Emerging Molecular Targets for the Management of Cancer Pain

Hai-Yan Sheng¹ · Yu-Qiu Zhang²

Received: 5 December 2019 / Accepted: 21 February 2020 / Published online: 8 June 2020
© Shanghai Institutes for Biological Sciences, CAS 2020

Pain is a common symptom in cancer patients, even long after the treatment has been completed. About 39.3%–66.4% of patients with cancer experience moderate to severe pain, especially those with advanced cancer. The experience of pain severely affects the quality of life, including eating, sleeping, thinking, working, and even continuing treatment. With the improvement of cancer treatment and the prolongation of survival time, safe and effective pain management has become a major problem encountered by many clinicians.

Current Analgesic Regimen for Cancer Pain

Cancer pain management often starts with the World Health Organization (WHO) analgesic ladder, which provides a guideline for clinicians to follow in treating cancer pain syndromes. The first step on the WHO ladder is focused on over-the-counter analgesics such as non-steroidal anti-inflammatory drugs. The second step is weak opioids, followed by stronger opioids in the third step. In the fourth step, adding interventions to cancer pain management is considered [1]. A recent paper by

Scarborough and Smith [2] provides an outline for the safe and effective management of cancer pain. The authors emphasize that, although opioids are the mainstay of treatment for moderate-to-severe cancer pain, several modalities of non-opioid treatment are available to these patients, including both pharmacological and non-pharmacological treatments. In addition, there are integrative therapies such as interventions, acupuncture analgesia, and adjuvant analgesics, that deserve consideration at each step in pain management [2]. Notably, antidepressants have been used as adjuvant medication in the management of cancer pain. Since pain has become a major fear and concern of cancer patients that makes them feel worried, lonely, stressed, angry, and depressed [3], relieving the pain-related negative emotions is clinically important in the improvement of their quality of life.

So far, knowledge of the effects of non-opioid analgesics on severe cancer pain is still limited. However, inflammation has been recognized as one of the hallmarks of cancer and is widely involved in the initiation and persistence of pathological pain in patients. Therefore, the development of drugs targeted at novel molecules based on anti-inflammatory mechanisms is essential for treating cancer pain.

✉ Yu-Qiu Zhang
yuqiuzhang@fudan.edu.cn

¹ Department of Pathophysiology, School of Basic Medical Sciences, Xinxiang Medical University, Xinxiang 453003, China

² State Key Laboratory of Medical Neurobiology and Ministry of Education Frontiers Center for Brain Science, Department of Translational Neuroscience, Jing'an District Centre Hospital of Shanghai, Institutes of Brain Science, Institute of Integrative Medicine, Fudan University, Shanghai 200032, China

Targeting Cytokines for the Treatment of Cancer Pain

Pro-inflammatory cytokines are critical regulators in tumor inflammation and the tumor microenvironment (Table 1). Strong evidence has shown that the expression of IL-1 β , TNF- α , and IL-6 is increased in malignant tumors and is involved in the development and maintenance of cancer pain [4]. IL-1 β is a downstream factor of the JAK2/STAT3

Table 1 Studies on cytokines and chemokines in cancer pain.

Study group	Cancer type	Study subject	Molecular target	Changes in level	Pain sensitization
Chen <i>et al.</i> 2019 [4]	Bone cancer	Rats	IL-6	↑	↑
			IL-1 β	↑	↑
			TNF- α	↑	↑
Xu <i>et al.</i> 2019 [5]	Bone cancer	Rats	IL-1 β	↑	↑
Liao <i>et al.</i> 2017 [6]	Bone cancer	Rats	TNF- α	↑	↑
Remeniuk <i>et al.</i> 2018 [7]	Breast cancer	Rats	IL-6	↑	↑
Al-Mazidi <i>et al.</i> 2018 [8]	Prostate cancer	Men	IL-6	↑	↑
Luo <i>et al.</i> 2019 [9]	Bone cancer	Mice	IL-17	↑	↑
Yang <i>et al.</i> 2015 [10]	Bone cancer	Rats	IL-18	↑	↑
Shen <i>et al.</i> 2014 [11]	Bone cancer	Rats	CXCL12/CXCR4	↑	↑
Ni <i>et al.</i> 2019 [13]	Bone cancer	Rats	CXCL1/CXCR2	↑	↑
Guo <i>et al.</i> 2016 [14]	Bone cancer	Rats	CCL2	↑	↑

