number of CTCs and survival rate of patients with breast cancer, indicating that a higher number of CTCs is associated with lower survival (9). The main host de-

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Tab. 1. Clinically relevant concentrations of the commonly used local anesthetics (according to Liu et al., 2020).

Local anesthetic	Circulation concentration	Local infiltration concentration
Lidocaine	10 μM (2.34 mg/L)	17.5 – 70 mM (0.5 – 2 %)
Mepivacaine	10 μM (2.46 mg/L)	40.6 – 81.2 mM (1 – 2 %)
Bupivacaine	2.8 μM (0.81 mg/L)	8.7 – 17.4 mM (0.25 % – 0.5 %)
Ropivacaine	3.5 μM (0.96 mg/L)	7.3 – 18.2 mM (0.75 – 1.0 %)
Levobupivacaine	2.5 μM (0.72 mg/L)	8.7 – 26.1 mM (0.25 – 0.5 %)

fense against tumor cells is represented by natural killer cells (NK cells) which can eliminate the cancer cells from circulation. The decreased activity of NK cells predicts a high risk of tumor recurrence. Therefore, it seems critical to preserve normal immune function. In cases of immunosuppression with lower activity and/or lower number of NK cells, the host has a lower ability to fight cancer cells.

Perioperative stress, inflammation, and immunosuppression

Tissue damage and pain during surgery generates neurohumoral and inflammatory response and causes immunological changes (10) (Fig. 1). Not only does the rapid increase in inflammatory mediators promote local tissue healing, it also stimulates cancer cell survival and proliferation. The mechanisms that lead to inflammation, pain, and cancer share some common pathways (11). The inflammatory response is mediated by neutrophils, macrophages, and monocytes, and initiates the production and secretion of proinflammatory cytokines such as interleukins IL-1β, IL-6, IL-4, IL-8, IL-10, tumor necrosis factor alpha (TNFα), reactive oxygen metabolites (HIF1-α, HIF2-α), angiogenic factors such as vascular endothelial growth factor (VEGF), matrix metalloproteases (MMP-9), cyclo-oxygenase-2 (COX-2), adhesive molecules (ICAM-1) which all together promote the tumor growth, angiogenesis, and metastatic spread. The activity of inflammatory cytokines results in loss of endothelial integrity, which enables leukocytes to migrate but also tumor cells to invade surrounding tissues via extravasation (12). The inflammatory response is directly proportional to the extent of the surgical procedure.

The stress response is initiated by the activation of the hypothalamic-pituitary-adrenal (PHA) axis caused by tissue damage and pain. The levels of glucocorticoid hormones and endogenous catecholamines (norepinephrine, epinephrine) rise, which leads to immunosuppression, lymphopenia, decrease in circulating NK cells, and increase in secretion of proinflammatory cytokines (5). Immunosuppression can stimulate the growth and migration of cancer cells and metastases. Catecholamines promote angiogenesis *via* VEGF and elevation of IL-6 levels (13). Epinephrine and norepinephrine may also act on beta-adrenergic receptors found in several tumor types such as breast, prostate or liver cancer and stimulate cancer cells' proliferation and migration (14). Painful stimuli have been shown to reduce NK lymphocytes and NK cytotoxic activity (15) (Fig. 1).

