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Concomitant Use of Analgesics and Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer: A Pharmacodynamics Perspective

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ABSTRACT

The invention of immunotherapy, such as immune checkpoint inhibitors (ICIs) for advanced-stage non-small cell lung cancer (NSCLC), has become a new standard of care for a defined group of NSCLC patients. However, the possible impacts of ICI interactions with analgesics for alleviating cancer-related pain are unclear and lack clinical evidence. Many studies have indicated that opioids detrimentally affect the immune system, possibly harming patients of ongoing immunotherapy. Opioids may repress the immune system in various ways, including impairing T cell function, upregulating immunosuppressor Treg cells, and interrupting intestinal microflora composition that disrupts the entire immune system. Furthermore, opioids can influence tumor progression and metastasis directly as opioid receptors are overexpressed in several types of NSCLC. In contrast, another analgesic acting on cyclooxygenase (COX) inhibition (i.e., NSAIDs) may be a candidate for adjuvant therapy since COX-2 is also expressed in the tumor cells of NSCLC patients. In addition, COX-2 is associated with tumor proliferation and metastasis. Therefore, both prospective and retrospective studies should confirm the advantages and disadvantages of the concurrent use of analgesics and ICIs in a clinical setting.

Keywords: immune checkpoint blockers, NSAIDs, opioids, T-lymphocyte, gut microbiota

1. Introduction

Lung cancer is the primary cause of cancer mortality in men and the second-highest contributor to cancer mortality (after breast cancer) in women globally. In 2018, the World Health Organization (WHO) estimated 2.09 million cases and 1.76 million deaths caused by this cancer (Torre et al., 2016; WHO, 2018). Among these cases, non-small cell lung carcinomas (NSCLC) accounted for 85%-90% of all lung cancer types (Lemjabbar-Alaoui et al., 2015). Treatment options for NSCLC vary, including surgery, radiotherapy, platinum-based chemotherapy, targeted therapy, and immunotherapy, depending on cancer stages, histologic classification, and genetic alteration. Most NSCLC patients (>70%) are diagnosed during stages III and IV (Cheema et al., 2019), and platinum-based chemotherapies have become standard care, although their clinical efficacy is restrained by hemato- and neuro-toxicities (Hirsch et al., 2017; Lemjabbar-Alaoui et al., 2015). Recently, molecularly targeted agents, such as erlotinib and gefitinib, which specifically block epidermal growth factor receptors (EGFRs), have been indicated as the first-line treatment for patients who carry an EGFR mutation in their tumors. However, these agents cover only 10%-17% of the NSCLC patient population (Hirsch et al., 2017; Langer, 2015). Meanwhile, 31% of NSCLC patients' tumor oncogenic drivers remain undetected. The availability of suitable drugs for patients lacking a detectable gene mutation presents a drawback to this targeted treatment (Hirsch et al., 2017; Mayekar and Bivona, 2017). Furthermore, improvement in lung cancer treatment has plateaued over the last ten years. Hence, a novel strategy is needed for broader applicability to encounter another pathophysiology of tumor evasion from immunosurveillance.

Although tumors express antigens recognizable by the immune system, they possess poor immunogenicity. Hence, antigen presentation alone is inadequate in activating T cells. Besides the binding of the T cell receptor (TCR) to the antigenic peptide bound to the major histocompatibility complex (MHC) of the antigen-presenting cell (APC), the additional stimulatory co-signal provided by co-receptors is necessary. These co-receptors are crucial for regulating T cell response and balancing co-stimulatory and inhibitory (i.e., immune checkpoint) signals. Cancerous cells utilize several strategies to evade immune checkpoints regulated by T cells, enabling them to grow and spread unchecked (Pardoll, 2012). These strategies provide a negative immune checkpoint signal to T cells, which is specific against tumor antigens. Thus, anticancer responses from the immune system could be repressed. Monoclonal antibodies have been indicated as a blockade to immune checkpoint pathways, including cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed death protein 1 (PD-1), and its ligands, PD-L1 (Abdel Karim and Kelly, 2019; Langer, 2015; Memon and Patel, 2019). To date, only PD-1 (pembrolizumab and nivolumab) and PD-L1 (atezolizumab and

durvalumab) have been used for NSCLC patients in a clinical setting after gaining Food and Drug Administration (FDA) approval, as first-line monotherapy, in combination, or as second-line therapy after chemotherapy (Abdel Karim and Kelly, 2019; Brahmer et al., 2017). Thus, immune checkpoint inhibitors (ICIs) have continued to expand as an active field of research in advanced NSCLC.

