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Review of the Interactions Between Anesthetic Agents and Chemotherapeutic Agents in Cancer Cell Lines Studied In Vitro

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Cancer remains the second leading cause of death worldwide, second to cardiovascular diseases. A significant number of patients with cancer require surgical interventions, highlighting the need to understand the interactions between popular agents used in general anesthesia and in chemotherapy, to provide safe anesthesia and effective anticancer treatment. Given that, for many clinicians, interactions between these 2 broad groups of drugs are not well known; therefore, this topic requires special attention. We have prepared this overview by presenting the actual findings in this field in order to introduce clinicians to this issue. The article considers commonly used drug groups in anesthesiology, such as intravenous and inhaled anesthetics, benzodiazepines, muscle relaxants, and opioids. Their interactions with commonly used antineoplastic drugs, described so far in the literature, are presented. These occurrences highlight the necessity of careful monitoring and control during perioperative care, to not interfere with chemotherapy targets and to prevent the severity of pharmacological adverse effects. To introduce these complex mechanisms, we prepared this article based on the most recent publications possible, considering the many studies carried out in vitro and in vivo, as well as clinical trials. This review was prepared on the basis of 73 articles published from 1989 to 2024, as well as on the authors' knowledge and clinical experience. This article aims to review the interaction between anesthetics and chemotherapeutic agents, based on clinical studies and studies conducted on in vitro cancer cell lines and in vivo animal models.

Keywords: Anesthesiology • Anesthetics, General • Benzodiazepines • Cytostatic Agents • Medical Oncology • Neuromuscular Agents

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Introduction

A drug interaction refers to the influence of one drug on the overall effect of another drug administered concurrently during treatment. Such interactions can result in the neutralization, reduction, or amplification of therapeutic outcomes. There are 3 primary types of drug interactions: pharmaceutical, pharmacokinetic, and pharmacodynamic [1,2]. Pharmaceutical interactions occur during drug preparation (eg, within a syringe), potentially leading to adverse chemical reactions. Pharmacokinetic interactions arise when drugs compete for enzyme systems or binding sites on plasma transport proteins, affecting their concentrations in the body. Pharmacodynamic interactions, the most common in anesthesiology, involve direct drug-to-drug interactions that either enhance or diminish the respective effects of the drugs [3].

Cancer incidence continues to rise, making it the second leading cause of death globally, after ischemic heart disease. It imposes the highest social, financial, and clinical burden in terms of disability-adjusted life years lost across all diseases. In 2018 alone, approximately 18 million new cancer cases were reported worldwide [4]. Since around 80% of patients with cancer undergo surgery, often more than once [5], understanding the potential interactions between chemotherapy and anesthetic drugs is critical for clinicians involved in perioperative care. The interactions of these 2 drug groups could at times have highly adverse effects on an oncology patient undergoing general anesthesia. They can both weaken the effect of a drug, causing ineffective anesthesia or chemotherapy, or intensify the adverse effects of the drugs, putting additional strain on the patient's system. Moreover, such interactions can have a beneficial effect, especially when certain anesthetic drugs potentiate the antitumor effects of selected chemotherapeutics, as has been found in numerous preclinical studies. Given that this unique but highly relevant issue is minimally explored by clinicians, we have prepared this article based on the latest available medical literature. In its compilation, we used 73 articles published between 1989 and 2024, as well as the knowledge and clinical experience of the authors. Among these, a number of articles contain the results of studies conducted on cell lines and animal models, as well as clinical trials and retrospective reviews.