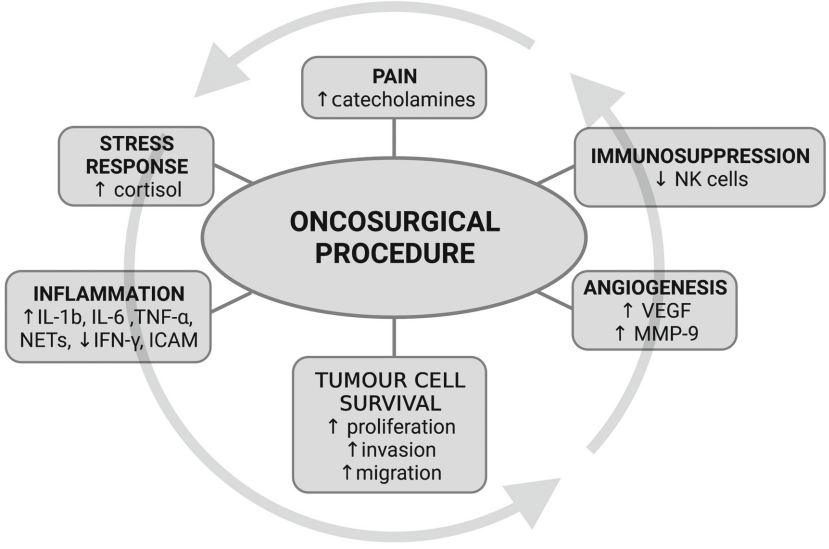

Fig. 1. Tissue damage and pain during surgery generates neurohumoral and inflammatory response and causes immunological changes. NK cells – natural killer cells

Direct and indirect effects of local anesthetics *in vitro*

Antiproliferative, antimetastatic, pro-apoptotic effects

In addition to the blockade of voltage-gated sodium channels expressed on the membrane of many tumors, local anesthetics affect the growth, proliferation, migration, invasion, and apoptosis of cancer cells by means of various mechanisms. Cell growth and proliferation can be inhibited by blocking the cell cycle mechanism, modulating the expression of the transcription factor NF-kB involved in the cell cycle, inducing mitochondrial dysfunction, modifying the epigenetic regulation with the enzyme DNA methyltransferase, and modulating transport proteins (GOLT1A, TRPV6) and receptors such as EGFR (16, 17). Bupivacaine and lidocaine significantly blocked the proliferation of melanoma and breast cancer cells while decreasing the production of cyclins (A2, B1, B2, D, E) responsible for the regulation of the cell cycle (18). Ropivacaine and bupivacaine stopped the growth of hepatocellular carcinoma cells by destroying the mitochondrial complexes I, II, III (19). Local anesthetics attenuate the process of migration, invasion, and formation of metastasis by means of altering the Ca^{2+}, and Mg^{2+} influx, and thus via changing the cytoskeleton function, they decrease cell motility. The mechanism of action of lidocaine and ropivacaine in concentrations of 10 – 100 μM lies in the blockade of voltage-gated sodium channels while reducing the metastatic spread and invasion of colon cancer and breast cancer cells (20). In addition, lidocaine and ropivacaine in clinical concentrations blocked the invasion of adenocarcinoma cells by inhibition of secretion of MMP-2 and MMP-9 (21). The

inhibitory effects of local anesthetics on cancer cell viability, growth and migration involve the role of many microRNAs. Lidocaine induced the expression of miR-145 and blocked mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK/ERK) and NF-κB, signaling pathways, thereby inhibiting proliferation, invasion, and migration of gastric cancer cells (22). Lidocaine can target EGFR *via* upregulating miR-520a-3p to inhibit the proliferation and induce apoptosis in colorectal carcinoma cells (23). Local anesthetics can induce apoptosis by increasing the expression of tumor suppressor *TP53*, downregulation of the *Bcl-2* gene family, activation of pro-apoptotic enzymes, induction of endoplasmic reticulum (ER) stress response, and mitochondrial dysfunction. Levobupivacaine induced apoptosis of non-small cell lung carcinoma cells by upregulation of *TP53* (24). Levobupivacaine, bupivacaine, ropivacaine, chloroprocaine, prilocaine, and lidocaine caused autophagy of HeLa cell lines and osteosarcoma cells inducing ER stress response (25). In concentrations much lower than those in hematopoietic stem cells, ropivacaine, lidocaine, and bupivacaine caused the inhibition of colony formation and self-renewal of leukemic stem cells, suggesting that local anesthetics preferentially target cancer stem cells rather than non-cancer stem cells (26).

Anti-inflammatory effects

Lidocaine and bupivacaine showed potent anti-inflammatory effects, suppressing the action of leukocytes and their metabolic secretion of all potent cytokines (27). Lidocaine in clinically significant concentrations increased the cytotoxic effect of NK cells (28), moreover decreased the secretion of proinflammatory cytokines, metalloproteases, and adhesion molecules (29). Lidocaine has inhibitory effects on angiogenesis by blocking the migration and proliferation of endothelial cells and causing the suppression of VEGF/VEGFR (30).

