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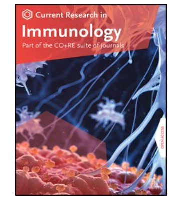

Role of chemotherapeutic drugs in immunomodulation of cancer

Oishi Mukherjee, Sudeshna Rakshit, Geetha Shanmugam, Koustav Sarkar *

Department of Biotechnology, SRM Institute of Science and Technology, Kattankulathur, Chennai, Tamil Nadu, 603203, India

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A B S T R A C T

The immune system has a variety of potential effects on a tumor microenvironment and the course of chemotherapy may vary according to that. Anticancer treatments can encourage the release of unwanted signals from senescent tumor cells or the removal of immune-suppressive cells, which can lead to immune system activation. Hence, by inducing an immunological response and conversely making cancer cells more vulnerable to immune attack, chemotherapeutic agents can destroy cancer cells. Furthermore, chemotherapy can activate anticancer immune effectors directly or indirectly by thwarting immunosuppressive pathways. Therefore, in this review, we discuss how chemotherapeutic agents take part in immunomodulation and the molecular mechanisms underlying them. We also focus on the importance of carefully addressing the conflicting effects of chemotherapy on immune responses when developing successful combination treatments based on chemotherapy and immune modulators.

1. Introduction

Globally, there is a serious public health issue with cancer. Previously, cancer was only identified and managed based on the organs from which it originated or basic histomorphologic characteristics. It was necessary to create molecularly targeted medicines and choose treatments based on specific molecular abnormalities. Since then, the acquisition of new technologies for tumor molecular profiling and the identification of predicted molecular targets have served as the two pillars that have pushed the evolution of cancer treatment. These two most recent revolutions in cancer treatment have come about as a result of their combined efforts (Zugazagoitia et al., 2016). While the modern ways of cancer treatment are quite advanced, due to the versatility of cancer, there are considerable amounts of limitations to these treatments. There are a few basic and common ways to treat cancer. One of the most common methods which is mostly treated in combination with other methods is chemotherapy. Surgeons created novel techniques for treating cancer in the latter decades of the 20th century by combining surgery with chemotherapy and/or radiation. Later, scientists discovered that nitrogen mustard can destroy lymphoma cancer cells that are multiplying quickly. Numerous forms of cancer have been successfully treated over time thanks to the use of chemotherapy medications (Sudhakar, 2009).

Another common method of treating cancer is radiation therapy, where X-rays was used for cancer diagnosis. Around 50 percent of all cancer patients go through radiation therapy, out of which 40 percent of them contribute toward curative treatment by radiation (Delaney et al., 2005). Hormone therapy is used for a variety of conditions including the prevention of estrogen deficiency and climacteric syndrome (Fait, 2019). For patients suffering from hormone-receptor-positive breast neoplasms, hormone treatment is a must and, in this case, both adjuvant and metastatic illnesses are responsive to it.

Hormone treatment helps people with low recurrence scores, whereas chemotherapy is required for individuals with high recurrence scores. Patients receiving hormonal therapy for breast cancer include those whose tumors exhibit hormone receptors for progesterone, estrogen, or both. Neoadjuvant, adjuvant, and metastatic illness can all be treated with hormonal treatment (Drăgănescu and Carmocan, 2017). Additionally, efforts have been made to clarify the root cause of ovarian cancer and a number of hormonal theories have been suggested, including gonadotropin signaling, the direct effects of progesterone and androgen, and persistent ovulation (Li et al., 2021). Other forms of cancer treatment, such as surgery, adjuvant therapy, and targeted therapy, have also made significant advancements in the field of cancer treatment and have helped treat many different types of cancer.

However, findings show that chemotherapeutic agents like cisplatin, doxorubicin, azacytidine, and others not only have cell-killing properties but also immunoregulatory properties. There are quite a few studies reporting that chemotherapeutics have direct and indirect correlations with the immune system. Since, chemoresistance leads to cancer recurrence, disease spread, and mortality, overcoming inherent and

* Corresponding author.
E-mail address: koustavsarkar@gmail.com (K. Sarkar).

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List of abbreviations

RT	Radiation Therapy
VEGF	Vascular endothelial growth factor
PARP	Poly-ADP -ribose polymerase
HER2	Human epidermal growth factor receptor 2
TNBC	Triple-negative breast cancer
MIS	Minimally invasive surgery
TME	Tumor microenvironment
MDSC	Myeloid-derived suppressor cells
DCs	Dendritic Cells
DOX	Doxorubicin
PI3K	Phosphatidylinositol 3-kinase
PKB	Protein kinase B
OVX	Ovariectomized
ERK	Extracellular signal-regulated kinase
MAPK	Mitogen-activated protein kinase
hTERT	human telomerase catalytic subunit gene
EGF	Epidermal growth factor
STAT	Signal Transducers and Activators of Transcription
JAK	Janus kinases
IL:	Interleukin
NFκB	Nuclear factor κ B
TNF	Tumor necrosis factor
IKK	Inhibitor of nuclear factor-κB (IκB) kinase
ROS	Reactive oxygen species
IFN	Interferon
mTNBC	metastatic Triple-Negative Breast Cancer
ICI	Immune Checkpoint Inhibitor
TMB	Tumor Mutational Burden
TILs	Tumor-infiltrating lymphocytes

acquired drug resistance is a significant problem in the treatment of cancer patients it is a major challenging limitation for patients undergoing long-term chemotherapy. In understanding chemoresistance, numerous molecular mechanisms and signaling networks associated with immune cells are underlying. On comprehending these molecular mechanisms, it may be easier to create viable therapeutic targets and possible chemosensitivity biomarkers for cancer therapies (Zheng, 2017).

2. Different modes of therapy for cancer

Treatment is often contingent on the type of cancer the patients suffer from. Based on location, cancer therapy is broadly classified into two, systemic and local. By traveling through the bloodstream, systemic treatments reach all target cells throughout the body, whereas localized treatments target only specific cells in a particular area of the body. Knowing about the proceeding of various therapies makes us aware of the benefits as well as the side effects associated with them. Described below are some common methods of cancer treatment.

2.1. Chemotherapy

The initial applications of nitrogen mustards and antifolate medicines in the 1940s marked the beginning of the age of chemotherapy. Since that time, the discovery of new cancer medications has gone from being a low-budget, government-supported research project to a highly competitive, multibillion-dollar industry. The principles and restrictions of chemotherapy that the early researchers identified still hold true despite the advent of the targeted-therapy revolution (Chabner and Roberts, 2005). The introduction of cisplatin in the late 1970s, which significantly altered the outlook for patients with, for example, testicular cancer, was a turning point in contemporary chemotherapy. Later, it was discovered to be effective in the treatment of other solid tumors (Galmarini et al., 2012). A chemotherapy regimen consists of cytotoxic chemicals, dosages, time points, and delivery techniques. Studies on cytotoxic medications' effects on cells have been conducted using developing tumor cell lines, but may not be suitable for human cancer. Some drugs disrupt cell membranes, while most interfere with cell survival and development. Alkylators and alkylator-related substances attach to cellular macromolecules, preventing DNA from functioning during cell division and gene expression.

The antimetabolites substitute for the usual molecules in the synthesis of DNA and RNA hinder crucial phases in the synthesis, disrupting the DNA or RNA's normal function and potentially impairing cell growth and survival. The topoisomerase inhibitors work by interfering with the regular operations of nuclear enzymes topoisomerase I and II. By causing temporary single or double strand breaks, these enzymes play a crucial role in the replication, transcription, and repair of DNA. On the other hand, atypical microtubule deficit or accumulation results from the microtubule interacting agents disrupting the normal synthesis and breakdown of the cellular cytoskeleton, or the microtubule machinery (Nygren & SBU-group, 2001). Fig. 1 depicts the types of chemotherapeutic drugs and their mechanism of action. However, malignant tumor chemotherapy often lacks cytotoxic drugs' significant antitumor efficacy, as tumor forms like lung, renal, and gastrointestinal cancers often exhibit resistance to cytotoxic medications. Other types may initially react but develop resistance to new medications. (Murray, 1990).