Propofol

Due to its rapid onset of action and favorable safety profile, propofol is the most commonly used agent for induction and maintenance of general anesthesia [6]. The effect of propofol on the efficacy of chemotherapy has been studied in numerous scientific articles, and its effect on cisplatin-based treatment regimens is strongly suggested. Zhang et al described a significant reduction in the cytostatic effect of cisplatin administered together with propofol in glioma cells by inhibiting gap junction-based intercellular communication [7]. On the other hand, in non-small cell lung cancer, propofol significantly increased the sensitivity of tumor cells to cisplatin by inactivating the Ras-proximate-1 nuclear factor kappa-light-chain-enhancer of activated B cells (RAP1-NF-κB) axis, thus providing a theoretical basis for the use of propofol in highly chemotherapy-resistant lung cancers [8]. In addition, in cervical cancer, Li et al showed that propofol selectively sensitized tumor cells to cisplatin-induced apoptosis and enhanced its inhibitory effect on cellular proliferation through modulation of the epidermal growth factor receptor/janus kinase 2/signal transducer and activator of transcription 3 (EGFR/JAK2/STAT3) signaling pathway [9]. In addition, in pancreatic cancer, propofol has been shown to significantly increase the cytotoxic potential of gemcitabine and, by downregulating NF-κB, increase the chemosensitivity of tumor cells to cytostatics [10]. The following iv vitro studies show that the effect of propofol on the activity of chemotherapeutics cannot be clearly assessed. Even when considering a single drug, such as cisplatin, the above evidence shows that the effect of this anesthetic can both promote and impair its cytotoxic properties. This allows us to conclude that the effect of propofol on the action of selected cytostatics depends on both the type of tumor and on the molecular point of action in the tumor cell. In addition to propofol's potential to affect chemotherapy outcomes, the effect of chemotherapeutic agents on propofol dosing is critical. Wu et al found that patients undergoing neoadjuvant chemotherapy (docetaxel, epirubicin, and cyclophosphamide) during breast cancer treatment showed increased sensitivity to propofol and required lower doses of the drug during radical mastectomy than did patients not treated with chemotherapy [11]. On the other hand, Kim et al found no statistically significant differences in propofol dosing between the neoadjuvant chemotherapy groups and non-chemotherapy treated groups and did not recommend dosage changes based on chemotherapy history [12]. A possible explanation for this discrepancy could be chemotherapy-induced neurotoxicity [13] or liver toxicity [14] individually affecting each patient and varying according to the chemotherapy regimen.

Therefore, particular caution should be exercised when dosing propofol in these patient groups, bearing in mind that the standard doses will not be adequate, especially in patients with chemotherapy-induced central nervous system and liver damage. Nonetheless, further clinical studies are required to determine the adequate dosage of propofol in terms of the cancer data and the type of chemotherapy received.

Ketamine

Ketamine is an N-methyl-D-aspartate (NMDA) antagonist. This anesthetic, in contrast to other anesthetics, has an analgesic

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component, and low (subanesthetic) doses of it have the potential to treat acute and chronic pain. According to a review of randomized controlled trials, intravenous ketamine (0.1-0.5 mg/kg) is most effective in the context of pain management in oncology patients up to 72 h after surgery, especially when it was administered in combination with other analgesics, mainly morphine [15].

Significant interactions between chemotherapeutics and ketamine have not been described. A potential use of ketamine can be in the treatment of chemotherapeutic-induced peripheral neuropathy, which occurs in approximately 68% of patients 1 month after completion of chemotherapy. This is a complication caused by the neurotoxicity of some chemotherapeutics; the most common ones causing it include oxaliplatin, cisplatin, paclitaxel, bortezomib, and vincristine [16]. Nevertheless, the use of ketamine in the treatment of this complication requires further study, as only a slight improvement was proven when topical ketamine was applied in gel form containing baclofen and amitriptyline simultaneously [15].

Thiopental and Etomidate

Thiopental belongs to the group of barbiturates, a group of drugs acting on gamma-aminobutyric acid (GABA)-A receptors, with a mechanism of action and clinical effect very similar to that of benzodiazepines. Thiopental has been used for induction of general anesthesia and has anti-anxiety and anticonvulsant properties. However, its use in routine clinical practice has declined significantly due to its replacement by propofol [17].

Etomidate is a short-acting intravenous sleeping agent with a favorable adverse effect profile, particularly due to its reduced cardiovascular effects, as it is associated with a lower risk of cardiovascular depression. However, it also partially inhibits adrenal function, which is an important factor to consider when administering it [18]. In the context of both anesthetics, no significant interactions with chemotherapeutics were noted. However, the following drugs have been studied in numerous preclinical studies in the context of their effects on the progression of individual cancers [19,20].

Interactions Between Volatile Anesthetics and Chemotherapeutics

Volatile anesthetics, including the most commonly used, sevoflurane and desflurane, are typically used to maintain inhaled general anesthesia, and therefore we mainly focused on them in our review.