Enhancement of the effect of chemotherapeutics

Lidocaine in concentrations of 0.01 – 1 mM sensitized breast cancer cells to cisplatin, leading to a significant increase in apoptosis. Similarly, lidocaine in concentration of 0 – 100 μM in combination with 5-fluorouracil had significant proapoptotic effects on melanoma and choriocarcinoma cells (31).

Analgesic effects

Lidocaine is the only local anesthetic that can be administered intravenously because of its indication as an antiarrhythmic drug for the treatment of ventricular arrhythmias. After i.v. administration, lidocaine has important analgesic and anti-hyperalgesic effects in the settings of acute and chronic pain, acting in the modulation of pain pathways at the level of the spinal cord. The analgesic effect can be explained by its action on many channels (Na^+, K^+, Ca^{2+}, TRP) and receptors (opioid, GABA, Toll-Like, NMDA, cannabinoid, α-2adrenergic, muscarinic, and nicotinic acetylcholine receptors, GABA, serotoninergic, G-protein coupled receptors) (32). Moreover, lidocaine has anti-inflammatory effects, which contributes also to the reduction of pain stimuli caused by pro-inflammatory molecules such as COX-2 (29). Meta-analysis of 12 RCTs demonstrated that lidocaine could be considered an alternative analgesic drug for the treatment of acute pain (33).

Conclusion

The use of local anesthetics during oncosurgery can be beneficial by various mechanisms. Their direct anticancer effects can lead to decreasing the chance of metastatic spread in the perioperative setting and after surgery. Moreover, local anesthetics have anti-inflammatory and antiangiogenic effects and thus worsen the normal functioning of the tumor microenvironment and can impair the tumor growth. By attenuating the extent of stress response mediated by the HPA axis and thus decreasing the release of cortisol and catecholamines, local anesthetics help to maintain the normal immune response. The analgesic effect of local anesthetics can help to decrease or even avoid the consumption of inhalational agents and opioids, which may have pro-cancer properties. The tendency to control the pain and immune function seems to be crucial.

An updated meta-analysis of retrospective and prospective studies with 52,000 patients demonstrated the beneficial effects of regional (mainly epidural) anesthetic techniques on the prognosis and survival of oncological patients in comparison with general anesthesia only (34).

However, the recent meta-analysis of 15 randomized clinical trials with 5,981 patients showed that when compared to general anesthesia, the regional anesthesia increased neither overall survival, nor recurrence-free days (35). It can be explained by the heterogeneity of patients involved (possible differences in SNP profiles of patients (36)), variations in anesthetic protocols, duration of administration and type of local anesthetic used, as well as by small cohorts of patients, and a small number of RCTs. The quality of evidence from *in vitro* studies is strong enough to state that local anesthetics have antiproliferative, antimetastatic effects on various types of cancer cells, and inhibit the process of angiogenesis. However, the concentrations and incubation times needed to achieve the desired effects vary according to cell type and anesthetic type. We still do not know what type of local anesthetic is the most potent, as well as in what dose and for how long it should be administered to the patients in order to improve their outcomes. Nevertheless, there are several ongoing RCTs primarily investigating the effects of i.v. lidocaine on oncological patients (e.g., VAPOR-C and NCT04316013, scheduled for completion in 2025), and we can anticipate interesting results (37). In the future research, it would be interesting to study the effects of local anesthetics directly on the patients´ cells *in vitro* and at the same time confirm the results *in vivo,* including the role of tumor suppressor or oncogenic miRNA which are showing promising results in animal studies.

References

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, Bray F. Cancer statistics for the year 2020: An overview. Int J Cancer 2021; 149 (4): 778–789.

2. Bernadic M Jr, Duchon R, Aziri R, Mladosievicova B. New principles of cancer therapy give new hope for oncological patients. Bratisl Med J 2019; 120 (1): 15–18.

3. Liu H, Dilger JP, Lin J. Effects of local anesthetics on cancer cells. Pharmacol Ther 2020; 212: 107558.

4. Taylor A, McLeod G. Basic pharmacology of local anaesthetics. BJA Educ 2020; 20 (2): 34–41.

5. Kim R. Effects of surgery and anesthetic choice on immunosuppression and cancer recurrence. J Transl Med 2018; 16 (1): 8.