2.2. Radiation therapy

Radiation oncology was founded after the discovery of x-rays in the late 19th century, following which radiation was used to treat cancer and inflammation-related malady (Alfouzan, 2021). As of today, radiation therapy (RT) or radiotherapy remains to be a highly cost-effective modality contributing around 40% to the curative process (Baskar et al., 2012). Radiation uses high-energy beams consisting of charged particles or ions to disturb the cell cycle of the cancer cells. The beam is aimed at the target cells to damage their DNA which further prevents them from proliferation. Although RT is a localized treatment, high radiation beams are often exposed to normal cells that surround the target area and cause their malfunctioning, hence the root cause of their side effects. Nevertheless, healthy cells are more competent in damage-repairing activities and retain their normal functions much faster than compared to cancer cells. This allows RT to maximize dose efficiency while limiting its effect on surrounding normal cells or tissues.

2.3. Targeted therapy

Cancer patients may become resistant to multiple chemotherapy treatments. Targeted therapy uses drugs or molecular inhibitors to regulate cancer progression pathways, making it more specific and effective than traditional treatments. This therapy has overcome difficulties in traditional cancer treatment. Ovarian cancer is the most common type of cancer-related to gynecology (Siegel et al., 2018). Molecular targeted therapy has proven to be effective for ovarian cancer by using anti-vascular endothelial growth factor (VEGF) monoclonal antibodies and poly ADP -ribose polymerase (PARP) inhibitors including targets such as PI3K/AKT and RAS/RAF/MER pathways (Guan and Lu, 2018). In the case of breast cancer, the human epidermal growth factor receptor 2 (HER2) gene encodes for a protein found on the breast cancer cell surface that is involved in cell growth. Its presence is notorious for breast cancer patients and this condition is called HER2-positive breast

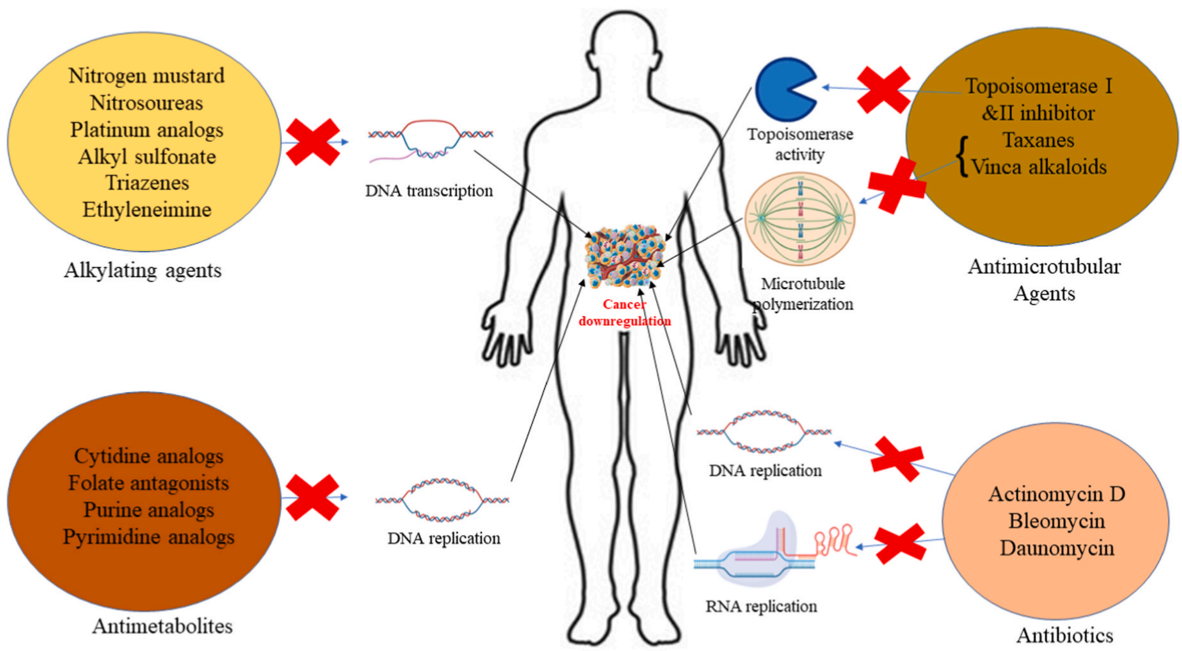

Fig. 1. Effects of different types of chemotherapeutic agents on various cellular activity.

cancer. Targeted therapy associated with HER2 as a target has proven to be highly effective showing its tremendous significance and improvement in cancer therapy (Lev, 2020). Another type of most lethal breast cancer is triple-negative breast cancer (TNBC), where it is negative in terms of the absence of expression of three receptors namely, progesterone receptor (PR), estrogen receptor (ER), and HER2. Standardized treatment of breast cancer doesn't seem to work in the case of TNBC due to its lack of these receptors and targeted therapy for its ailment is only evolving. So far categorizing TNBC into its subtype and assembling their different molecular models has helped in identifying the target molecules responsible for cancer progression (Yin et al., 2020). Meanwhile, targeted therapy is approved for several other cancers like lung, colon, malignant lymphoma, and biliary tract tumors and others as well (Merla et al., 2015; Wang et al., 2020).

2.4. Excisional surgery

Solid cancer is a type of cancer where a mass of tumor cells grow on an organ and surgery is the most effective way of curing it. Advances in technology and oncology have led to increased survival rates and improved postoperative quality. Patients are expected to experience long-term benefits after a year of surgery. (Wang et al., 2020; Schwarzer et al., 2006). In many cases, chemotherapy or other modes of treatment may help in cancer cell growth resistance and prolonged survival of an individual but otherwise, surgery falls under the category of curative treatment for several types of cancer. Surgery is often suggested by doctors for advanced cancer stages as risk reduction surgery along with postoperative adjuvant treatments such as ionization RT or chemotherapy (Wyld et al., 2015). Broadly, any surgery can be classified into two types-minimally invasive surgery (MIS) and open surgery. MIS surgery focuses on limiting incision size, aiding postoperative recovery, and reducing blood loss, scarring, pain, and infection risk. It offers advantages such as reduced scarring, pain, and infection risk. (Huo et al., 2019).

Laparoscopy surgery, developed 100 years ago, is considered safer than open surgery for cancer patients. It offers multi-visceral restrictions, better screening, visualization, and early access to adjuvant chemotherapy. (Amodu et al., 2022). High-quality cameras and monitor screens are used in surgery to visualize the insides of a body, aiding in cancer treatment, screening, and staging, and aiding in diagnosis. (Ramshaw, 1997). MIS offers advantages but can be risky due to cancer's metastatic nature. It aims to invade and clean up tumor cells, preventing infection in different locations (Huo et al., 2019). On the other hand, open surgery is ill-advised for advanced cancer patients due to large incisions, while MIS has better short-term effects but yields similar long-term postsurgical results. (Cleary et al., 2018). The conversion rate of laparoscopy to open surgery ranges between 11 percent to 29 percent and the reason for this is cancer extension at adjacent organs. Controversy still exists as to which surgery is better, open or minimal but the preference is clearly based on the type and stage of cancer including the physiological condition of the patient (Reza et al., 2006).

3. Association of chemotherapeutic drugs with the immune system

As discussed earlier, there are several well-known chemotherapeutic drugs that are used in cancer therapy. The use of chemicals to treat diseases was established in the early 1900s but in order to understand the functioning of drugs for cancer drug screening, a program was established in the year 1935 at the National Cancer Institute (NCI) to test over 3000 naturals as well as synthetic compounds on murine models. This also gave rise to hormonal therapy to treat breast cancer in women and prostate cancer in men. However, combinational or adjuvant chemotherapy to RT and surgery was only introduced to treat cancer around the 1970s (DeVita and Chu, 2008). Based on the mechanism of action, classifications of chemotherapeutic drugs have been done. Alkylating agents like cisplatin, bendamustine, dacarbazine, busulfan, etc. inhibit the replication and transcription of DNA. Antimetabolites like azacitidine, methotrexate, cladribine, etc. inhibit the replication of DNA. Antimicrotubular agents like anthracyclines (doxorubicin), irinotecan, vinblastine, etc. prevent repair and replication of DNA by inhibiting Topoisomerase I & II, and disruption and inhibition of microtubule synthesis. Antibiotics like bleomycin, actinomycin D, daunomycin, etc. inhibit DNA and RNA synthesis. Other miscellaneous chemotherapeutic drugs are tretinoin, proteasome inhibitors, arsenic trioxide, and hydroxyurea (Amjad et al., 2023). In Tables 1 and 2 some commonly used chemotherapeutic agents are stated with their class and mechanism of

Table 1
Different classes of chemotherapeutic drugs and their mechanism of action.