In clinical practice, challenges in treating cancer patients rely on eradicating the tumor and addressing the symptoms while focusing on the current medication's adverse events (Simoff et al., 2013; Temel et al., 2006; Walling et al., 2015). Pain, the most distressing symptom causing depression and anxiety, is experienced by 58.2% of advanced-stage lung cancer patients (Walling et al., 2015). Hence, analgesic use is critical but generates new challenges for drug interactions due to concomitant medications. Therefore, this review provides information on (i) the pharmacological mechanism in which analgesics interfere with the therapeutic efficacy of the ICI specific for NSCLC, and (ii) the best type of analgesics, including dosage regimentation when used concomitantly. The ICI here is limited to the drugs acting on CTLA-4 and PD-1 pathways as they have been widely used in clinical settings and trials.

2. Pharmacodynamics of Immune Checkpoint Inhibitors

Under non-pathologic conditions, immune checkpoints are essential to prevent autoimmunity and protect tissue damage from excessive inflammation when the immune system neutralizes pathogenic infections. Moreover, tumor cells can dysregulate immune checkpoint ligands and receptors, resulting in overexpression in the cell itself and surrounded non-transformed cells in the tumor microenvironment. Therefore, ICIs target the receptors or ligands expressed on the lymphocyte to augment antitumor activity (Pardoll, 2012).

This section first discusses the pharmacodynamics of ICIs before elaborating on the analgesic interference mechanism. The concomitant use of ICIs and analgesics is mainly interconnected in the immune system. Thus, each drug's adverse effects are highlighted to determine if side effects increase when a drug is combined simultaneously.

2.1 Blockage of CTLA-4 in the early phase of T cell activation

CTLA-4 was the first clinically targeted inhibitory T cell co-receptor because the antagonist CTLA-4 antibody could induce therapeutic antitumor immunity in the mouse model in 1996 (Leach et al., 1996). Essentially, CTLA-4 is a counterbalance of CD28, a co-stimulatory receptor of T cell. T cell activation mostly requires CD28 colligation, in addition to the binding of TCR to the peptide antigen,

for stabilizing messenger RNA (mRNA) of cytokines and inducing the activation of the nuclear factor κB (NF-κB) and the nuclear factor of activated T cells (NFAT). CD28 is expressed and localized on the surface of naive and activated T cells, while CTLA-4 is primarily located in intracellular compartments and expressed in response to TCR/CD28 co-stimulation at the early activation stages. Upon TCR ligation, calcium influx and the TCR-interacting molecule (TRIM) control the release of CTLA-4 from the trans-Golgi network (TGN) or lysosome or endosome to the cell surface (Rudd et al., 2009).

To our knowledge, the intrinsic signaling in which CTLA-4 dampens T cells' immune response has been controversially discussed with no consensus of the distinct signaling pathway of CTLA-4 (Mitsuiki et al., 2019; Walker and Sansom, 2015). However, it is widely accepted that CTLA-4 and CD28 bind to the same ligands CD80 (B7-1) and CD86 (B7-2). The overall binding affinity is higher for CTLA-4 than CD28, so that the intrinsic inhibitory signal will rise after CTLA-4 outcompetes the binding of CD28, whereas CTLA-4 is activated later than CD28 (Figure 1). Furthermore, other concepts of CTLA-4 functions have been proposed and discussed, including a magnification of regulatory T (Treg) cell immunosuppressive activity (Gardner et al., 2014; Leach et al., 1996; Pardoll, 2012; Rudd et al., 2009). Specifically, in NSCLC patients, Erfani et al. (2012) stated that CTLA-4 molecules found in the intracellular compartment were higher than presented on the surface of lymphocytes subsets. However, only surface CTLA-4 on the $CD8^+$ lymphocytes was significantly higher than control healthy subjects, which was inconsistent with the regulation of CTLA-4 expression. Nevertheless, CTLA-4 is rapidly internalized immediately after activation. Thus, this internalization would also serve as an inhibitory mechanism due to the TCR-antigen complex's co-internalization resulting in the unresponsiveness of lymphocytes (Erfani et al., 2012).

Anti-CTLA-4 agents like ipilimumab and tremelimumab have received FDA approval to treat advanced melanoma and mesothelioma, respectively, but not for lung cancer. Moreover, the clinicaltrial.gov database lists at least 16 active phase-3,4 clinical trials for NSCLC treatment using anti-CTLA-4, such as ipilimumab and tremelimumab. Among these trials, anti-CTLA-4 is mostly used in combination with anti-PD-1 (e.g., pembrolizumab, nivolumab, REGN2810) or PD-L1 (durvalumab), as shown in Table 1 (US National Library of Medicine, 2015). Many studies used drug combination of ipilimumab and nivolumab, and one of them has completed results (NCT02477826). It showed that among patients with a tumor mutational burden of at least ten mutations per megabase, those who received nivolumab plus ipilimumab have significantly longer progression-free survival (PFS) than patients receiving platinum doublet chemotherapy (Hellmann et al., 2018). Regarding the safety profile of this combination, the incidence of treatment-related adverse events was similar compared

to chemotherapy. Then, the most common adverse events were related to skin reactions (33.9%); (Hellmann et al., 2018).

