Best Practice & Research Clinical Anaesthesiology 28 (2014) 139–151

Contents lists available at ScienceDirect

Best Practice & Research Clinical Anaesthesiology

journal homepage: www.elsevier.com/locate/bean

4

The role of analgesics in cancer propagation

Jonathan R. Meserve, MD, Senior Resident [a, *], Alan David Kaye, MD, PhD, DABA, DABPM, DABIPP, Professor and Chairman [b], Amit Prabhakar, MD, MS, Senior Resident [b], Richard D. Urman, MD, MBA, Assistant Professor [c]

[a] *Combined Pediatrics and Anesthesia Residency, Boston Children's Hospital and Brigham and Women's Hospital, Boston, MA, USA*
[b] *Department of Anesthesiology, Louisiana State University Health Science Center, New Orleans, LA, USA*
[c] *Brigham and Women's Hospital, Department of Anesthesiology, Perioperative and Pain Medicine, Boston, MA, USA*

Keywords:
analgesia
cancer recurrence
metastases
regional anesthesia
opioids

The treatment of cancer pain is paramount to both medical practitioner and patient in order to maximize quality of life. Cancer pain results from direct tumor effects as well as from surgical and medical treatments. Despite therapeutic advancements, morbidity and mortality in cancer care remains high, often from local recurrence or metastasis. Increasing evidence suggests analgesics affect the cellular milieu of malignant and nonmalignant cells and may influence cancer outcomes by directly stimulating tumor growth and inhibiting immune surveillance. Opioids have been shown to cause immunosuppression and stimulate malignant cells in vitro, though adjunct analgesics may additionally promote tumor cell growth. These results have led many to hypothesize that regional analgesic techniques may offer survival advantages to systemic analgesics. Thus far, the data do not support specific analgesic recommendations for the cancer patient, though ongoing prospective, randomized clinical trials are under way to better characterize the safest analgesic regimens for cancer patients.

* Corresponding author. Tel.: +1 617 877 8697; Fax: +1 617 582 6131.
E-mail addresses: jrmeserve@partners.org, jonathan.meserve@childrens.harvard.edu (J.R. Meserve).

http://dx.doi.org/10.1016/j.bpa.2014.04.004
1521-6896/

Introduction

Cancer treatment and cancer pain management are major health burdens worldwide. In 2008, 13% of all deaths worldwide and 25% of deaths in the United States were attributable to cancer. In the same year, an estimated 12.7 million new cases of cancer were diagnosed and by 2030, this number is projected to grow to 22 million new cases annually [1]. Despite many advances in cancer treatment modalities including novel surgical techniques, chemotherapy, radiation, and immunotherapy, tumor recurrence and metastasis are common and mortality high. In an effort to improve these outcomes, researchers and investigators have begun to look at the effect of anesthetics and analgesics on cancer biology and cancer outcomes.

The anesthesiologist's role in cancer pain management has historically focused on the treatment of acute surgical pain at the time of resection and refractory chronic pain from disease burden and therapy. Though most cancer patients will interact with an anesthesiologist for only a short period of time during treatment, recent reviews suggest that perioperative techniques and analgesics may stimulate cancer cells and suppress host anticancer immunity [2–5]. As such, the safety of analgesics in these patients has come under increasing scrutiny.

Analgesic agents are a diverse group of medications with multiple effecter sites in the human body and, as such, several mechanisms by which analgesics may worsen cancer outcomes have been suggested [2–5]. Many analgesics cause immunosuppression of the innate and humoral defense systems, which the body relies upon for cancer regulation. Of particular interest has been the suppressive effects of many different analgesics on natural killer (NK) cell function, a subgroup of the innate immune system responsible for lysing metastatic cancer cells and the primary host defense against malignant spread [6]. Analgesics additionally exert negative effects on the endocrine system further diminishing host tumor response. Finally, there are growing data on the direct effects of analgesics on cancer cell function and propagation, leading some to question the safety of certain systemic analgesics in cancer patients.

These investigations have prompted research into the potential benefit of regional anesthesia in cancer patients to prevent metastasis and improve cancer outcomes by limiting systemic analgesic exposure. This research is complicated, however, by data which demonstrate that both surgery and inadequately treated pain cause immunosuppression and are suspected to influence metastasis and recurrence [7].

The following is an evidence-based review of the influence of analgesics and postoperative pain modalities on cancer cells and cell-mediated immunity with specific interest in human studies demonstrating cancer outcomes based on postoperative and cancer pain management.

A literature search of PubMed© until June 2013 of the terms "anesthesia and cancer recurrence," "anesthesia and tumor progression," "opioids and cancer progression," "cox inhibitors and cancer," "regional anesthesia and cancer outcomes," "alpha agonists and cancer," "pain and immunosuppression," "endocrine effects of opioids," and "nonsteroidal anti-inflammatory drugs (NSAIDs) and cancer" were used as the sources of information for this article. Pertinent references from the reviewed articles were additionally included.

Opioid analgesia

Overview

Opioid pharmacotherapy has served as a mainstay of the treatment of cancer and surgical pain since morphine was isolated by Serturner in 1803 [8]. Our knowledge of opioids has expanded to the refinement of natural (codeine and morphine), semisynthetic (oxycodone and hydrocodone), and fully synthetic (fentanyl, methadone, and tramadol) opioids. Four different opioid receptors (mu, delta, kappa, and nociceptin) are expressed in the body with endogenous and exogenous opioid binding in the central nervous system (CNS) modulating downstream effectors and the perception of pain [6]. In the past 15 years, there has been a flurry of studies investigating the effects of opioids on tumor cell growth via direct (receptor stimulation) and indirect (immunosuppression and endocrine modulation) pathways.