S.I. No	Class of Drug	Mechanism of Action	Types	References
1	Alkylating Agent	These compounds react with nucleophilic sites on proteins and nucleic acids to produce an unstable alkyl group, R–CH2+. Disrupts transcription and DNA replication.	Nitrogen mustard (cyclophosphamide, ifosfamide, etc.)	Singh et al. (2018)
			Nitrosoureas (lomustine, etc.)	Amjad et al. (2023)
			Platinum analogs (carboplatin, cisplatin, etc.)	Fouladi et al. (2009)
			Alkyl sulfonate (Busulfan)	Pishnamazi et al. (2020)
			Triazenes (Procarbazine, dacarbazine, etc.)	Irfan et al. (2020)
			Ethyleneimine (Thiotepa)	Alexander et al. (2019)
2	Antimetabolites	Replication of DNA is inhibited.	Cytidine analogs (cytarabine, azacitidine, gemcitabine, etc.) - Inhibits DNA polymerase or methyltransferase activity	Khan et al. (2012)
			Folate antagonists (pemetrexed, methotrexate, etc.) - decreases folate availability which inhibits the synthesis of purine nucleotides and thymidylate	Koźmiński et al. (2020)
			Purine analogs (clofarabine, nelarabine, etc.) - guanine imitations that act as false metabolite	Löwenberg et al. (2017)
			Pyrimidine analogs (capecitabine) - interferes with DNA synthesis and repair	O'Shaughnessy et al. (2012)
3	Antimicrotubular Agents	Inhibits DNA and RNA synthesis as well as Topoismorease II activity	Topoisomerase II inhibitors - Anthracyclines (doxorubicin, daunorubicin, idarubicin, etc.)	Thorn et al. (2011)
		Forms a ternary complex structure and prevents the release of Topoisomerase I	Topoisomerase I inhibitors: Irinotecan, Topotecan	Fujita et al. (2015)
		Interferes with microtubule polymerization/depolymerization balance and causes abnormal cell functioning leading to apoptosis.	Taxanes – paclitaxel, docetaxel, cabazitaxel	Zhu and Chen (2019)
		Prevents the cell from proceeding from the metaphase by binding to tubulin	Vinca alkaloids: vinblastine, vincristine, vinorelbine	Mohseni et al. (2016)
4	Antibiotics	Inhibits RNA and DNA replication	actinomycin D, bleomycin, daunomycin	Murphy and Yee (2017)

action and their effect on different immune cells.

Cancer cell variations capable of evading host defense mechanisms against uncontrolled proliferation and anticancer immunosurveillance may arise in circumstances of particularly aggressive neoplastic lesions. In such a case, the host immune system may begin to operate by undertaking cancer immunoediting, which may result in the development of cancer cells that are highly immunoevasive and resistant to antitumor immunity (Garg et al., 2015). Immunogenic cell death (ICD) is characterized by changes in the makeup of the cell surface as well as the release of soluble mediators in a time-dependent manner. These signals enhance the presentation of tumor antigens to T lymphocytes via a variety of receptors produced by dendritic cells (Kroemer et al., 2013). As the cell membranes permeabilize during secondary necrosis, cells undergoing ICD release the nuclear protein HMGB1. This promotes DC recruitment into the tumor bed driven by ATP, tumor antigen engulfment by DCs, and optimum antigen presentation to T cells. Overall, these mechanisms produce a powerful IL-1- and IL-17-dependent, and IFN-mediated immune response including CTLs, which can finally lead to the elimination of chemotherapy-resistant tumor cells. Based on these assumptions, it is suggested that a limited panel of chemotherapeutics (some of which are now linked with significant rates of success) can elicit an immunogenic combination of tumor cell stress and death (Galluzzi et al., 2012).

In the immune system, not all cells exhibit antitumor activities. Different kinds of chemotherapeutic drugs have been seen to eliminate antitumor as well as protumor T cells. For instance, paclitaxel and cyclophosphamide can inhibit Foxp3+ T cells or regulatory T cells (T_{regs}) inhibition in a tumor microenvironment (TME), and with the high influx of CD8+T cells showed overall better survival in breast cancer patients. Some drugs like cisplatin can inhibit the activity of myeloid-derived suppressor cells (MDSC) and hinder their immune suppressing capability, also can activate dendritic cells (DCs) in mice. On the other hand, docetaxel, 5-FU, and gemcitabine can kill MDSC while they show no cytotoxic effects on DC functioning (Rébé and Ghiringhelli, 2015). There are few *invitro* studies show chemotherapeutic agents like doxorubicin, vinblastine, paclitaxel, mitomycin C, and methotrexate at non-cytotoxic concentrations have the ability to increase the antigen-presenting ability of immature DCs in IL-12 dependent manner (Shurin et al., 2009). On the other hand, research has shown that chemotherapy has significantly reduced the levels of lymphocytes such as B, NK, and T cells in breast cancer patients, a matter which should be considered effectively while the clinical treatment of cancer patients (Verma et al., 2016). This shows that chemotherapy and the drugs used in this mode of treatment directly affect the regulation and functioning of different immune cells both positively and negatively or maybe not at all contributing to its immunomodulatory property (Zitvogel et al., 2011). Hence, some chemotherapy drugs activate immunomodulatory pathways in cancer cells through molecular mechanisms that do not always correspond to their cytotoxic mechanism of action (Galluzzi et al., 2020).

Several immune-based combinations are being studied in order to improve overall response and clinical outcomes, one of which is immune checkpoint inhibitor (ICI) monotherapy. ICI supports the investigation of techniques to improve the efficacy of immunotherapy and has recently appeared to be successful in a limited group of patients with metastatic triple-negative breast cancer (mTNBC) (Rizzo et al., 2022a,b; Santoni et al., 2023). Some common potential biomarkers in response to ICI therapy in mTNBC patients are PD-L1, tumor mutational burden (TMB), Ladiratuzumab vedotin (LIV-1) and tumor-infiltrating lymphocytes (TILs). Since chemoimmunotherapy has been shown to be beneficial in PD-L1 positive patients, PD-L1 is now regarded as the most significant prognostic biomarker (Rizzo and Ricci, 2022; Rizzo et al., 2022a,b).

4. Therapeutic application of chemotherapeutic drugs in immunomodulation in cancer

Conventional chemotherapeutic drugs aim to kill the cancer cell and prevent it from its progression. However, anti-cancer chemotherapeutic drug resistance is a real issue that slows down the treatment procedure. Insights into the molecular mechanism involved in its effect on the

Table 2
Different chemotherapeutic drugs and their effect on the immune cells.