2.2 Anti PD-1/PD-L1: The more specific the target, the more potent the activity

PD-1, like CTLA-4, is a member of the co-inhibitory receptor that serves as an immune checkpoint. In contrast to CTLA-4, which has a significant role in the early stage of T cell activation, PD-1 mainly expresses on cells within the tumor microenvironment to limit inflammatory response and autoimmunity in later stages. PD-1-known ligands, PD-L1 (B7-H1 or CD274) and PD-L2 (B7-DC or CD273), are inhibitory. However, PD-L1 expression is more prevalent than PD-L2 in various cancers, hence becoming a target for immunotherapy. PD-1/PD-L1 interaction is activated by several potent inducers, such as IFN-γ and TNF-α, produced by activated type 1 T cells. Meanwhile, GM-CSF and VEGF are secreted by a variety of cancer stromal cells (Figure 2a), and PD-L1 is upregulated by oncogenes (inherent immune resistance) so that cancer cells can overexpress PD-L1 (He et al., 2015; Pardoll, 2012; Figure 2b). D'Incecco et al. (2015) confirmed this finding in their study of PD-1/PD-L1 expression in tumor cells of NSCLC patients, revealing that PD-1 expression was mostly presented in the patients with KRAS mutations, while the ligand PD-L1 was significantly associated with the presence of EGFR mutations or ALK translocations (D'Incecco et al., 2015). Comparing PD-1/PD-L1 expression in NSCLC patients and healthy donors, Arrieta et al. (2017) and Meniawy et al. (2016) observed peripheral blood mononuclear cells (PBMCs) from both subjects. They found that NSCLC patients had a significantly higher proportion of PD-L1 in circulating $CD3^+$ T lymphocyte and $CD3^+CD8^+$ cytotoxic T-lymphocyte cells than healthy donors (Arrieta et al., 2017; Meniawy et al., 2016). PD-1/PD-L1 ligation affects the immune system's suppression through multiple mechanisms, such as inducing apoptosis of activated T cells, facilitating T cell energy and exhaustion, and enhancing Treg cell function (He et al., 2015).

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer V.2.2020 include all FDA-approved anti-PD-1/PD-L1 in the therapy recommendation for advanced or metastatic NSCLC with PD-L1 expression ≥ 1% (guideline code NSCL-28/29), except for durvalumab. Durvalumab is proposed as a consolidation treatment following the absence of disease progression after radiation therapy regardless of the cancer type or stage (guideline code NSCL-E/3/6/7/9/12/13/). Among these immunotherapies, pembrolizumab (Keytruda®) is the only assigned single agent for the first-line treatment of patients expressing PD-L1 ≥ 50%, and even ≥1%-49% expression can be considered for patients with poor performance status or contraindicated to combination chemotherapy (National Comprehensive Cancer Network, 2019). Besides, many ongoing phase-3/4 clinical trials investigate the efficacy and safety of PD-1 or PD-L1

either as monotherapy or in combination with chemotherapy, kinase inhibitors, or monoclonal antibody targetting TIGIT receptor (Table 1).

Thus, the ICI works mainly to manipulate the endogenous antitumor activity of T lymphocyte subsets, mainly by blocking the inhibitory co-receptors that affect downstream signaling. T cells become the main focus of efforts to regain their immune capacity to (1) selectively distinguish cancerous antigens from their normal counterparts, (2) directly kill cancer cells, and (3) govern the diverse immune response that integrates many other cells, including dendritic cells, B lymphocytes, NK cells, and others (Pardoll, 2012). Since ICI therapy's success relies on patients' immunity response, other substances that intervene in the immune system could hamper ICI effectiveness, such as drugs to alleviate symptoms like pain.

Table 1. Ongoing clinical trials phase 3/4 of immune checkpoint inhibitors for NSCLC (The data was compiled from clinicaltrials.gov and accessed on April 2021)