According to Zhang et al, chemotherapeutic agents can increase sensitivity to sevoflurane and desflurane, as demonstrated in a group of patients undergoing neoadjuvant chemotherapy for hepatocellular carcinoma. In patients treated preoperatively with oxaliplatin and tegafur, the minimal alveolar concentrations (MAC) values (ie, the minimum amount of gas administered that caused insensitivity to a standard surgical stimulus, such as a skin incision) of both anesthetics were reduced [21]. Moreover, Du et al found that neoadjuvant chemotherapy, specifically, a combination of oxaliplatin and Gio, potentiated the inhibitory effect of sevoflurane on the sympathetic response in patients with gastric cancer undergoing radical gastrectomy. It was observed on the basis of a decrease in MAC necessary to block the autonomic response (BAR; MAC-BAR) [22]. The above evidence suggests that the anesthetic concentration administered to the patient should be titrated based on the initial chemotherapy administered to the patient. For this reason, the possible effects of other chemotherapeutics on sensitivity to inhaled anesthetics should be investigated. A titration method that rationalizes the delivery of anesthetics can be additionally beneficial, in the context of reducing the risk of postoperative nausea and vomiting, as these adverse effects of inhaled anesthetics, among others, can be exacerbated by chemotherapeutics, which also cause them [23].

Moreover, in vitro studies on cancer cell lines have demonstrated the additive properties of volatile anesthetics on the primary actions of selected chemotherapeutics. Liang et al found that sevoflurane and cisplatin showed synergistic effects on the growth and invasion of human lung adenocarcinoma cells, which can be related to the reduction of survivin expression, along with X chromosome-associated apoptosis inhibitor and matrix metalloproteinases type 2 and 9, respectively [24]. On the other hand, these synergistic effects are determined by the type of cancer and the point of action of the present substances. This is demonstrated by a study by Ciechanowicz et al, in which it was shown that sevoflurane increased the chemosensitivity to cisplatin of non-small cell lung adenocarcinoma cells, while, against renal cell carcinoma, sevoflurane increased viability, migratory capacity, and chemoresistance to cisplatin [25].

In addition, isoflurane, a volatile anesthetic significantly less commonly used in modern anesthesiology, caused an increase in resistance to chemotherapy (docetaxel) of prostate cancer cells through prior activation of hypoxia-inducible factor-1 α expression [26].

Interactions Between Benzodiazepines and Chemotherapeutics

Diazepam

Diazepam, a drug of the benzodiazepine class, which acts by allosterically modulating the activity of ionotropic GABA-A

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receptors in the central nervous system, increases the likelihood of GABA-induced opening of the associated chloride channel, leading to a decrease in neuronal excitation, with clinical sedative and anti-anxiety effects and muscle relaxation [27]. Diazepam is commonly used in premedication, such as before endoscopic procedures, and in the treatment of seizures from various causes. In oncology patients, its use is particularly prevalent among those with central nervous system tumors, as these malignancies are associated with a higher incidence of seizures [28].

In the human body, diazepam is metabolized to active metabolites by cytochrome P450 CYP3A4 and CYP2C19 [29]. This causes complications during treatment with substances that act as CYP3A4 inhibitors. One such drug is idelalisib, a protein kinase inhibitor and drug used to treat chronic lymphocytic leukemia. Concomitant use of idelalisib and diazepam results in an approximately 2-fold increase in the half-life of diazepam. This phenomenon is particularly pronounced in elderly patients and can lead to mental status disorders and respiratory failure [30].

Despite preclinically proven antiproliferative properties [31-33], diazepam's effect on the cell cycle can dramatically reduce the efficacy of some chemotherapeutics. In a human glioma cell line, diazepam caused cell cycle arrest in the G0/G1 phase, which reduced the therapeutic effect of temozolomide [34,35].

Midazolam

Midazolam, along with diazepam, is a representative of the benzodiazepine class of drugs. With a mechanism and action analogous to that of diazepam, it is popularly chosen for premedication and sedation of patients.

Most of the interactions involving this drug are pharmacokinetic in nature, as a significant number of chemotherapeutics are inhibitors of the CYP3A4 isoenzyme. This isoenzyme is also mainly responsible for the metabolism of midazolam, as it is for the metabolism of diazepam [29]. These agents include, for example, a number of protein kinase inhibitors, including nilotinib [36], idelalisib [37], and certinib [38], which significantly affect midazolam metabolism and lead to significantly increased AUC. Similarly, the metabolism of midazolam can be altered during concomitant use with paclitaxel, crizotinib, and pazopanib; however, for these drugs, further studies are required to confirm clinical significance [39]. Concomitant use of these drugs, which are CYP3A4 inhibitors, therefore requires increased caution and in some cases can require a reduction in the dose of midazolam, or replacement with another drug group. It should be noted that the above-mentioned chemotherapeutics whose metabolism involves the CYP3A4 isoenzyme will have similar effects on the metabolism of diazepam and midazolam and other drugs metabolized by this isoenzyme. In such cases, another drug from the benzodiazepine group, lorazepam, which is not metabolized by the CYP3A4 isoenzyme, can be used or substituted with drugs from other groups with similar properties [30].