6. Missair A, Cata JP, Votta-Velis G, Johnson M, Borgeat A, Tiouririne M, Gottumukkala V, Buggy D, Vallejo R, Marrero EB, Sessler D, Huntoon MA, Andres J, Casasola OL. Impact of perioperative pain management on cancer recurrence: an ASRA/ESRA special article. Reg Anesth Pain Med 2019 (1): 13–28.

7. McGranahan N, Swanton C. Cancer Evolution Constrained by the Immune Microenvironment. Cell 2017; 170 (5): 825–827.

8. Zhang C, Xie C, Lu Y. Local Anesthetic Lidocaine and Cancer: Insight Into Tumor Progression and Recurrence. Front Oncol 2021; 11: 669746.

9. Cristofanilli M, Budd GT, Ellis MJ, Stopeck A, Matera J, Miller MC, Reuben JM, Doyle GV, Allard WJ, Terstappen LW, Hayes DF. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. N Engl J Med 2004; 351 (8): 781–791.

10. Ben-Eliyahu S, Golan T. Harnessing the Perioperative Period to Improve Long-term Cancer Outcomes. J Natl Cancer Inst 2018; 110 (10): 1137–1138.

11. Greten FR, Grivennikov SI. Inflammation and Cancer: Triggers, Mechanisms, and Consequences. Immunity 2019; 51 (1): 27–41.

12. Grivennikov SI, Karin M. Inflammatory cytokines in cancer: tumour necrosis factor and interleukin 6 take the stage. Ann Rheum Dis 2011; 70 Suppl 1: i104–8.

13. Yang EV, Kim SJ, Donovan EL, Chen M, Gross AC, Webster Marketon JI, Barsky SH, Glaser R. Norepinephrine upregulates VEGF, IL-8, and IL-6 expression in human melanoma tumor cell lines: implications for stress-related enhancement of tumor progression. Brain Behav Immun 2009; 23 (2): 267–275.

14. Bernabé DG, Tamae AC, Biasoli ÉR, Oliveira SH. Stress hormones increase cell proliferation and regulates interleukin-6 secretion in human oral squamous cell carcinoma cells. Brain Behav Immun 2011; 25 (3): 574–583.

15. Page GG, Blakely WP, Ben-Eliyahu S. Evidence that postoperative pain is a mediator of the tumor-promoting effects of surgery in rats. Pain 2001; 90 (1–2): 191–199.

16. Jiang Y, Gou H, Zhu J, Tian S, Yu L. Lidocaine inhibits the invasion and migration of TRPV6-expressing cancer cells by TRPV6 downregulation. Oncol Lett 2016; 12 (2): 1164–1170.

17. Zhang L, Hu R, Cheng Y, Wu X, Xi S, Sun Y, Jiang H. Lidocaine inhibits the proliferation of lung cancer by regulating the expression of GOLT1A. Cell Prolif 2017; 50 (5): e12364.

18. Liu H, Dilger JP, Lin J. The Role of Transient Receptor Potential Melastatin 7 (TRPM7) in Cell Viability: A Potential Target to Suppress Breast Cancer Cell Cycle. Cancers (Basel) 2020; 12 (1): 131.

19. Gong X, Dan J, Li F, Wang L. Suppression of mitochondrial respiration with local anesthetic ropivacaine targets breast cancer cells. J Thorac Dis 2018; 10 (5): 2804–2812.

20. Baptista-Hon DT, Robertson FM, Robertson GB, Owen SJ, Rogers GW, Lydon EL, Lee NH, Hales TG. Potent inhibition by ropivacaine of metastatic colon cancer SW620 cell invasion and NaV1.5 channel function. Br J Anaesth 2014; 113 Suppl 1: i39–i48.

21. Piegeler T, Schläpfer M, Dull RO, Schwartz DE, Borgeat A, Minshall RD, Beck-Schimmer B. Clinically relevant concentrations of lidocaine and ropivacaine inhibit TNFα-induced invasion of lung adenocarcinoma cells in vitro by blocking the activation of Akt and focal adhesion kinase. Br J Anaesth 2015; 115 (5): 784–791.

22. Sui H, Lou A, Li Z, Yang J. Lidocaine inhibits growth, migration and invasion of gastric carcinoma cells by up-regulation of miR-145. BMC Cancer 2019; 19 (1): 233.