Sl. No.	Immune Cell Type	Chemotherapy Treatment	Cancer Type	Effect on Immune Cells	References
1.	$CD8^+$ T cells	Cyclophosphamide	Brain tumor Non-Hodgkin lymphoma Sarcoma	The first cycle of treatment resulted in a 50% drop in pre-treated peripheral $CD8^+$ T cell levels, and $CD8^+$ T cell numbers did not recover after three cycles. $CD8^+$ T cell levels did not recover after 10 cycles	Truong et al. (2021)
		Platinum-based agents coupled with paclitaxel or gemcitabine	Malignant mesothelioma Non-small cell lung cancer (NSCLC)	After the first week, there is a fast decrease in $CD8^+$ T cell numbers.	Scurr et al. (2017)
			Colorectal cancer	The mean absolute number of $CD8^+$ T cells increased in the first week of therapy, then declined and remained around baseline during the first course of treatment.	
2.	$CD4^+$ T cells	Temozolomide	Glioblastoma	The number of $CD4^+$ T cells was reduced by half as compared to pre-treatment values.	Verma et al. (2016)
		Docetaxel, Doxorubicin and Cyclophosphamide	Breast Cancer	The number of $CD4^+$ T cells was reduced by half as compared to pre-treatment values.	Verma et al. (2016)
		Fluorouracil, leucovorin, doxorubicin and cyclophosphamide		drop in $CD4^+$ cell count upto 12 months	Hakim et al. (1997)
3.	NK cells	Combination of cisplatin, bleomycin, etoposide and granulocyte-macrophage colony-stimulating factor (GM-CSF)	Testicular cancer	The mean absolute number of NK cells declined dramatically after treatment began, then gradually rose but did not recover to pre-treatment levels by the conclusion of the first cycle (day 21).	Kubota et al. (2001)
		Combination of doxorubicin with fluorouracil and cyclophosphamide	Breast cancer	After the first two cycles, there was a considerable rise in NK cell number, which remained until the end of therapy (at cycle 6).	Wijayahadi et al. (2007)
4.	Regulatory T cells	5-fluorouracil, leucovorin and oxaliplatin (FOLFOX 6) 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI)	Gastric cancer Colorectal cancer	A substantial reduction in the frequency and number of Tregs among PBMCs seven days after the first dose of therapy, particularly in a group of patients who had a high proportion of Tregs before treatment	Wang et al. (2018) and Maeda et al. (2011)
		Cisplatin-based chemotherapy	NSCLC	After the first week of treatment, there was a decrease in circulating Treg levels, and this suppressive effect lasted until the completion of therapy (four cycles).	
		Cyclophosphamide	On different animal models of cancer	Treg depletion and lack of suppressive activity were proven to improve immunological dysfunction.	
5.	B-Lymphocytes	Cyclophosphamide-, epirubicin/ doxorubicin, paclitaxel and platinum-containing chemotherapy regimens		The absolute quantity and frequency of all B-cell subsets were dramatically reduced in patients over the course of two to twelve weeks.	Waidhauser et al. (2020)
		Platinum-based chemotherapy		B cells recover in the long run, with cell counts returning to pre-treatment levels one year after therapy is stopped.	Ziebart et al. (2017)

immune system are relatively unknown. On the condition that we understand the underlying mechanism associated with these drugs and immune cell responses, therapeutic applications to treat cancer patients may boost the field of cancer therapy. Fig. 2 shows how different chemotherapeutic agents affect the signaling pathway responsible for immune regulation in our body. In this section of the review, we discuss some common chemotherapeutic drugs and their direct correlation with immunomodulation via molecular pathway and their therapeutic applications.

4.1. PI3k/Akt pathway

The phosphatidylinositol 3-kinase (PI3K)-Akt signaling pathway controls essential cellular processes like transcription, translation,

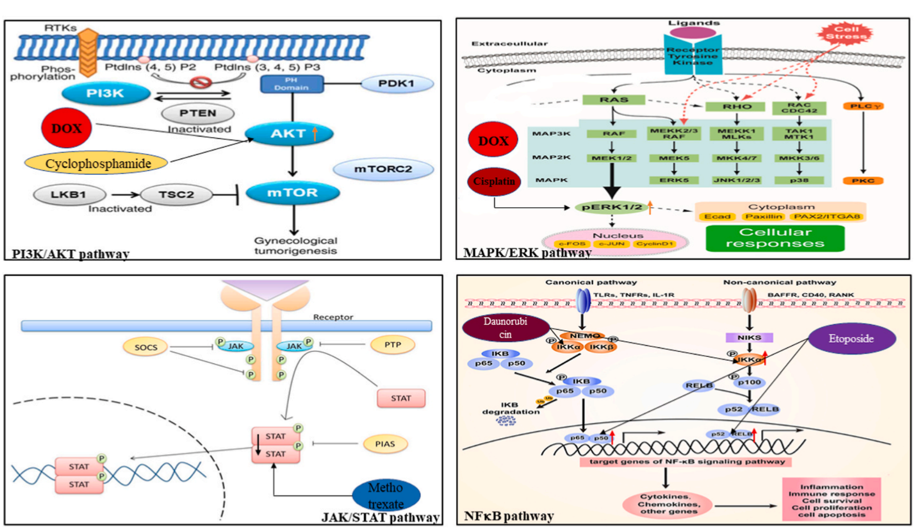

Fig. 2. Different chemotherapeutic agents affecting signaling pathways that take part in immunomodulation.

proliferation, growth, and survival. It is activated by a variety of physiological stimuli or toxic insults (Vivanco and Sawyers, 2002). The kinase Akt/PKB, where PKB stands for protein kinase B, a serine/threonine kinase, is essential in this pathway. Disordered PI3K-Akt pathway activation has been linked to the emergence of illnesses like cancer, type 2 diabetes, and autoimmune disease. PI3K is in charge of phosphorylating PI (4, 5) P2's inositol ring at position 3 to produce PI (3, 4, 5) P3, a potent second messenger needed for insulin action and survival signaling (Nicholson and Anderson, 2002; Osaki et al., 2004).

As understood, in cancer unregulated PI3K signaling is very common. Increased PI3K production results in excessive production of lipid second messengers, which then unnecessarily stimulate signal transduction and cause cell transformation. Considering the role of Akt in promoting cell survival through inhibiting proapoptotic proteins and pathways, Akt's activation state may influence a tumor cell's sensitivity to chemotherapy (Dibble and Manning, 2009). Research made on the effects of chemotherapeutic drugs to study cranial activity showed that DOX and cyclophosphamide, an anthracycline and an alkylating agent respectively activate extracellular signal-regulated kinase (Erk) and Akt signaling pathways. Western blot analysis showed phosphorylated or activated forms of Erk 1/2 and Akt in chemotherapeutically treated ovariectomized (OVX) murine models (Salas-Ramirez et al., 2015). Another anti-cancer drug is triciribine which has been used in clinical trials for its Akt-inhibiting property for phase I and phase II hypertriglyceridemia and hyperglycemia patients (Falasca, 2010).

4.2. MAPK/ERK pathway

Cell survival and proliferation are two crucial cellular processes that are fundamentally regulated by the Mitogen-activated protein kinase/ERK (MAPK/ERK) signaling pathway, and its improper activation is linked to cellular transformation and carcinogenesis (Guo et al., 2020). Through transcriptional stimulation of the human telomerase catalytic subunit gene (hTERT), the Ets transcription factor, which is phosphorylated by ERK, replenishes telomere repeats and aids in senescence avoidance. By suppressing the activity of pro-apoptotic BCL-2 family proteins like BAX and BIM and promoting the production of anti-apoptotic BCL-2 family members including BCL-2, BCL-XL, and MCL-1, the MAPK/ERK signaling pathway promotes survival. The expression of EMT-related genes, including those that code for mesenchymal proteins and transcriptional inhibitors of epithelial genes, is also increased by this pathway, which helps to induce and maintain the mesenchymal state of the tumor cells (Yue and López, 2020; Moon and Ro, 2021).

Cell proliferation and survival have been associated with the activation of the ERK pathway. ERK can affect proliferation in dual ways (Marshall, 1999). In the human carcinoma cell line, A431 with overexpressed epidermal growth factor (EGF) receptors, anti-cancer drugs like taxol, ceramide, and etoposide increased with the activity of ERK with delayed response. In the MCF7 cell line, taxol didn't induce any initial ERK activation but was followed by hyperactivation between 9 and 12 h. On the other hand, only ceramide initiated two-phased activation similar to what has been noticed in HeLa cells (Boldt et al., 2002). Another chemotherapeutic drug, cisplatin has also been reported to activate ERK in HeLa cells or ovarian carcinoma cells (Persons et al., 1999; Wang et al., 2000). Inhibition of cisplatin-induced phosphorylation of ERK increased the cytotoxicity effect. Additionally, tamoxifen-responsive breast cancers dependent on estrogen frequently develop resistance over time. It has been demonstrated that this change in the hormone-response pattern is accompanied by a change in cell growth from MAPK-independent to MAPK-dependent (Sebolt-Leopold, 2000). Hence, as the potential benefits of MAPK inhibition are limited to a specific subset of tumor cells, treatment must be customized for each patient.