Moreover, it has been found that midazolam enhances the effects of established chemotherapeutics. Kang et al showed that midazolam significantly enhanced the therapeutic efficacy of anti-programmed death-1 immunotherapy in hepatocellular carcinoma by inhibiting the NF-κB signaling pathway, leading to reduced depletion of CD8+ cytotoxic T cells [40]. Also, Sun et al demonstrated its ability to increase the sensitivity of non-small cell lung cancer to cisplatin-based therapy by regulating microRNA-194-5p and hook microtubule tethering protein 3 (HOOK3; miR-194-5p/HOOK3 axis) [41]. On the other hand, Braun et al showed that pretreatment with midazolam reduced the cytotoxicity of temozolomide on a human immature neuroblastoma cell line [42].

Interactions Between Muscle Relaxants and Chemotherapeutics

Neuromuscular conduction blocking is one of the 3 main components of general anesthesia, along with sedation and analgesia. The role of neuromuscular conduction blockers is to relax muscles, which facilitates intubation and surgery [43]. Peripheral nerve damage and skeletal muscle dysfunction caused by chemotherapy can affect neuromuscular function. The mechanism includes inhibition of mitochondrial oxidative phosphorylation, disruption of the intracellular respiratory chain and energy production in muscle, leading to altered intracellular calcium concentration and muscle fiber damage [44]. Frequent destruction of muscle fibers can cause changes in the connective tissues around the neuromuscular junction, which alters the pharmacokinetics of neuromuscular conduction blockers [45].

Non-Depolarizing Muscle Relaxants

Rocuronium bromide is one of the fastest-acting non-depolarizing neuromuscular conduction blockers and is eliminated mainly by the liver and to a lesser extent by the kidneys. It does not raise intrathoracic or intracranial pressure and does not accumulate in the body, making it a safe option for patients with cranial hypertension or a full stomach [45]. To date, no significant interactions between rocuronium bromide and anticancer drugs have been identified.

Cisatracurium, one of the isomers of atracurium, has similar properties, but minimizes adverse effects such as histamine release and has little effect on the cardiovascular system [46].

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Atracurium is metabolized independently of liver and kidney function, undergoing hydrolysis by non-specific esterases and Hofmann elimination. However, administration of large doses can result in histamine release, potentially leading to sudden fluctuations in blood pressure and heart rate, as well as the risk of allergic reactions. Vecuronium, a derivative of pancuronium bromide, is mainly used in combination with anesthetics for various procedures, including endotracheal intubation [45].

Studies indicate that recent chemotherapy with cyclophosphamide, adriamycin (doxorubicin), and 5-fluorouracil (CAF regimen) delays the development of optimal relaxation, providing favorable conditions for intubation after administration of non-depolarizing muscle relaxants, which includes the above-mentioned drugs. In addition, the accelerated resolution of muscle relaxation has been observed with these drugs, requiring more frequent drug administration in the chemotherapy group than in those not receiving chemotherapy [47]. Patients receiving neoadjuvant chemotherapy with taxane, adriamycin, and cyclophosphamide for breast cancer showed similar results. Compared with patients not receiving chemotherapy, in patients undergoing chemotherapy, cisatracurium showed a delayed onset of action, shorter duration of action, and faster resolution of the relaxant effect, which in some cases could result in failed intubation attempts [47,48]. The cause of patient resistance to cisatracurium remains controversial. Some studies point to hypercalcemia as the cause [47], while others suggest hypomagnesemia [48]. It can be surmised that analogous resistance would occur with the other non-depolarizing muscle relaxant drugs. In the context of the delayed development of the blockade, as well as its accelerated remission, the intraoperative use of techniques to measure the degree of relaxation and the dosing of drugs at the appropriate dose and intervals appears to be essential.

Depolarizing Muscle Relaxants: Succinylcholine

Succinylcholine, a depolarizing agent that blocks neuromuscular conduction, is often used in emergency situations because of its rapid onset and short duration of action [43].