ICI agents	Treatment Regimen	Clinical Trial Identifier
Anti-CTLA-4		
Ipilimumab	Ipilimumab+Nivolumab	NCT02477826, NCT02998528, NCT03351361, NCT03469960, NCT03391869, NCT02869789
	Ipilimumab+Nivolumab+Chemoradiotherapy	NCT04026412, NCT03215706
	Ipilimumab+Pembrolizumab	NCT03302234
	Ipilimumab+REGN2810	NCT03515629
	Ipilimumab+REGN2810 with Chemoterapy	NCT03409614
Tremelimumab	Tremelimumab+Durvalumab	NCT02453282, NCT02542293
	Tremelimumab+Durvalumab+Chemotherapy	NCT03164616
Anti-PD-1		
Nivolumab	Nivolumab (monotherapy)	NCT03542461, NCT02066636, NCT02477826, NCT01673867, NCT01642004, NCT03195491, NCT02613507, NCT02595944, NCT02713867, NCT04157985, NCT02041533
	Nivolumab+Chemoradiotherapy	NCT04026412
	Nivolumab+Chemotherapy	NCT02477826, NCT02864251, NCT02998528, NCT04025879, NCT04564157
	Nivolumab+ Sitravatinib	NCT03906071
Pembrolizumab	Pembrolizumab (monotherapy)	NCT03134456, NCT04676412, NCT04738487, NCT03715205, NCT03867175, NCT04475939
	Pembrolizumab+Chemotherapy	NCT04547504, NCT03425643, NCT03774732, NCT04267848, NCT04222972, NCT04194944, NCT03793179
	Pembrolizumab+Lenvatinib	NCT04676412, NCT03976375
	Pembrolizumab+Radiation	NCT03924869, NCT03867175
	Pembrolizumab+Chemoradiation	NCT04380636
	Pembrolizumab+Chemotherapy+Lenvatinib	NCT04716933
	Pembrolizumab+Carboplatin+Taxane+ Olaparib	NCT03976362, NCT03976323

	Pembrolizumab+Chemotherapy+ Radiotherapy	NCT03774732
	Pembrolizumab+Niraparib	NCT04475939
Anti-PD-L1		
Durvalumab	Durvalumab (monotherapy)	NCT04381494, NCT04513925, NCT04642469, NCT03706690, NCT04078152
	Durvalumab+Chemotherapy	NCT03800134, NCT04385368, NCT04092283
	Durvalumab+Chemoradiotherapy	NCT04026412, NCT04380636, NCT01993810
	Durvalumab+Tremelimumab+Chemotherapy	NCT03164616
	Durvalumab+Radiotherapy	NCT03833154
Atezolizumab	Atezolizumab (monotherapy)	NCT03991403, NCT03735121, NCT03178552
	Atezolizumab+Tiragolumab	NCT04513925, NCT04294810
	Atezolizumab+Chemotherapy	NCT03977194, NCT03456063
	Atezolizumab+Radiotherapy	NCT04214262
	Atezolizumab+Bevazicumab+Chemotherapy	NCT04194203
	Atezolizumab+Cabozantinib	NCT04471428

3

3. Analgesics Affecting the Immune System

The chance of drug interaction occuring between ICIs and analgesics is high, as Simone et al. (2012) reported that 92% of lung cancer patients experience pain either due to the malignancy or the treatment (Simone et al., 2012). Moreover, a retrospective study of analgesic prescription patterns in over 10,000 lung cancer patients showed that approximately 55% were prescribed level 3 analgesics, including morphine, diamorphine, fentanyl, alfentanil. Meanwhile, another half of the patients received weaker opioids (e.g., codeine, tramadol) or non-steroidal anti-inflammatory drugs (NSAIDs). This study recorded the prescription of these analgesics in the last three months of lung cancer patients' lives (Gao et al., 2011). Although the information on the cancer type and previous/current cancer therapy were unavailable, this study demonstrated that at least half the patients received opioids for any purpose.

Opioids are potent analgesics for severe pain, yet they are accompanied by many non-analgesic effects ranging from constipation to respiratory depression. Another potential risk is immune response suppression, which could be a drawback for immune-related anticancer treatment. The crosstalk between opioids and anticancer immunity has been investigated widely, with varying results depending on drug type and duration of use (Liang et al., 2016). Unlike opioids that may repress the immune system, NSAIDs, particularly selective cyclooxygenase-2 (COX-2) inhibitors, may corroborate cancer therapy's response rate or at least not contraindicate it (Yokouchi and Kanazawa, 2015). Hence, this section discusses the effects of analgesics, both opioids, and NSAIDs, within the immune system, particularly which potentially interrupt the mechanism of ICI pharmacodynamics, either directly or indirectly.

3.1 Opioid-mediated adaptive immune compromise

Many studies have shown that chronic opioid exposure is associated with the shorter survival of NSCLC patients, although conclusions have been drawn from retrospective studies of morphine use in postoperative settings as palliative care or before chemotherapy initiation (Hasegawa et al., 2018; Wang et al., 2015; Zylla et al., 2014). Recent studies have emerged that identify opioids' immunosuppressive characteristics, causing NSCLC patients' poor survival. Review articles written by Liang et al.(Liang et al., 2016), Plein and Rittner(Plein and Rittner, 2018), Roy et al.(Roy et al., 2011), and Zajączkowska et al.(Zajaczkowska et al., 2018) have comprehensively presented the mechanism of how opioids affect both innate and adaptive immunity.