4.3. Jak/Stat pathway

Janus kinases-Signal Transducers and Activators of Transcription (JAK-STAT) signaling is essential for the development of cancer, either as a tumor-specific growth/metastasis driver or as a regulator of immune surveillance. The enhanced production of cytokines is just one of several pathways that might lead to constitutive activation of JAK-STAT signaling. The most notable instance is increased interleukin (IL)-6, which communicates either by a traditional technique that is constrained by cell-type-specific expression of IL-6 receptor (IL-6R), which interacts with the widely expressed -subunit receptor, GP130, or through a novel mechanism. Increased STAT 3 oncogenic transcription factor signal transducer and activator of transcription (JAK)-mediated activation is the end outcome. As an alternative, JAK-STAT signaling can be activated in any cell by IL-6 ″trans-signaling," which is mediated by IL-6 contact with a soluble IL-6R.

The transcription factor family includes STAT proteins that relay signals produced by cytokine receptors into the nucleus. When cytokine receptors are activated, JAK is phosphorylated, which produces receptor docking sites for cytoplasmic STAT protein recruitment. Numerous growth factors, including epidermal growth factor, hepatocyte growth factor, and platelet-derived growth factor, also influence the activation of STAT signaling. The dimerized, translocated STATs bind to particular DNA response elements before modulating cell proliferation and differentiation. Methotrexate and aminopterin at noncytotoxic concentrations reduced the levels of phosphorylated Jak-1 and Jak-2 in HDLM-2 cells. Methotrexate can also reduce the levels of phosphorylated STAT3 and STAT5 in HEL cells (Thomas et al., 2015). Time and dose-dependent administration of a proposed chemotherapeutic agent named Cucurbitacin B have been reported to cause cell cycle arrest at the G2-M phase, leading to a cell apoptotic pathway in pancreatic cancer cells. It also boosts the antiproliferative properties of gemcitabine when used in combination. Cucurbitacin B is also associated with the inactivation of phosphorylated JAK2, STAT3, and STAT5 (Toyonaga et al., 2003; Thoennissen et al., 2009).

4.4. NFκB pathway

Nuclear factor κB (NFκB) controls a number of cellular processes such proliferation, survival, invasion, and angiogenesis. It plays a significant role in the initiation and spread of cancer. NFκB signaling dysregulation is widely seen in a variety of cancer forms, including breast, lung, colon, and prostate cancer. In cancer cells, upstream signaling pathways such the tumor necrosis factor (TNF) receptor, Toll-like receptor, and EGFR pathways frequently act as a mediator for the activation of NFκB. By increasing the expression of cytokines like IL-6 and IL-8, which encourage inflammation and angiogenesis, as well as anti-apoptotic genes like Bcl-2 and Bcl-xL, NFκB activation in cancer cells can promote tumor growth and survival. Moreover, by activating genes that control cell motility like MMP-9 and uPA, NFκB can encourage invasion and metastasis (Xia et al., 2014).

Due to its critical role in cancer development and progression, NFκB has emerged as an attractive target for cancer therapy. Inhibitors of nuclear factor-κB (IκB) kinase (IKK), the upstream kinase that activates NFκB, and inhibitors of NFκB DNA-binding activity are two classes of drugs that are currently being developed in preclinical and clinical settings. These medications have the potential to treat cancer, either on their own or in conjunction with other therapies (Xia et al., 2018).

However, DOX-induced hepatotoxicity NFκB expression can be downregulated to lessen the inflammatory response. Reactive oxygen species (ROS), a key player in anti-cancer signaling events such as the release of the tumor suppressor p53 and cytochrome-c, followed by the activation of caspase enzymes and induction of apoptosis, are sparked by DOX (Lu et al., 2019). DOX also increases the expression of NFκB p65 subunit *in vivo* cardiac tissues. There are reports that another chemotherapeutic agent daunorubicin enhances the expression of IκBα protein in fibrosarcoma cells hence being able to activate the NFκB pathway. Additionally, we find that etoposide, an anti-cancer drug, activates NFκB whereas, the drug vincristine kills cells and this process is enhanced by the inhibition of NFκB (Yamamoto and Gaynor, 2001). Hence, the approaches which target to inhibit or block NFκB complex to suppress its pro-oncogenic property in combination with anti-cancer drugs can be beneficial to treat cancer.

5. Discussion

Chemotherapy has been demonstrated to be a highly successful method for treating a number of cancers, including testicular cancer, infantile CML, ALL, Hodgkin disease, choriocarcinoma, etc. being prominently included in the contemporary therapeutic archives. However, for some cancers (such as NSCLC, pancreatic, melanoma, liver, etc.) the findings have reached a plateau, and it is caused by the outdated assumptions that underlie the existing systemic therapy approaches thus that must be changed (Trédan et al., 2007). Chemo-immunotherapy still has certain knowledge gaps that must be filled so that it can be used effectively. One challenge in chemoimmunotherapy is determining the best chemotherapeutic drugs to use in conjunction with various immunotherapies. Different chemotherapeutic drugs can have variable effects on the immune system, making it difficult to discover the appropriate combination that maximizes the immune response against cancer cells while minimizing damage. While the fundamental concept of chemoimmunotherapy is to combine the cytotoxic effects of chemotherapy with the immune-boosting benefits of immunotherapy, the precise mechanisms behind this interaction are not entirely known. Researchers are still working to understand how chemotherapy affects the tumor microenvironment and immune response, and how this interaction might be used to improve treatment results (Fujimoto et al., 2023). Table 3 lists a few popular chemotherapeutic medications and the cancers they treat, as well as their side effects.

The reason why chemotherapy-induced tumor cell death occurs is that stressed and dying cancer cells emit immunogenic signals. Certain anticancer chemotherapeutics cause immunogenic cell death (ICD), which causes cancer cells to emit danger-associated molecular patterns (DAMP). DAMP attracts, activates, and matures dendritic cells (DC), which in turn primes effector T cells. In this situation, calreticulin, which is exposed at the surface of cancer cells during an early stage of ICD, acts as a phagocytic signal and initiates the development of immunological synapses between cancer cells and innate immune effector cells (such as dendritic cells) (Cerrato et al., 2020). These signals recognized by dendritic cells cause a corresponding immunological response (including $CD8^+$ T cells and Interferon (IFN)γ signaling) to be triggered, enabling the immune system to manage leftover tumor cells. Hence, there is a need for extensive clinical trials to investigate this situation on all fronts. Pharmacological substances should be assessed to determine which ones cause immunogenic cell death and which ones do not at the level of pharmacology. So far, we understood that prior to the loss of cell viability, common chemotherapeutic drugs like DOX caused IκB degradation and NF–B transcriptional activation (Bian et al., 2001). On the other hand, methotrexate causes the phosphorylation of STAT molecules. To elude this, for each potential immune-related flaw that results in treatment failure, compensatory strategies can be developed. When paired with substances that restore their immunogenicity in mice, cytotoxic chemotherapy drugs that cannot kill immune cells on their own become more effective (Martins et al., 2011). Additionally, other DNA-damaging drugs like etoposide and mitomycin C do not cause immunogenic cell death, whereas, anthracyclin-treated tumor cells are particularly good at inducing an anticancer immune response. Calreticulin, a conserved protein present in the endoplasmic reticulum and involved in cellular functions, is translocated quickly and at a pre-apoptotic state to the cell surface due to the presence of anthracyclines. A blockade or knockdown of CRT prevented tumor cells from being phagocytosed by dendritic cells and after being treated with anthracyclin their immunogenicity was restored in mice (Obeid et al., 2007). This suggests that treatment failure is caused by the absence of immunogenic signals like calreticulin exposure and may be resolved by reactivating the signaling system. Thus, therapeutic treatments can be used to block any of the several immunosuppressive pathways that could explain why immune effectors are unable to assault tumor cells.