Typically, paralysis resolves within minutes because succinylcholine is broken down by butyrylcholinesterase. However, patients with atypical pseudocholinesterase activity can experience prolonged paralysis, lasting more than an hour in some cases. Although rare, some cytotoxic drugs can exacerbate this effect [49,50]. Individuals with genetically abnormal pseudocholinesterase activity can experience neuromuscular blockade for 70 to 120 min after succinylcholine administration [50]. Acquired butyrylcholinesterase deficiency, which can be associated with conditions such as cancer, can also lead to prolonged paralysis, and some cytotoxic drugs can further prolong this effect. While prolonged neuromuscular blockade is generally not a serious clinical problem, it can result in prolonged apnea [51]. Because of prolonged blockade, the use of succinylcholine in oncology patients should be considered for butyrylcholinesterase deficiency, and then the use of intraoperative neuromuscular conduction monitoring appears to be necessary to ensure safety during awakening. In addition, the use of non-depolarizing muscle relaxants should be considered if possible.

Effects of Cytostatic Agents on Neuromuscular Blockade

Cyclophosphamide, which is classified as an alkylating agent, has numerous adverse effects, such as myelosuppression, hemorrhagic cystitis, and pulmonary and myocardial toxicity [52]. In addition, it inhibits pseudocholinesterase, which prolongs succinylcholine-induced muscle relaxation [53]. Fluorouracil, as an antimetabolic agent, is associated with a risk of cardiotoxicity. Although here are no studies describing changes in striated muscle function after exposure to these substances, this should not exempt anesthesia personnel from vigilance [47].

Doxorubicin causes extensive muscle dysfunction, and cardiotoxicity is one of its main adverse effects. It can lead to symptoms such as tachycardia, changes in electrocardiogram, ventricular dilation, and heart failure [54]. The effect of this drug on neuromuscular blockade should be considered mainly because of its effect on skeletal muscle tissue. The toxic effects of doxorubicin on skeletal muscle fibers can manifest as fatigue, weakness, and myasthenic syndrome, which can persist for up to 5 years after exposure. The mechanism of skeletal muscle and myocardial damage after doxorubicin exposure is related to oxidative processes, leading to intracellular disorganization of myocytes and changes in mitochondria [55]. Toxic radicals cause a number of structural changes, including vacuolization of the sarcoplasmic reticulum and degeneration of mitochondria, leading to muscle dysfunction [47]. Thus, it is important to keep in mind that regardless of the type of muscle relaxant used, oncology patients taking the above cytostatic agents (especially cyclophosphamide and doxorubicin) should have intraoperative monitoring of neuromuscular conduction and need to be prepared to change the dosage regimen of muscle relaxants.

Fentanyl

Fentanyl is a potent opioid with a rapid onset of action, making it extremely effective in the induction of anesthesia and the prevention of intraoperative pain. It is further used for pain control in cancer patients [56,57]. The drug is mainly metabolized by CYP3A4 and CYP2D6, and is transported by P-glycoprotein. A number of chemotherapy drugs are metabolized by the same

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isoenzymes, which are part of cytochrome P450 [56,58]. Such drugs include paclitaxel, which is used as a first-line treatment for breast cancer, ovarian cancer, and non-small cell lung cancer. Among the adverse effects of paclitaxel are hepatotoxicity, cardiotoxicity, and neurotoxicity. Similar to fentanyl, CYP3A4, among others, is responsible for metabolism of paclitaxel; therefore, concomitant use of these drugs increases hepatotoxicity, as demonstrated by Xie et al in a mouse study. In addition, fentanyl acts as an inhibitor of the ATP-binding cassette subfamily B member 1 (ABCB1) transporter, which potentially enhances the antitumor effects of paclitaxel, as it decreases the removal of paclitaxel from cells but also increases its toxicity. Also in this study, the authors, using in vitro assays, demonstrated increased cytotoxicity of paclitaxel and doxorubicin, which is also an ABCB1 substrate, against oral epithelial carcinoma and breast cancer cell lines expressing ABCB1 [59]. Anticancer drugs that are CYP3A4 inhibitors mentioned in the literature are imatinib, nilotinib [58,60], ribociclib [60], and idelalisib [61] which can potentiate the effects of fentanyl; however, in vivo studies are required to unequivocally confirm this effect. In contrast, a potent CYP3A4 and CYP2D6 inducer contraindicated for use with fentanyl is enzalutamide, a non-steroidal anti-androgen drug used to treat castration-resistant prostate cancer. By reducing the concentration of the analyzed opioid, it can make pain control difficult to achieve, even with dose modification. This was confirmed by a small clinical study and a case report [60]. Platinum drugs, especially cisplatin, are most commonly used in the treatment of lung cancer. A study by Yao et al on non-small cell lung cancer cell lines showed that fentanyl reduces apoptosis induced by cisplatin at the level of the c-Jun N-terminal kinase signaling pathway [62].