Because of ICIs' modulation to T lymphocyte subsets, we examine the effect of opioids, especially morphine, on T cells and their relation to the adaptive immune system. Morphine is the first-line

opioid employed to manage cancer-related pain. Morphine's effects are typically mediated by specific opioid receptors (μ, δ, and κ) either in the central or peripheral nervous system. Outside the nervous system, opioid receptors are also found in T lymphocytes, indicating opioids' ability to modulate the immune system. Liang et al. (2016) stated that chronic use of morphine (at least 12 months) causes an increase of μ opioid receptor (MOR) mRNA expression in T lymphocytes (also in B lymphocytes) compared to healthy subjects (Liang et al., 2016). Interestingly, this increase is induced by CD3/CD28-mediated T cell activation, and the transcription of MOR is further mediated by activator protein-1 (AP-1), NF-κB, and NFAT. These proteins are activated following CD28 ligation (Börner et al., 2008), as mentioned above (Section 2.1).

Another *in vitro* study demonstrated that morphine inhibits the transcription of IL-2, a hallmark cytokine of T cell activation, as well as AP-1, NF-κB, and NFAT, which transactivate IL-2. Furthermore, the incubation of opioids (morphine, β-endorphin, and D-penicillamine2-D-penicillamine5-enkephalin) causes a marked increase of cAMP, which in turn activates protein kinase A that augments the activity of C-terminal Src kinase culminating in blocking the initiation of TCR signaling (Börner et al., 2009). Thus, the overexpression of MOR leads to T cell function impairment at the activation stage.

In the professional APC that links the innate and adaptive immune systems, Wang et al. (2011) showed that IL-23, produced by dendritic cells, was inhibited by morphine in the *S. pneumoniae* infection model (Wang et al., 2011). Nevertheless, the disruption of IL-23 is considered in the context of innate immunity. In terms of the APC function in T cell activation, morphine exposure down-regulates MHC class II expression, especially on B cells, which inhibits the activation and proliferation of the $CD4^+$ T cell (Roy et al., 2011). Single morphine injection (10 mg/kg) has been shown to decrease basal MHC class II protein expression on B lymphocytes through the hypothalamic-pituitary-adrenal axis. In the central nervous system, opioids activate the hypothalamus, increasing corticosterone release from the adrenal gland. Thus, corticosterone could also reduce basal MHC class II expression. Additionally, this suppression was not presented in morphine-treated adrenalectomized rat models. Eventually, the authors showed that prolonged morphine exposure (using protocol demonstrated to produce tolerance) does not down-regulate MHC-II expression, while morphine withdrawal exerts both a renewed increase in circulating corticosterone levels and a renewed suppression of MHC-II (Nugent et al., 2011; Roy et al., 2011).

However, not all immune cells are favorable to the antitumor response like the immunosuppressive regulatory T (Treg) cell. Long-term morphine exposure (12 weeks) exhibited an increase of circulating

Treg ($CD25^{+}FoxP3^{+}$) cells by approximately five-fold in PBMCs sample of rhesus macaques (Cornwell et al., 2013). Furthermore, in breast cancer patients who have undergone resection and were given sufentanil or fentanyl, their Treg number increased after seven days compared to day zero before anesthesia. However, this study did not determine the patients' long-term outcome and the Treg function (Boland and Pockley, 2018; Gong et al., 2014). It is also reported that the percentage of Treg cells obtained from 23 new cases of NSCLC was significantly higher than 16 healthy volunteers. Moreover, this proportion was higher with the increase of cancer stage and in metastatic stage (Erfani et al., 2012), indicating Treg cells' role in cancer progression. Given Treg cells' capacity to repress antitumor immunity, their role becomes crucial for patients with immunotherapy. Takeuchi and Nishikawa (2016) mentioned that Treg cells express immune checkpoint molecules such as CTLA-4 and PD-1. Thus, the success of antibodies blocking these molecules depends on Treg cells' depletion that expresses CTLA-4 or PD-1 (Takeuchi and Nishikawa, 2016).

Although research has possibly identified how opioids can affect immunity, appropriate *in vitro* and *in vivo* studies must elucidate the detailed mechanism in which the opioids could affect ICI efficacy. Thus, exploring mechanisms could help predict the interaction between opioids and ICIs to avoid detrimental effects when used concomitantly.