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Declaration of competing interest

The authors declare that they have no known competing financial

Table 3
Some common Chemotherapeutic drugs along with common side effects.

Sl. No.	Chemotherapeutic Drug	Type of Cancer	Side Effects	References
1.	Cisplatin	Human cancers including bladder, head and neck, lung, ovarian, and testicular cancers.	Mild nausea Vomiting Diarrhoea Temporary hair loss Loss in the ability to taste food	Dasari and Tchounwou (2014) and Gold and Raja. (2023)
2.	**Paclitaxel**	Ovarian, breast, and lung cancer, Kaposi's sarcoma	Hypersensitivity and neuropathies	Weaver, 2014
3.	Doxorubicin	Soft tissue and bone sarcomas, as well as breast, ovary, bladder, and thyroid cancer. It is also used to treat acute lymphoblastic leukemia, acute myeloblastic leukemia, Hodgkin lymphoma, and small-cell lung cancer.	Acute nausea and vomiting, stomatitis, gastrointestinal disturbances, alopecia, baldness, neurologic disturbances, cumulative cardiotoxicity, and bone marrow aplasia	Johnson-Arbor and Dubey (2022) and Carvalho et al. (2009)
4.	**Fluorouracil (5-FU)**	various visceral and dermatologic malignancies	Mainly Cardiotoxicity	Casale and Patel (2022) and Alter et al. (2006)
5.	**Methotrexate**	Many types of cancers including ulcerative colitis, lymphoma (non-Hodgkin's type), carcinoma of the breast, small-cell carcinoma of the lung, epidermal tumors of the head and neck, and carcinoma of the ovary.	Liver damage leading to fibrosis or cirrhosis	Hanoodi and Mittal (2023) and Zachariae (1990)
6.	**Vincristine**	Acute lymphocytic leukemia, lymphoid blast crisis of chronic myeloid leukemia, and Hodgkin and Non-Hodgkin lymphoma	Peripheral neuropathy	Below and Das (2022) and Elshamy et al. (2022)

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Data availability

No data was used for the research described in the article.

References

Alexander, T.C., Kiffer, F., Groves, T., Anderson, J., Wang, J., Hayar, A., Chen, M.T., Rodriguez, A., Allen, A.R., 2019. Effects of thioTEPA chemotherapy on cognition and motor coordination. Synapse (New York, N.Y.) 73 (6), e22085. https://doi.org/10.1002/syn.22085.

Alfouzan, A.F., 2021. Radiation therapy in head and neck cancer. Saudi Med. J. 42 (3), 247–254. https://doi.org/10.15537/smj.2021.42.3.20210660.

Alter, P., Herzum, M., Soufi, M., Schaefer, J.R., Maisch, B., 2006. Cardiotoxicity of 5-fluorouracil. Cardiovasc. Hematol. Agents Med. Chem. 4 (1), 1–5. https://doi.org/10.2174/187152506775268785.

Amjad, M.T., Chidharla, A., Kasi, A., 2023. Cancer chemotherapy. In: StatPearls. StatPearls Publishing.

Amodu, L.I., Howell, R.S., Daskalaki, D., Allendorf, J.D., 2022. Oncologic benefits of laparoscopic and minimally invasive surgery: a review of the literature. Ann. Laparosc. Endosc. Surg. 7 (0) https://doi.org/10.21037/ales-21-19.

Baskar, R., Lee, K.A., Yeo, R., Yeoh, K.W., 2012. Cancer and radiation therapy: current advances and future directions. Int. J. Med. Sci. 9 (3), 193–199. https://doi.org/10.7150/ijms.3635.

Below, J., Das, J., 2022. Vincristine. In: StatPearls. StatPearls Publishing.

Bian, X., McAllister-Lucas, L.M., Shao, F., Schumacher, K.R., Feng, Z., Porter, A.G., Castle, V.P., Opipari Jr., A.W., 2001. NF-kappa B activation mediates doxorubicin-induced cell death in N-type neuroblastoma cells. J. Biol. Chem. 276 (52), 48921–48929. https://doi.org/10.1074/jbc.M108674200.

Boldt, S., Weidle, U.H., Kolch, W., 2002. The role of MAPK pathways in the action of chemotherapeutic drugs. Carcinogenesis 23 (11), 1831–1838. https://doi.org/10.1093/carcin/23.11.1831.

Carvalho, C., Santos, R.X., Cardoso, S., Correia, S., Oliveira, P.J., Santos, M.S., Moreira, P.I., 2009. Doxorubicin: the good, the bad and the ugly effect. Curr. Med. Chem. 16 (25), 3267–3285. https://doi.org/10.2174/092986709788803312.

Casale, J., Patel, P., 2022. Fluorouracil. In: StatPearls. StatPearls Publishing.

Cerrato, G., Liu, P., Martins, I., Kepp, O., Kroemer, G., 2020. Quantitative determination of phagocytosis by bone marrow-derived dendritic cells via imaging flow cytometry. Methods Enzymol. 632, 27–37. https://doi.org/10.1016/bs.mie.2019.07.021.

Chabner, B.A., Roberts Jr., T.G., 2005. Timeline: chemotherapy and the war on cancer. Nat. Rev. Cancer 5 (1), 65–72. https://doi.org/10.1038/nrc1529.

Cleary, R.K., Morris, A.M., Chang, G.J., Halverson, A.L., 2018. Controversies in surgical oncology: does the minimally invasive approach for rectal cancer provide equivalent oncologic outcomes compared with the open approach? Ann. Surg Oncol. 25 (12), 3587–3595. https://doi.org/10.1245/s10434-018-6740-y.

Dasari, S., Tchounwou, P.B., 2014. Cisplatin in cancer therapy: molecular mechanisms of action. Eur. J. Pharmacol. 740, 364–378. https://doi.org/10.1016/j.ejphar.2014.07.025.

Delaney, G., Jacob, S., Featherstone, C., Barton, M., 2005. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. Cancer 104 (6), 1129–1137. https://doi.org/10.1002/cncr.21324.

DeVita Jr., V.T., Chu, E., 2008. A history of cancer chemotherapy. Cancer Res. 68 (21), 8643–8653. https://doi.org/10.1158/0008-5472.CAN-07-6611.

Dibble, C.C., Manning, B.D., 2009. A molecular link between AKT regulation and chemotherapeutic response. Cancer Cell 16 (3), 178–180. https://doi.org/10.1016/j.ccr.2009.08.011.

Drăgănescu, M., Carmocan, C., 2017. Hormone therapy in breast cancer. Chirurgia (Bucharest, Romania: 1990) 112 (4), 413–417. https://doi.org/10.21614/chirurgia.112.4.413.

Elshamy, A.M., Salem, O.M., Safa, M.A.E., Barhoma, R.A.E., Eltabaa, E.F., Shalaby, A.M., Alabiad, M.A., Arakeeb, H.M., Mohamed, H.A., 2022. Possible protective effects of CO Q10 against vincristine-induced peripheral neuropathy: targeting oxidative stress, inflammation, and sarmoptosis. J. Biochem. Mol. Toxicol. 36 (3), e22976 https://doi.org/10.1002/jbt.22976.

Fait, T., 2019. Menopause hormone therapy: latest developments and clinical practice. Drugs in context 8, 212551. https://doi.org/10.7573/dic.212551.

Falasca, M., 2010. PI3K/Akt signalling pathway specific inhibitors: a novel strategy to sensitize cancer cells to anti-cancer drugs. Curr. Pharmaceut. Des. 16 (12), 1410–1416. https://doi.org/10.2174/138161210791033950.

Fouladi, M., Gururangan, S., Moghrabi, A., Phillips, P., Gronewold, L., Wallace, D., Sanford, R.A., Gajjar, A., Kun, L.E., Heideman, R., 2009. Carboplatin-based primary chemotherapy for infants and young children with CNS tumors. Cancer 115 (14), 3243–3253. https://doi.org/10.1002/cncr.24362.