23. Qu X, Yang L, Shi Q, Wang X, Wang D, Wu G. Lidocaine inhibits proliferation and induces apoptosis in colorectal cancer cells by upregulating mir-520a-3p and targeting EGFR. Pathol Res Pract 2018; 214 (12): 1974–1979.

24. Meng M, Huang M, Liu C, Wang J, Ren W, Cui S, Gu J, Xie J, Ma B, Yang G, He S. Local anesthetic levobupivacaine induces ferroptosis and inhibits progression by up-regulating p53 in non-small cell lung cancer. Aging (Albany NY) 2021; 13.

25. Bezu L, Wu Chuang A, Sauvat A, Humeau J, Xie W, Cerrato G, Liu P, Zhao L, Zhang S, Le Naour J, Pol J, van Endert P, Kepp O, Barlesi F, Kroemer G. Local anesthetics elicit immune-dependent anticancer effects. J Immunother Cancer 2022; 10 (4): e004151.

26. Ni J, Xie T, Xiao M, Xiang W, Wang L. Amide-linked local anesthetics preferentially target leukemia stem cell through inhibition of Wnt/β-catenin. Biochem Biophys Res Commun 2018; 503 (2): 956–962.

27. Hollmann MW, Gross A, Jelacin N, Durieux ME. Local anesthetic effects on priming and activation of human neutrophils. Anesthesiology 2001; 95 (1): 113–122.

28. Cata JP, Ramirez MF, Velasquez JF, Di AI, Popat KU, Gottumukkala V, Black DM, Lewis VO, Vauthey JN. Lidocaine Stimulates the Function of Natural Killer Cells in Different Experimental Settings. Anticancer Res 2017; 37 (9): 4727–4732.

29. Lan W, Harmon DC, Wang JH, Shorten GD, Redmond PH. Activated endothelial interleukin-1beta, -6, and -8 concentrations and intercellular adhesion molecule-1 expression are attenuated by lidocaine. Anesth Analg 2005; 100 (2): 409–412.

30. Gao J, Hu H, Wang X. Clinically relevant concentrations of lidocaine inhibit tumor angiogenesis through suppressing VEGF/VEGFR2 signaling. Cancer Chemother Pharmacol 2019; 83 (6): 1007–1015.

31. Zhang X, Pang W, Liu H, Wang J. Lidocine potentiates the cytotoxicity of 5-fluorouracil to choriocarcinoma cells by downregulating ABC transport proteins expression. J Cell Biochem 2019; 120 (10): 16533–16542.

32. Hermanns H, Hollmann MW, Stevens MF, Lirk P, Brandenburger T, Piegeler T, Werdehausen R. Molecular mechanisms of action of systemic lidocaine in acute and chronic pain: a narrative review. Br J Anaesth 2019; 123 (3): 335–349.

33. Zhong J, Hu J, Mao L, Ye G, Qiu K, Zhao Y, Hu S. Efficacy of Intravenous Lidocaine for Pain Relief in the Emergency Department: A Systematic Review and Meta-Analysis. Front Med (Lausanne) 2022; 8: 706844.

34. Weng M, Chen W, Hou W, Li L, Ding M, Miao C. The effect of neuraxial anesthesia on cancer recurrence and survival after cancer surgery: an updated meta-analysis. Oncotarget 2016; 7 (12): 15262–15273.

35. Li T, Meng X, Wang D, Wang Q, Ma J, Dai Z. Regional anesthesia did not improve postoperative long-term survival of tumor patients: a systematic review and meta-analysis of randomized controlled trials. World J Surg Oncol 2023; 21 (1): 68.

36. Duffek M, Skerenova M, Halasova E, Sarlinova M, Dzian A, Repiska V, Dobrovodsky A, Mistuna D, Bernadic M, Matakova T, Risk genetic polymorphism and haplotype associated with papillary thyroid cancer and their relation to associated diseases in Slovak population. Bratisl Med J 2022; 123 (7): 475–482.

37. Dubowitz JA, Cata JP, De Silva AP, Braat S, Shan D, Yee K, Hollande F, Martin O, Sloan EK, Riedel B; Global Onco-Anaesthesia Research Collaboration Group. Volatile anaesthesia and peri-operative outcomes related to cancer: a feasibility and pilot study for a large randomised control trial. Anaesthesia 2021; 76 (9): 1198–1206.

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