3.2 Opioids directly affect cancer cells

Opioids can also directly affect cancer cells due to MOR overexpression in several types of NSCLC. MOR expression on human NSCLC biopsies has revealed a significant increase compared to healthy adjacent tissue samples using immunohistochemistry. Narrowed analysis of samples with lymph node metastasis have demonstrated even a higher increase of MOR than the total lung cancer cohort. Furthermore, MOR staining intensity also increased with the increase of cancer stage (Singleton et al., 2014). Thus, cancer may potentially progress and metastasize through Akt and mTOR pathways. In this case, both exogenous and endogenous opioids can have the same effect, although the former is still debatable (Lennon et al., 2012). Furthermore, morphine has been shown to induce EGFR phosphorylation via MOR, leading to downstream signaling of MAPK/ERK, Akt, and corroborating cancer cell proliferation and invasion. Therefore, there is direct involvement of opioids in the progression of NSCLC (Fujioka et al., 2011). From the other perspective, there is an opportunity to develop adjunctive therapy using antagonists targeting peripheral opioid receptors.

3.3 Opioid causes gut dysbiosis

Morphine and other opioid types interrupt the immune system directly to the immune cell or indirectly to the first layer of surface barriers located in the gut. In the gut lumen, a symbiotic

relationship is established between commensal microbiota and the host immunity constructed by intestinal epithelial cells and several mucosal barriers. This complex and dynamic interaction contributes to gut homeostasis, whereby the gut microbiota stimulates epithelial cells, releasing cytokines and chemokines, inducing T cells, and delivering antigens to APC in lymphoid tissue. These barriers also spatially segregate microorganisms and host immune cells avoiding unnecessary immune response. Moreover, intestinal microbiota provides vital aids by digesting dietary fibers, producing vitamin B and K, and metabolizing bile acids (Okumura and Takeda, 2017). Therefore, any changes in the structural or functional microbiota known as "gut dysbiosis" increase the susceptibility to pathogenic infection while reciprocally, the host immune dysregulation causes a perturbation in the intestinal microbiome as well (Cianci et al., 2019; Wang and Roy, 2017).

Chronic opioid administration has been associated with several GI-adverse reactions, such as constipation, bloating, nausea, and vomiting. Precisely, it further affects (1) intestinal function by inhibiting protective mucus and bicarbonate secretion and disrupting coordination of myenteric activity, hence prolonging the transit time and increasing the risk potential of bacterial translocation, (2) intestinal epithelial integrity by damaging tight junction protein (ZO-1) coordination via activation of TLR (toll-like receptor) 2 and 4 by MOR ligands, and (3) gut microbial by shifting composition towards the expansion of gram-positive pathogens resulting in a reduction of bile-deconjugating bacteria strains (Banerjee et al., 2016; Plein and Rittner, 2018; Wang and Roy, 2017). Thus, opioids possess harmful effects on the gut microenvironment leading to disruption of the immune system.

3.4 COX inhibitor for NSCLC patient: Analgesic or anticancer?

In contrast to opioids, NSAIDs seem to have a favorable effect on the immune system in eradicating tumor cells. A wealth of evidence obtained from *in vitro* and *in vivo* studies has demonstrated that COX-2 is expressed in many solid tumors, including NSCLC, and is associated with tumor proliferation, metastasis, poor prognosis, and resistance to certain antitumor and even radiation (Hattar et al., 2013; Jiang et al., 2019; Wang, 2019; Zhang et al., 2019).

In 2018, a meta-analysis of seven randomized controlled trials (RCTs) involving 1,559 patients revealed that adding celecoxib to systemic cancer therapy or radiotherapy did not significantly improve the overall response rate (ORR) compared to the placebo. However, further subgroup analysis considering the line of treatment showed that concomitant celecoxib with first-line chemotherapy significantly increased the ORR while the second-line treatment showed no significant difference (Yi et al., 2018). Unfortunately, this study did not consider the expression of COX-2 from tumor cells as not all patients had abundant expression.