↑ Increase.

signal pathway that plays a role in the response to neuron injury and inflammation. Bone cancer pain (BCP) is attenuated in rats when the activation of JAK2/STAT3 cascades is pharmacologically inhibited and the IL-1 β expression is downregulated in the spinal dorsal horn [5]. Etanercept, a TNF- α inhibitor, reduces sensitivity to pain and inhibits the expression of inflammatory factors in a BCP model [6]. The systemic administration of TB-2-081, a novel IL-6 signaling antagonist, prevents tumor-induced bone remodeling, reduces fractures, and diminishes the ongoing pain [7]. Besides, it has been found in clinical practice that an increased level of IL-6 is positively correlated with pain intensity in cancer pain patients treated with chemotherapy [8]. In a recent study, we showed that IL-17 from astrocytes enhances excitatory synaptic transmission, suppresses inhibitory synaptic transmission in spinal dorsal horn neurons, and elicits chemotherapy-induced pain [9]. The selective blockade of IL-17 receptors reduces paclitaxel-induced hypersensitivity. Another study from our lab found that inhibition of the P2X7/p-38/IL-18 pathway alleviates pain in the advanced phase of BCP [10].

Based on the above evidence, pro-inflammatory cytokines such as IL-1 β , TNF- α , IL-6, IL-17, and IL-18 might be considered as potential therapeutic targets for cancer-related pain management.

Targeting Chemokines for the Treatment of Cancer Pain

It has been suggested that chemokines, like cytokines, are involved in the development of cancer-related inflammation and pain sensitivity. Besides, chemokines play a role

in the regulation of cancer cell proliferation, metastasis, and angiogenesis and play an indispensable role in the modulation of the tumor microenvironment (Table 1).

The CXCL12/CXCR4 axis is involved in a series of physiological, biochemical, and pathological processes including cancer-induced bone pain. Targeting CXCR4 in both cancer cells and the surrounding stroma may provide a new and efficient strategy for cancer treatment. In BCP model, CXCL12 and CXCR4 are upregulated in the spinal cord. Inhibition of CXCL12 and CXCR4 suppresses tumor cell implantation-induced pain behaviors [11]. Recent studies have suggested that the CXCL8–CXCR1/2 signaling axis mediates the initiation and development of various cancers including breast cancer, prostate cancer, lung cancer, colorectal carcinoma, and melanoma, through the modulation of tumor proliferation, invasion, and migration in an autocrine or paracrine manner [12]. BCP-induced persistent mechanical allodynia is associated with upregulated expression of CXCL1 in the spinal cord and ventrolateral periaqueductal gray (vlPAG) as well as CXCR2, the primary receptor of CXCL1, in the vlPAG [13]. Either micro-administration of CXCL1-neutralizing antibody or antagonizing CXCR2 attenuates the BCP-induced mechanical allodynia [13]. Another important chemokine involved in the pathogenesis of BCP in the spinal cord is CCL2. In a rat model, prominent BCP-induced mechanical allodynia and thermal hyperalgesia are associated with upregulated expression of CCL2 in spinal astrocytes. Conversely, inhibition of the spinal JNK/CCL2 pathway and the attenuation of astrocytic activation downregulate the expression of CCL2 in rats and reduce pain behaviors [14]. CCL2 increases N-methyl-D-aspartate-induced excitatory postsynaptic currents in CCR2-

expressing excitatory neurons in spinal lamina IIo, which promotes central sensitization and leads to chronic pain [15]. Together, CXCL12/CXCR4, CXCL1/CXCR2, and CXCL8-CXCR1/2 signaling might be potential drug targets for alleviating cancer pain.