Remifentanyl and Sufentanyl

Along with fentanyl, remifentanyl and sufentanyl are commonly used opioids in general anesthesia. Particularly distinctive is remifentanyl, which alongside propofol is used in the total intravenous anesthesia technique, excelling in continuous infusion, due to its very short half-life [63]. Analogous to fentanyl, both of these opioids are metabolized by CYP3A4 [64], but no interactions between chemotherapeutics metabolized by this isoenzyme and remifentanyl or sufentanyl have been described to date. Despite the deficiencies in the literature, it is conceivable that some anticancer drugs that interact with CYP3A4 can cause abnormalities in their pharmacokinetics.

Oxycodone

Oxycodone is an opioid, like morphine, which, in addition to its use during general anesthesia, is widely used to relieve cancer-related pain. CYP3A4, CYP3A5, and CYP2D6 are enzymes involved in its metabolism [58,60]. According to a review [58], aldesleukin (Proleukin), dasatinib, and tamoxifen, being CYP3A4 inhibitors, and imatinib with nilotinib, as inhibitors of CYP3A4 and CYP2D6, can increase plasma concentrations of oxycodone, undermining the risk of overdose; however, further in vivo studies are required. According to Aapro et al, ribocyclib, which is also a CYP3A4 inhibitor, should not be combined with this opioid; however, the authors could not verify this in the literature [60].

Icotinib, used to treat non-small cell lung cancer with epidermal growth factor receptor expression, and apatinib, used to treat non-small cell lung cancer and advanced gastric cancer, being tyrosine kinase inhibitors, have evidence of inhibiting CYP3A and CYP2D6, respectively. Zhou et al conducted studies in vivo in rats and in vitro using rat and human microsomal enzymes that showed inhibition of oxycodone metabolism [65].

Enzalutamide, a non-steroidal anti-androgen used in castration-resistant prostate cancer, being an inducer of CYP3A4 and CYP2D6, should not be given together with oxycodone. According to numerous reports, including those of prospective and retrospective studies, enzalutamide significantly impaired the effect of the analyzed opioid, depriving it of its analgesic effect [60].

Morphine

In addition to being used in general anesthesia, morphine is the most commonly used opioid for cancer pain relief. The CYP450 enzyme system has minimal effect on the metabolism of morphine, which in turn is a substrate of glucuronosyltransferase 1A1 (UGT1A1) [58]. Therefore, to ensure patient safety and prevent other adverse interactions, it is recommended to replace other opioids metabolized by CYP450 enzymes with morphine [60]. In addition, the gastric absorption of morphine and transport through the blood-brain barrier is dependent on the P-glycoprotein pump. Although no clinically relevant interactions between morphine and specific chemotherapeutics have been reported, according to the following review [60], nilotinib, which is both a P-glycoprotein and UGT1A1 inhibitor, can pose a problem when administered simultaneously with morphine by increasing its toxicity [58].

An interesting report by Rodríguez-Muñoz et al is about the potentiation of the supraspinal antinociceptive effect of morphine by cannabidiol [66], which is used to treat adverse symptoms associated with cancer and chemotherapy, and is, according to in vitro studies, a promising therapeutic and adjuvant substance in the treatment of some cancers [67]. However, the study by Rodríguez-Muñoz et al has some limitations to its clinical usefulness, as it was conducted on mice and the strongest effect occurred when both drugs were administered directly into the brain ventricles [66]. The interactions described in the article are summarized in **Table 1**.

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Table 1. Summary of interactions between drugs used in general anesthesia and anticancer drugs.