144

145 COX-2 expression analysis can be beneficial as a biomarker to determine the prognosis value of the
146 disease or as a predictive marker for patients who may benefit from COX-2 inhibitors. To our
147 knowledge, the latest systematic review and meta-analysis explaining the association between COX-2
148 expression and its impact on patient survival was published in 2013. Two studies were issued almost
149 concurrently, with some similar resources. However, their results were slightly different. Jiang et al.
150 (2013) stated that overexpressed COX-2 in NSCLC patients' tumor biopsies was implicated with the
151 poor prognosis, while Zhan et al. (2013) showed no significant impact. Nonetheless, both research
152 teams had a common result with their subgroup analysis for stage I NSCLC: COX-2 overexpression
153 had a detrimental effect on patient survival (Jiang et al., 2013; Zhan et al., 2013). Thus, at the earliest
154 phase of NSCLC development, COX-2 could serve as either a prognostic factor of the disease or a
155 predictor in selecting patients eligible for adjuvant cancer therapy.
156
157 The first biomarker-driven phase III RCT in the US, CALGB 30203, used the COX-2 index to select
158 patients eligible for the study before they were randomized for the treatment arm receiving
159 celecoxib or the placebo arm. Despite this advanced method, the PFS or OS value of the celecoxib
160 group did not considerably improve compared to the placebo group, including the subgroup of
161 patients whose tumors had COX-2 index ≥ 4. Hence, the authors argued against using
162 immunohistochemistry (IHC) in examining COX-2, suggesting the use of urinary prostaglandin E2
163 metabolite (PGE-M) instead. PGE-M allows for a real-time measurement compared to IHC, which is
164 usually only assessed once and has an issue in antibodies' specificity (Edelman et al., 2017).
165
166 **4. Drug Interaction between Analgesics and ICIs**
167 The potency of long-term and concomitant exposure to analgesics and ICIs is undeniable. However,
168 the role of analgesic use for relieving pain in cancer patients treated with ICIs lacks clinical evidence.
169 Hence, this review discusses these drugs' possible interactions, drawing connections based on their
170 pharmacodynamic activities. Generally, chronic opioid exposure is associated with the shorter
171 survival of NSCLC patients due to opioids' immunosuppressive properties (Hasegawa et al., 2018;
172 Wang et al., 2015; Zylla et al., 2014). Meanwhile, cancer therapy employing ICI requires a robust
173 immune response from the patient; thus, antitumor like T cells still have enough energy to limit
174 cancer growth and possibly eradicate it. As mentioned, opioids may hamper ICIs within the immune
175 system in many ways, such as reducing T cell function through the overexpression of MOR (Börner et
176 al., 2009, 2008) or downregulation of MHC class II (Liang et al., 2016), increasing immunosuppressor
177 Treg cells (Erfani et al., 2012), directly promoting tumor cell proliferation and invasion (Singleton et
178 al., 2014), and interrupting the gut microbiome composition leading to disruption of gut homeostasis

and the whole immune system (Banerjee et al., 2016; Plein and Rittner, 2018; Wang and Roy, 2017; Figure 3).

Regarding the effect of opioids interrupting ICI through microbiota, Routy et al. (2018) demonstrated that gut microbiome composition influences anti-PD-1 efficacy. They also showed that fecal microbiota transplantation (FMT) taken from ICI-sensitive cancer patients enhanced the antitumor activity of PD-1 inhibitor in germ-free or antibiotic-treated mice. In contrast, FMT from ICI-insensitive cancer patients did not show a significant result. This latter group was then treated with oral supplementation of *Akkermansia muciniphila* (considered "good bacteria"), resulting in the restoration of PD-1 blockade activity (Routy et al., 2018). Furthermore, other studies have explained that ICI (anti-CTLA-4 and PD-1) response requires the presence of distinct bacteria species such as *Bacteroides* sp. and *Bifidobacterium* (Sivan et al., 2015; Vétizou et al., 2015).

However, to our knowledge, no article explicitly explains the correlation between opioid exposure and ICI efficacy, especially with the case of NSCLC. Therefore, we can only hypothesize that opioids affect ICI efficacy based on two separate articles. For instance, one article stated that opioids cause gut dysbiosis (Banerjee et al., 2016), while another article stated that gut microbiota influences anti-PD-1 efficacy (Routy et al., 2018). Thus, we conclude that opioids impact ICI efficacy through gut homeostasis disruption. Therefore, further *in vitro* and *in vivo* studies are needed to prove our hypothesis.

Besides, two retrospective studies evaluated the effect of opioids on the prognosis of patients treated with ICIs. The first study from Taniguchi et al. (2020) reported that regular opioid usage during nivolumab treatment initiation impairs the ORR and progression-free survival (PFS) of NSCLC patients receiving nivolumab monotherapy (Taniguchi et al., 2020). Likewise, Iglesias-Santamaria (2020) also showed that concomitant use of opioids had a detrimental effect on the ICI outcome in patients with advanced cancer (including NSCLC) (Iglesias-Santamaría, 2020). Therefore, in the clinical setting, it is suggested to choose opioids with the least effect on immune function deliberately. A list of opioids categorized by the degree of immune modulation effect appears in Table 2. Moreover, dosage regimentation is another critical aspect to consider. Zylla et al. (2014) demonstrated that a group of patients with mild to no pain requiring <5 mg of daily oral morphine equivalent (OME) had a longer survival rate compared to those requiring ≥5 mg/day OME (Zylla et al., 2014). However, Hasegawa et al. (2018), who stratified patients according to daily OME of <60 mg or ≥60 mg, did not indicate a difference in patient survival (Hasegawa et al., 2018). Hence, opioid use for advanced-stage NSCLC patients should not exceed the dose equal to OME of 5 mg per day.