Other Molecular Targets for the Treatment of Cancer Pain

Endothelin-1 (ET-1) is a well-known amino-peptide, which causes pain during tumor growth by binding to its receptor ETAR. Blocking ETARs with BQ-123 reverses ET-1-induced pain in a breakthrough cancer pain model. Interestingly, ETBR, another ET-1 receptor, is significantly downregulated in oral cancer pain and BCP models. Re-expression of the transcriptionally-silenced ETBR gene by the DNA methyltransferases inhibitor decitabine attenuates nociceptive behavior in mice [16]. Thus, inhibiting ETARs or activating ETBRs could be an effective treatment for cancer pain.

Vascular endothelial growth factor A (VEGFA) promotes tumor neovascularization by binding to VEGF receptor 2 (VEGFR2), which is recognized as a potential target for anti-cancer pain. The mRNA and protein expression of both VEGFA and VEGFR2 are upregulated in a model of metastatic breast cancer and a bone pain model. Blocking VEGFA or VEGFR2 in the spinal cord significantly attenuates tumor-induced mechanical allodynia [17]. Tumor-derived VEGF increases pain sensitivity by selectively activating the expression of VEGFR1 in sensory neurons in both humans and mouse models. Genetic deletion and silencing of VEGFR1 in sensory neurons specifically attenuates cancer pain [18]. These findings suggest a parallel effect of targeting VEGFA/VEGFR2 and VEGF/VEGFR1 in cancer pain therapy.

The family of bioactive lipids such as fatty acids, sphingolipids, glycerophospholipids, sterol lipids, and prenol lipids, plays pro- and anti-tumorigenic roles in cancer pathogenesis. It is worth noting that resolvins and lipoxins, with anti-inflammatory, non-toxic, and non-immunosuppressive characteristics, are likely to be adjuvant therapeutic targets in cancer treatment. The level of sphingosine 1-phosphate (S1P), a bioactive sphingolipid metabolite, is increased in a BCP model. Consistent with this, antagonizing S1P receptor subtype 1 attenuates cancer-induced spontaneous flinching and guarding [19]. Another molecular target of great concern in relation to the treatment of cancer pain is programmed cell death ligand-1 (PD-L1). In melanoma-bearing mice, PD-L1 from the melanoma potently inhibits acute and chronic pain, whereas blocking either PD-L1 or its receptor PD-1 elicits spontaneous pain and mechanical allodynia, suggesting an

unrecognized role of PD-L1 as an endogenous pain inhibitor in cancer pain [20].

Conclusions

In conclusion, although clinicians have a consensus on the importance of cancer-pain management, efficient treatment remains limited. At least one-third of cancer patients suffer from undertreated pain. Given the predominant use of opioids and its intolerable side-effects, strong non-opioid analgesics are urgently needed. Preclinical studies suggest that specific targeting of inflammatory molecules effectively alleviates cancer pain in animal models. Therefore, targeted molecular therapy is a promising strategy in cancer pain management.

Acknowledgements This insight was supported by the National Natural Science Foundation of China (31420103903 and 31771164), funds from the Innovative Research Team of High-Level Local Universities in Shanghai, Shanghai Municipal Science and Technology Major Project (2018SHZDZX01), and funds from ZJLab.

Conflict of interest The authors declare that there is no conflict of interest.