Drug	Effect on chemotherapy	Effect of chemotherapy on the drug
Propofol	Reduces the effectiveness of cisplatin in glioblastoma. Increases the sensitivity of cisplatin in non-small cell lung cancer and cervical cancer. Increases the sensitivity of pancreatic cancer to gemcitabine	Possible increase in patient sensitivity to propofol during neoadjuvant therapy
Ketamine	Potential attenuation of CPIN (caused mainly by oxaliplatin, cisplatin, paclitaxel, bortezomib, vincristine)[1]	No relevant data available
Thiopental and Etomidate	No relevant data available	No relevant data available
Volatile anesthetics (sevoflurane, desflurane, isoflurane)	Sevoflurane potentiated the effect of cisplatin to inhibit growth and invasion of lung adenocarcinoma. Sevoflurane increased the chemosensitivity to cisplatin of non-small cell lung adenocarcinoma. Sevoflurane increased viability, migratory capacity, and chemoresistance to cisplatin of renal cell carcinoma. Isoflurane increased prostate cancer resistance to docetaxel. Volatile anesthetics (sevoflurane, desflurane) intensified nausea and vomiting after chemotherapeutics	Neoadjuvant chemotherapy (oxaliplatin and tegafur) reduced MAC values for sevoflurane and desflurane in operated hepatocellular carcinoma patients. Neoadjuvant chemotherapy (oxaliplatin and Gio) decreased MAC-BAR values for sevoflurane in gastric cancer patients undergoing radical gastrectomy. Chemotherapeutics increased the risk of PONV occurring after volatile anesthetics (sevoflurane, desflurane)
Diazepam	Reduced effect of temozolamide against human glioma cells	Idelalisib increased diazepam concentration (potential impact of other drugs that affect the activity of CYP3A4 and CYP2C19)
Midazolam	No available data	Nilotinib, idelalisib, certinib increased midazolam concentration. Paclitaxel, crizotinib, and pazopanib can potentially increase midazolam coccentration2 (potential impact of other drugs that affect the activity of CYP3A4)
Non-depolarizing muscle relaxants	Chemotherapy (CAF: cyclophosphamide, doxorubicin, 5-fluorouracil) delays the onset of myorelaxation, especially with cisatracurium	Non-depolarizing muscle relaxants require more frequent doses, have a delayed onset of action and a quicker cessation of the relaxation effect
Depolarizing muscle relaxants	No available data	Possible prolongation of paralysis in patients with atypical pseudocholinesterase activity and the effects of some cytostatics
Fentanyl	Increased cytotoxicity of paclitaxel and doxorubicin against oral epithelial carcinoma and breast cancer cell lines expressing ABCB1*, increased hepatotoxicity of paclitaxel. Reduced apoptosis of non-small cell lung cancer cell lines induced by cisplatin	Enzalutamide significantly impaired the fentanyl effect. Imatinib, nilotinib, ribociclib, idelalisib can potentially increase fentanyl concentration[2] (potential impact of other drugs that affect the activity of CYP3A4 and CYP2D6)

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Table 1 continued. Summary of interactions between drugs used in general anesthesia and anticancer drugs.

Drug	Effect on chemotherapy	Effect of chemotherapy on the drug
Remifentanyl and sufentanyl	No available data	No available data (potential impact of drugs that affect the activity of CYP3A4)
Oxycodone	No avaliable data	Ribocyclib, aldesleukin, dasatinib, tamoxifen, imatinib, nilotinib can potentially increase oxycodone concentration[2]. Icotinib and apatinib inhibited oxycodone metabolism*. ** Enzalutamide significantly impaired the oxycodone effect (potential impact of other drugs that affect the activity of CYP3A4, CYP3A5 and CYP2D6)
Morphine	No avaliable data.	Nilotinib can potentially increase morphine toxicity[3]. CBD[4] potentiated the supraspinal antinociceptive effect of morphine**[5]

[1] Promising results have been obtained using ketamine topically in the form of a gel containing additionally baclofen and amitriptyline; [2] Require further confirmatory studies; [3] Due to the inhibition of p-gp (p-glycoprotein) and UGT1A1 (glucuronosyltransferase 1a1), which is involved in morphine transport and metabolism, respectively; [4] CBD is used to treat adverse symptoms associated with cancer and chemotherapy as well as, according to in vitro studies, is a promising therapeutic and adjuvant substance in the treatment of some cancers; [5] The strongest effect occurred when both drugs were administered directly into the brain ventricles. * Demonstrated in in vitro studies; ** demonstrated in in vivo studies. CPIN – chemotherapeutic-induced peripheral neuropathy; MAC – minimal alveolar concentration; MAC-BAR – minimal concentration of anesthetic necessary to block the autonomic response; PONV – postoperative nausea and vomiting; CYP3A4 – cytochrome P450 3A4; CYP2C19 – cytochrome P450 2C19; CYP3A5 – cytochrome P450 3A5; CTP2D6 – cytochrome P450 2D6; ABCB1 – ATP-binding cassette subfamily B member 1; CBD – cannabidiol.