Table 2. Opioids categorized by the degree of their immunosuppressive effect (Zajaczkowska et al., 2018)

Strong immune modulation	Weak or no immune modulation
Morphine	Buprenorphine (the least or no effect)
Fentanyl	Oxycodone
Sufentanil	Hydromorphone
Codeine	Tramadol

In contrast, the lower class of analgesics acting on inhibition of the COX-2 enzyme was suggested to support anticancer activity instead of being repressive to the immune system, as shown in an article written by Kobayashi et al. (2020). They reported a case of a 57-years old-male with adenocarcinoma who was treated with nivolumab and celecoxib. As an additional treatment, celecoxib could recover the sensitivity of nivolumab, whereas the patient experienced tumor regrowth after two years following nivolumab monotherapy (Kobayashi et al., 2020). Moreover, a retrospective study evaluating concomitant use of COX inhibitor (aspirin, NSAID, selective COX-2 inhibitor) and ICI revealed that among 37 metastatic NSCLC patients, those receiving the drug combination had significantly longer time-to-progression (TTP) and ORR than ICI alone (Wang et al., 2020). However, Kanai et al. (2021) showed the contrary that COX inhibitor did not have additional or negative impacts on the ICI efficacy based on PFS, OS, response rate, and disease control rate (Kanai et al., 2021). Likewise, COX-2 inhibition in lung cancer cell lines did not affect the PD-L1 expression suggesting no significant benefit of celecoxib during ICI treatment. Although, PD-L1 expression was significantly associated with the COX-2 expression in the resected lung adenocarcinoma specimens (Shimizu et al., 2018). Hence, the usefulness of COX inhibitors is still debatable and necessitates further prospective study (e.g., randomized controlled trial).

However, in a real situation, for particular patients, NSAIDs are not adequate for relieving moderate-to-severe pain, while opioids as a last resource come with concerning effects. Hence, effective pain management must balance providing pain-free periods without disrupting the causal treatment. For the clinician, the first consideration is the drug of choice. Following WHO and NCCN guidelines to use non-opioids as the first step seems to be the safest way. Next, the clinician may move to opioids with minimum immune modulation (Table 2) before using morphine in response to previous treatment's inadequacy. Lastly, potential adverse events from the combination of analgesics and ICIs should be managed, including immune-related adverse events.

5. Conclusion and Future Direction

In conclusion, prolonged opioid use should be limited or replaced with NSAIDs whenever possible to prevent negative impacts on the current immunotherapy and increase the survival rate. Moreover, due to lack of evidence, further studies on concomitant medications using analgesics (either NSAIDs or opioids) and ICIs are essential to avoid unexpected side effects and not compromise both drugs' therapeutic efficacy. Proposed studies should explore the detailed mechanism in which the interaction occurred compared with dosage regimentation, usage duration, drug selection, and administration route.

6. Author contributions

RAP conducted the literature search and selection, then wrote the manuscript; MMA designed the outline study, analyzed information, and contributed to manuscript writing; FE contributed to study design and critically reviewed the manuscript. All of the authors have read and approved the final manuscript.

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8. Declaration of interests

The authors declare no competing interest.

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Figure legends

Figure 1. Mechanism of CTLA-4 modulating the immune response

The CTLA-4-mediated immune checkpoint is activated in naïve T cells during their initial response to the antigen. Once CD28 is ligated to the ligands (CD80/CD86), it conveys positive or stimulatory signals to the T cell along with signals from the MHC-TCR interaction. Subsequently, the signals triggers CTLA-4 to be expressed on the T cell surface. The stronger the induction through the TCR (and CD28), the greater the amount of CTLA-4 appears on the T cell surface. Hence, the negative signals from CTLA-4 eventually dampens the stimulatory signal to maintain the balance of T cell activation. This figure is adapted from Pardol (2012) (Pardoll, 2012) and created with BioRender.com. TCR, T cell receptor; MHC, major histocompatibility complex; DC, Dendritic cell.

Figure 2. Mechanism of PD-1/PD-L1 modulating the immune response

a. In tumor or stromal cells, PDL1 is not constitutively presented but rather is expressed in response to activated T cell inflammatory signals. b. In some tumors, oncogenes constitutive signaling can enhance PD-L1 expression on cancer cells, regardless of inflammatory signals in the tumor microenvironment. This figure is adapted from Pardol (2012)(Pardoll, 2012), created with BioRender.com. MHC, major histocompatibility complex; IFN-γ, interferon-γ; STATs, signal transducer and activator of transcriptions; TNF-α, tumor nuclear factor- α; TCR, T cell receptor.

Figure 3. Possible pharmacodynamic interactions between ICIs and analgesics (opioids and COX inhibitors)

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