Fujimoto, D., Morimoto, T., Tamiya, M., Hata, A., Matsumoto, H., Nakamura, A., Yokoyama, T., Taniguchi, Y., Uchida, J., Sato, Y., Yokoi, T., Tanaka, H., Furuya, N., Masuda, T., Sakata, Y., Miyauchi, E., Hara, S., Saito, G., Miura, S., Kanazu, M., et al., 2023. Outcomes of chemoimmunotherapy among patients with extensive-stage small cell lung cancer according to potential clinical trial eligibility. JAMA Netw. Open 6 (2), e230698. https://doi.org/10.1001/jamanetworkopen.2023.0698.

Fujita, K., Kubota, Y., Ishida, H., Sasaki, Y., 2015. Irinotecan, a key chemotherapeutic drug for metastatic colorectal cancer. World J. Gastroenterol. 21 (43), 12234–12248. https://doi.org/10.3748/wjg.v21.i43.12234.

Galluzzi, L., Senovilla, L., Zitvogel, L., Kroemer, G., 2012. The secret ally: immunostimulation by anticancer drugs. Nature reviews. Drug Discov. 11 (3), 215–233. https://doi.org/10.1038/nrd3626.

Galluzzi, L., Humeau, J., Buqué, A., Zitvogel, L., Kroemer, G., 2020. Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors. Nat. Rev. Clin. Oncol. 17 (12), 725–741. https://doi.org/10.1038/s41571-020-0413-z.

Galmarini, D., Galmarini, C.M., Galmarini, F.C., 2012. Cancer chemotherapy: a critical analysis of its 60 years of history. Crit. Rev. Oncol.-Hematol. 84 (2), 181–199. https://doi.org/10.1016/j.critrevonc.2012.03.002.

Garg, A.D., Dudek-Peric, A.M., Romano, E., Agostinis, P., 2015. Immunogenic cell death. Int. J. Dev. Biol. 59 (1–3), 131–140. https://doi.org/10.1387/ijdb.150061pa.

Gold, J.M., Raja, A., 2023. Cisplatin. In: StatPearls. StatPearls Publishing.

Guan, L.Y., Lu, Y., 2018. New developments in molecular targeted therapy of ovarian cancer. Discov. Med. 26 (144), 219–229.

Guo, Y.J., Pan, W.W., Liu, S.B., Shen, Z.F., Xu, Y., Hu, L.L., 2020. ERK/MAPK signalling pathway and tumorigenesis. Exp. Ther. Med. 19 (3), 1997–2007. https://doi.org/10.3892/etm.2020.8454.

Hakim, F.T., Cepeda, R., Kaimei, S., Mackall, C.L., McAtee, N., Zujewski, J., Cowan, K., Gress, R.E., 1997. Constraints on CD4 recovery postchemotherapy in adults: thymic insufficiency and apoptotic decline of expanded peripheral CD4 cells. Blood 90 (9), 3789–3798.

Hanoodi, M., Mittal, M., 2023. Methotrexate. In: StatPearls. StatPearls Publishing.

Huo, Q., Yang, Q., Gorczynski, R.M., Li, T., 2019. Oncological minimally invasive surgery. JAMA Oncol. 2019, 1903297 https://doi.org/10.1155/2019/1903297. Published 2019 Sep. 12.

Irfan, N., Samuel, E., Rafi Ranjha, F., Waheed, A., Abu Bakar, M., Usman, S., Butt, S., Rashid, A., Yousaf, I., 2020. Toxicity profile of procarbazine lomustine and vincristine chemotherapy in low-grade glioma - retrospective review. Cureus 12 (10), e11070. https://doi.org/10.7759/cureus.11070.

Johnson-Arbor, K., Dubey, R., 2022. Doxorubicin. In: StatPearls. StatPearls Publishing.

Khan, C., Pathe, N., Fazal, S., Lister, J., Rossetti, J.M., 2012. Azacitidine in the management of patients with myelodysplastic syndromes. Therapeut. Adv. Hematol. 3 (6), 355–373. https://doi.org/10.1177/2040620712464882.

Koźmiński, P., Halik, P.K., Chesori, R., Gniazdowska, E., 2020. Overview of dual-acting drug methotrexate in different neurological diseases, autoimmune pathologies and cancers. Int. J. Mol. Sci. 21 (10), 3483. https://doi.org/10.3390/ijms21103483.

Kroemer, G., Galluzzi, L., Kepp, O., Zitvogel, L., 2013. Immunogenic cell death in cancer therapy. Annu. Rev. Immunol. 31, 51–72. https://doi.org/10.1146/annurev-immunol-032712-100008.

Kubota, Y., Ohji, H., Itoh, K., Sasagawa, I., Nakada, T., 2001. Changes in cellular immunity during chemotherapy for testicular cancer. Int. J. Urol. 8 (11), 604–608. https://doi.org/10.1046/j.1442-2042.2001.00392.x.

Lev, S., 2020. Targeted therapy and drug resistance in triple-negative breast cancer: the EGFR axis. Biochem. Soc. Trans. 48 (2), 657–665. https://doi.org/10.1042/BST20191055.

Li, H., Liu, Y., Wang, Y., Zhao, X., Qi, X., 2021. Hormone therapy for ovarian cancer: emphasis on mechanisms and applications. Oncol. Rep. 46 (4), 223. https://doi.org/10.3892/or.2021.8174. Review.

Löwenberg, B., Pabst, T., Maertens, J., van Norden, Y., Biemond, B.J., Schouten, H.C., Spertini, O., Vellenga, E., Graux, C., Havelange, V., de Greef, G.E., de Weerdt, O., Legdeur, M.J., Kuball, J., Kooy, M.V., Gjertsen, B.T., Jongen-Lavrencic, M., van de Loosdrecht, A.A., van Lammeren-Venema, D., Hodossy, B., et al., 2017. Therapeutic value of clofarabine in younger and middle-aged (18-65 years) adults with newly diagnosed AML. Blood 129 (12), 1636–1645. https://doi.org/10.1182/blood-2016-10-740613.

Lu, J., Li, J., Hu, Y., Guo, Z., Sun, D., Wang, P., Guo, K., Duan, D.D., Gao, S., Jiang, J., Wang, J., Liu, P., 2019. Chrysophanol protects against doxorubicin-induced cardiotoxicity by suppressing cellular PARylation. Acta Pharm. Sin. B 9 (4), 782–793. https://doi.org/10.1016/j.apsb.2018.10.008.

Maeda, K., Hazama, S., Tokuno, K., Kan, S., Maeda, Y., Watanabe, Y., Kamei, R., Shindo, Y., Maeda, N., Yoshimura, K., Yoshino, S., Oka, M., 2011. Impact of chemotherapy for colorectal cancer on regulatory T-cells and tumor immunity. Anticancer Res. 31 (12), 4569–4574.

Marshall, C., 1999. How do small GTPase signal transduction pathways regulate cell cycle entry? Curr. Opin. Cell Biol. 11 (6), 732–736. https://doi.org/10.1016/s0955-0674(99)00044-7.

Martins, I., Kepp, O., Schlemmer, F., Adjemian, S., Tailler, M., Shen, S., Michaud, M., Menger, L., Gdoura, A., Tajeddine, N., Tesniere, A., Zitvogel, L., Kroemer, G., 2011. Restoration of the immunogenicity of cisplatin-induced cancer cell death by endoplasmic reticulum stress. Oncogene 30 (10), 1147–1158. https://doi.org/10.1038/onc.2010.500.

Merla, A., Liu, K.G., Rajdev, L., 2015. Targeted therapy in biliary tract cancers. Curr. Treat. Options Oncol. 16 (10), 48. https://doi.org/10.1007/s11864-015-0366-0.

Mohseni, M., Samadi, N., Ghanbari, P., Yousefi, B., Tabasinezhad, M., Sharifi, S., Nazemiyeh, H., 2016. Co-treatment by docetaxel and vinblastine breaks down P-glycoprotein mediated chemo-resistance. Iran. J. Basic Med. Sci. 19 (3), 300–309.

Moon, H., Ro, S.W., 2021. MAPK/ERK signaling pathway in hepatocellular carcinoma. Cancers 13 (12), 3026. https://doi.org/10.3390/cancers13123026.

