

Do local anesthetics have anticancer effects?

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Before answering this question some facts about surgery for cancer and the role of local anesthetics during perioperative period need to be re-emphasized.

Surgery is, at the moment, probably the main procedure in the context of multimodal approach of many cancer diseases with the intention to remove the whole tumor, or contrary, with palliative intention. Despite the intention to completely remove the tumor, surgery may promote metastasis; the following pathophysiological mechanisms may be involved:

- dispersal of tumor cells during surgical manipulation
- suppression of cell-mediated immunity (T-cell, B-cell, NK function) due to surgical stress, inflammation, etc
- augmented inflammatory response (e.g. IL-6, TNF)
- pain (during intra- and postoperative period)
- angiogenesis determined by increased plasma levels of VEGF and decreased plasma levels of endostatin (endogenous anti-angiogenetic factor) and angiostatin.

Local anesthetics can be administered during the perioperative period using multiple ways:

- infiltration (local anesthesia) for biopsy, resection of superficial tumors, during surgery (especially for pain management), percutaneously for cancer removal (e.g. ablation)
- regional anesthesia/analgesia (epidural, spinal) for cancer surgery or for pain management
- i.v. infusion during cancer surgery for analgesia/pain management (acute and postoperative chronic pain)
- others: TACE (transarterial chemoembolization).

Studies published in the last years have shown that, besides their use for perioperative pain management, local anesthetics may have anticancer effects.

There are multiple effects and mechanisms that may be responsible for these effects as it has been demonstrated by studies published so far. Local anesthetics may cause direct cytotoxicity, inhibition of cell proliferation and migration and have anti-invasive effects.

Cytotoxicity is characterized by cell apoptosis and the involved mechanisms may include caspase, MAPK pathway (p38) and, probably, Na⁺-channels (VGSC) and

apoptosis protein pathway.

Antiproliferative effects of local anesthetics may be mediated by epidermal growth factor receptors (EGFR), modulation of gene expression, DNA demethylation, inhibition of Src, modulation of p38, p53 and by VGSC.

Inhibition of migration is probably mediated by inhibition of Src, ICAM-1 and VGSC while, finally, anti-invasive effects may be produced via inhibition of Src, ICAM-1 and VGSC as demonstrated by some studies.

As can be seen, inhibition of VGSC is probably one of the most important mechanisms responsible for anticancer effects of local anesthetics, but other mechanisms may also be important.

This mosaic of actions leads to antiproliferative effects of local anesthetics that were demonstrated both in in vitro and in animal studies. Most of the in vitro studies on different types of cancer cells (breast, colon, hepatocarcinoma, tongue, etc) concluded that local anesthetics have anti-proliferative effects and these effects are time-, cancer type- and dose- dependent. Lidocaine is the most important drug that has been approached due to its pharmacokinetic/pharmacodynamic profile and possibilities to administer it.

Clinical evidences published so far were focused mostly on the effects of regional anesthesia in cancer patients undergoing surgery and the results are controversial. While there are some studies showing differences in outcome in patients (reduction in cancer recurrences and increase in recurrence-free survival) with regional anesthesia, there are studies showing no difference in outcome.

At the moment there is no randomized clinical study focusing on the effects of i.v./infiltration local anesthetics on the postoperative outcome in cancer patients that has been finalized but some clinical trials are on the way (ClinicalTrials.gov Identifier:NCT02839668 and ClinicalTrials.gov Identifier:NCT0278632, etc). There is also quite a great number of randomized clinical studies investigating the impact of regional anesthesia/analgesia on the outcome of patients undergoing surgery for cancer that are on the way.

Future randomized clinical trials on big numbers of patients will have to identify if the in vitro effects will be confirmed in humans, if these effects are the same in all tumors or are tumor-dependent and what is the most effective plasma concentration of local anesthetics (lidocaine) and duration of infusion (lidocaine) perioperatively during surgery for cancer.

References

Heaney A, Buggy DJ. *Br J Anaesth* 2012; 109 (suppl 1): i17-i28.

Tedore T. *Br J Anaesth* 2015;115 (suppl_2): ii34-ii45.

Chang YC, Liu CL, Chen MJ, et al. *Anesth Analg* 2014;118: 116-24

Chang YC, Hsu YC, Liu CL, Huang SY, Hu MC, Cheng SP. *PLoS ONE* 2014; 9: e89563

Sakaguchi M, Kuroda Y, Hirose M. *Anesth Analg* 2006; 102: 1103-7

Piegeler T, Votta-Velis EG, Liu G, et al. *Anesthesiology* 2012; 117: 548–59
Fraser SP, Diss JK, Chioni AM, et al. *Clin Cancer Res* 2005; 11: 5381–9
Lirk P, Berger R, Hollman MV, Fiegl H. *BJA* 2012;109 (2):200-207
Brisson L, Gillet L, Calaghan S, et al. *Oncogene* 2011; 30: 2070–6
Xing W, Chen DT, Pan JH, et al. *Anesthesiology* 2017;126(5):868-881.
Jurj A, Tomuleasa C, Tat T, Berindan-Neagoe I, Vesa S, Ionescu D. *JGLD* 2017;26
(1):45-50