Conclusions

This review outlining the described interactions provides new insight into what significant aberrations in anesthesia and the subsequent effects of pharmacological oncology treatment can result from the drug interactions between anesthesia used for surgical procedures and non-operative cancer treatment. The described interactions come from various sources and include the most commonly used agents in general anesthesia. The sources of this review include potential interactions due to a common metabolism handle points found in drug interaction databases cited by authors of the reviews; preclinical studies conducted on both tumor cell lines and animal models; and retrospective reviews and clinical trials. The described interactions can affect each group's agents in 2 directions, both weakening their effects and intensifying them. Changing the action of anesthetic drugs is generally unfavorable, because disrupting their kinetics can cause unpredictable development of anesthesia or expose the patient to disorderly actions. In turn, the anesthetic's exacerbation of the chemotherapeutic agent, without taking into account the exacerbation of its side effects, can intensify its cytotoxic effect against tumor cells. Therefore, anesthetic drugs have the potential to be used as adjuvant substances in chemotherapy in the future. In addition, many of the drugs described in the article have been studied, particularly preclinically, in terms of their effects on the development of specific cancers. Propofol has been particularly extensively studied for its increasing importance as an anesthetic in oncologic surgery. This is attributed to its proven antitumor potential, mainly due to the enhancement of the cytotoxic activity of natural killer and cytotoxic lymphocytes and less side effects on the immune system than other anesthetics [68]. There are clinical studies demonstrating the superiority of propofol-based total intravenous anesthesia over inhalational anesthesia in terms of suppressing further cancer development, especially of the gastrointestinal and digestive systems [69]. Interestingly, in multiple studies on cancer cell lines, propofol has shown effective anti-tumor activity in the context of breast cancer [70], esophageal cancer [71], glioblastoma, and others [72]. On the other hand, studies on mouse models have shown propofol promotes tumor metastasis to the lungs [73]. This citation is intended only to show the potential directions of contemporary research on antitumor potential, which includes many other drugs, including anesthetics.

Future Directions

To provide safe anesthesia along with simultaneous effective pharmacological treatment of cancer, as many interactions as

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possible between chemotherapy and anesthetic drugs must be elucidated. In addition, drug interactions that are unconfirmed by studies can be found in online databases. These interactions can be due to a common metabolic handle point (when both substances interact on a common isoenzyme, predominantly in the range of cytochrome P450), and these effects should be investigated first. Confirmation in preclinical and then clinical studies, when possible, could contribute to the development of guidelines for the mode of anesthesia, depending on the initial cancer and the neoadjuvant chemotherapy used preoperatively. The idea is that such guidelines should include compositions of preferred, optional, non-recommended, and unacceptable drugs and also dosages, depending on how the chemotherapeutic modulates the metabolism of the anesthetic drug.

Given that opioids are an extremely important group of drugs used in the management of pain associated with oncologic disease, it would be highly valuable to improve the guidelines in the context of pain management. The guidelines would consider the primary treatment with chemotherapeutics and the selection of appropriate analgesics at the optimal dose, which would prevent interference with chemotherapy and ineffective pain relief. However, the concept of the above guidelines for the current state of knowledge seems strongly idealized and requires exploring a significantly larger pool of interactions.

Another research goal should be to further investigate the effects of selected anesthetic drugs on potentiating the effects of particular chemotherapeutics. Drugs like propofol, sevoflurane, and fentanyl in preclinical studies show potential for future usage as adjuvant substances alongside selected chemotherapeutics in the treatment of concurrent cancers. However, it is important to keep in mind that, according to the preclinical studies presented in this review, these substances in combination with other anticancer drugs can impair their effects. Therefore, the molecular mechanisms that determine in which direction these substances modulate the activity of selected cancer drugs should be further understood before appropriate clinical trials are conducted.

In addition, the CPIN-relieving potential of ketamine, which currently has been confirmed only in the form of a mixture with other drugs applied topically, should be further investigated.

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