References

1. Sindhi V, Erdek M. Interventional treatments for metastatic bone cancer pain. *Pain Manag* 2019, 9: 307–315.
2. Scarborough BM, Smith CB. Optimal pain management for patients with cancer in the modern era. *CA Cancer J Clin* 2018, 68: 182–196.
3. Guo QH, Tong QH, Lu N, Cao H, Yang L, Zhang YQ. Proteomic analysis of the hippocampus in mouse models of trigeminal neuralgia and inescapable shock-induced depression. *Neurosci Bull* 2018, 34: 74–84.
4. Chen J, Cong X, Zhan X, Zhou Z, Zheng W. Effects of parecoxib on pain threshold and inflammatory factors IL-1 β , IL-6 and TNF- in spinal cord of rats with bone cancer pain. *J Coll Physicians Surg Pak* 2019, 29: 528–531.
5. Xu M, Ni H, Xu L, Shen H, Deng H, Wang Y, *et al.* B14 ameliorates bone cancer pain through downregulating spinal interleukin-1 β via suppressing neuron JAK2/STAT3 pathway. *Mol Pain* 2019, 15: 1744806919886498.
6. Liao Y, Xu M. Efficacy and mechanism of action of etanercept in bone cancer pain. *Pharmazie* 2017, 72: 219–222.
7. Remeniuk B, King T, Sukhtankar D, Nippert A, Li N, Li F, *et al.* Disease modifying actions of interleukin-6 blockade in a rat model of bone cancer pain. *Pain* 2018, 159: 684–698.
8. Al-Mazidi S, Farhat K, Nedjadi T, Chaudhary A, Zin Al-Abidin O, Rabah D, *et al.* Association of interleukin-6 and other cytokines with self-reported pain in prostate cancer patients receiving chemotherapy. *Pain Med* 2018, 19: 1058–1066.
9. Luo H, Liu HZ, Zhang WW, Matsuda M, Lv N, Chen G, *et al.* Interleukin-17 regulates neuron-glia communications, synaptic transmission, and neuropathic pain after chemotherapy. *Cell Rep* 2019, 29: 2384–2397 e2385.
10. Yang Y, Li H, Li TT, Luo H, Gu XY, Lü N, *et al.* Delayed activation of spinal microglia contributes to the maintenance of

- bone cancer pain in female Wistar rats via P2X7 receptor and IL-18. *J Neurosci* 2015, 35: 7950–7963.
11. Shen W, Hu XM, Liu YN, Han Y, Chen LP, Wang CC, *et al.* CXCL12 in astrocytes contributes to bone cancer pain through CXCR4-mediated neuronal sensitization and glial activation in rat spinal cord. *J Neuroinflammation* 2014, 11: 1–14.
 12. Liu Q, Li A, Tian Y, Wu JD, Liu Y, Li T, *et al.* The CXCL8-CXCR1/2 pathways in cancer. *Cytokine Growth Factor Rev* 2016, 31: 61–71.
 13. Ni H, Wang Y, An K, Liu Q, Xu L, Zhu C, *et al.* Crosstalk between NF κ B-dependent astrocytic CXCL1 and neuron CXCR2 plays a role in descending pain facilitation. *Neuroinflammation* 2019, 16: 1–16.
 14. Guo CH, Bai L, Wu HH, Yang J, Cai GH, Wang X, *et al.* The analgesic effect of rolipram is associated with the inhibition of the activation of the spinal astrocytic JNK/CCL2 pathway in bone cancer pain. *Int J Mol Med* 2016, 38: 1433–1442.
 15. Xie RG, Gao YJ, Park CK, Lu N, Luo C, Wang WT, *et al.* Spinal CCL2 promotes central sensitization, long-term potentiation, and inflammatory pain via CCR2: Further insights into molecular, synaptic, and cellular mechanisms. *Neurosci Bull* 2018, 34: 13–21.
 16. Appel CK, Scheff NN, Viet CT, Schmidt BL, Heegaard AM. Decitabine attenuates nociceptive behavior in a murine model of bone cancer pain. *Pain* 2019, 160: 619–631.
 17. Hu XM, Yang W, Du LX, Cui WQ, Mi WL, Mao-Ying QL, *et al.* Vascular endothelial growth factor A signaling promotes spinal central sensitization and pain-related behaviors in female rats with bone cancer. *Anesthesiology* 2019, 131: 1125–1147.
 18. Selvaraj D, Gangadharan V, Michalski CW, Kurejova M, Stosser S, Srivastava K, *et al.* A functional role for VEGFR1 expressed in peripheral sensory neurons in cancer pain. *Cancer Cell* 2015, 27: 780–796.
 19. Grenald SA, Doyle TM, Zhang H, Slosky LM, Chen Z, Largent-Milnes TM, *et al.* Targeting the S1P/S1PR1 axis mitigates cancer-induced bone pain and neuroinflammation. *Pain* 2017, 158: 1733–1742.
 20. Chen G, Kim YH, Li H, Luo H, Liu DL, Zhang ZJ, *et al.* PD-L1 inhibits acute and chronic pain by suppressing nociceptive neuron activity via PD-1. *Nat Neurosci* 2017 20: 917–926.