Murphy, T., Yee, K.W.L., 2017. Cytarabine and daunorubicin for the treatment of acute myeloid leukemia. Expet Opin. Pharmacother. 18 (16), 1765–1780. https://doi.org/10.1080/14656566.2017.1391216.

Murray, J.M., 1990. Some optimal control problems in cancer chemotherapy with a toxicity limit. Math. Biosci. 100 (1), 49–67. https://doi.org/10.1016/0025-5564(90)90047-3.

Nicholson, K.M., Anderson, N.G., 2002. The protein kinase B/Akt signalling pathway in human malignancy. Cell. Signal. 14 (5), 381–395. https://doi.org/10.1016/s0898-6568(01)00271-6.

Nygren, P., SBU-group. Swedish Council on Technology Assessment in Health Care, 2001. What is cancer chemotherapy? Acta Oncol. (Stockholm, Sweden) 40 (2–3), 166–174. https://doi.org/10.1080/02841860151116204.

O'Shaughnessy, J.A., Kaufmann, M., Siedentopf, F., Dalivoust, P., Debled, M., Robert, N. J., Harbeck, N., 2012. Capecitabine monotherapy: review of studies in first-line HER-2-negative metastatic breast cancer. Oncol. 17 (4), 476–484. https://doi.org/10.1634/theoncologist.2011-0281.

Obeid, M., Tesniere, A., Ghiringhelli, F., Fimia, G.M., Apetoh, L., Perfettini, J.L., Castedo, M., Mignot, G., Panaretakis, T., Casares, N., Métivier, D., Larochette, N., van Endert, P., Ciccosanti, F., Piacentini, M., Zitvogel, L., Kroemer, G., 2007. Calreticulin exposure dictates the immunogenicity of cancer cell death. Nat. Med. 13 (1), 54–61. https://doi.org/10.1038/nm1523.

Osaki, M., Oshimura, M., Ito, H., 2004. PI3K-Akt pathway: its functions and alterations in human cancer. Apoptosis 9 (6), 667–676. https://doi.org/10.1023/B:APPT.0000045801.15585.dd.

Persons, D.L., Yazlovitskaya, E.M., Cui, W., Pelling, J.C., 1999. Cisplatin-induced activation of mitogen-activated protein kinases in ovarian carcinoma cells: inhibition of extracellular signal-regulated kinase activity increases sensitivity to cisplatin. Clin. Cancer Res. 5 (5), 1007–1014.

Pishnamazi, M., Zabihi, S., Jamshidian, S., Hezaveh, H.Z., Hezave, A.Z., Shirazian, S., 2020. Measuring solubility of a chemotherapy-anti cancer drug (busulfan) in supercritical carbon dioxide. J. Mol. Liq. 317, 113954.

Ramshaw, B.J., 1997. Laparoscopic surgery for cancer patients. CA A Cancer J. Clin. 47 (6), 327–350. https://doi.org/10.3322/canjclin.47.6.327.

Rébé, C., Ghiringhelli, F., 2015. Cytotoxic effects of chemotherapy on cancer and immune cells: how can it be modulated to generate novel therapeutic strategies? Future Oncol. (London, England) 11 (19), 2645–2654. https://doi.org/10.2217/fon.15.198.

Reza, M.M., Blasco, J.A., Andradas, E., Cantero, R., Mayol, J., 2006. Systematic review of laparoscopic versus open surgery for colorectal cancer. Br. J. Surg. 93 (8), 921–928. https://doi.org/10.1002/bjs.5430.

Rizzo, A., Ricci, A.D., 2022. Biomarkers for breast cancer immunotherapy: PD-L1, TILs, and beyond. Expet Opin. Invest. Drugs 31 (6), 549–555.

Rizzo, A., Cusmai, A., Acquafredda, S., Rinaldi, L., Palmiotti, G., 2022a. Ladiratuzumab vedotin for metastatic triple negative cancer: preliminary results, key challenges, and clinical potential. Expet Opin. Invest. Drugs 31 (6), 495–498. https://doi.org/10.1080/13543784.2022.2042252.

Rizzo, A., Ricci, A.D., Lanotte, L., Lombardi, L., Di Federico, A., Brandi, G., Gadaleta-Caldarola, G., 2022b. Immune-based combinations for metastatic triple negative breast cancer in clinical trials: current knowledge and therapeutic prospects. Expet Opin. Invest. Drugs 31 (6), 557–565. https://doi.org/10.1080/13543784.2022.2009456.

Salas-Ramirez, K.Y., Bagnall, C., Frias, L., Abdali, S.A., Ahles, T.A., Hubbard, K., 2015. Doxorubicin and cyclophosphamide induce cognitive dysfunction and activate the ERK and AKT signaling pathways. Behav. Brain Res. 292, 133–141. https://doi.org/10.1016/j.bbr.2015.06.028.

Santoni, M., Rizzo, A., Kucharz, J., Mollica, V., Rosellini, M., Marchetti, A., Tassinari, E., Monteiro, F.S.M., Soares, A., Molina-Cerrillo, J., Grande, E., Battelli, N., Massari, F., 2023. Complete remissions following immunotherapy or immuno-oncology combinations in cancer patients: the MOUSEION-03 meta-analysis. Cancer immunology, immunotherapy: CII 72 (6), 1365–1379. https://doi.org/10.1007/s00262-022-03349-4.

Schwarzer, R., Luszczynska, A., Boehmer, S., Taubert, S., Knoll, N., 2006. Changes in finding benefit after cancer surgery and the prediction of well-being one year later. Soc. Sci. Med. 63 (6), 1614–1624. https://doi.org/10.1016/j.socscimed.2006.04.004.

Scurr, M., Pembroke, T., Bloom, A., Roberts, D., Thomson, A., Smart, K., Bridgeman, H., Adams, R., Brewster, A., Jones, R., Gwynne, S., Blount, D., Harrop, R., Hills, R., Gallimore, A., Godkin, A., 2017. Low-dose cyclophosphamide induces antitumor T-cell responses, which associate with survival in metastatic colorectal cancer. Clin. Cancer Res. 23 (22), 6771–6780. https://doi.org/10.1158/1078-0432.CCR-17-0895.

Sebolt-Leopold, J.S., 2000. Development of anticancer drugs targeting the MAP kinase pathway. Oncogene 19 (56), 6594–6599. https://doi.org/10.1038/sj.onc.1204083.

Shurin, G.V., Tourkova, I.L., Kaneno, R., Shurin, M.R., 2009. Chemotherapeutic agents in noncytotoxic concentrations increase antigen presentation by dendritic cells via an IL-12-dependent mechanism. J. Immunol. (Baltimore, Md.: 1950) 183 (1), 137–144. https://doi.org/10.4049/jimmunol.0900734.

Siegel, R.L., Miller, K.D., Jemal, A., 2018. Cancer statistics, 2018. CA A Cancer J. Clin. 68 (1), 7–30. https://doi.org/10.3322/caac.21442.

Singh, R.K., Kumar, S., Prasad, D.N., Bhardwaj, T.R., 2018. Therapeutic journey of nitrogen mustard as alkylating anticancer agents: historic to future perspectives. Eur. J. Med. Chem. 151, 401–433. https://doi.org/10.1016/j.ejmech.2018.04.001.

Sudhakar, A., 2009. History of cancer, ancient and modern treatment methods. J. Cancer Sci. Ther. 1 (2), 1–4. https://doi.org/10.4172/1948-5956.100000e2.

Thoennissen, N.H., Iwanski, G.B., Doan, N.B., Okamoto, R., Lin, P., Abbassi, S., Song, J. H., Yin, D., Toh, M., Xie, W.D., Said, J.W., Koeffler, H.P., 2009. Cucurbitacin B induces apoptosis by inhibition of the JAK/STAT pathway and potentiates antiproliferative effects of gemcitabine on pancreatic cancer cells. Cancer Res. 69 (14), 5876–5884. https://doi.org/10.1158/0008-5472.CAN-09-0536.

Thomas, S., Fisher, K.H., Snowden, J.A., Danson, S.J., Brown, S., Zeidler, M.P., 2015. Methotrexate is a JAK/STAT pathway inhibitor. PLoS One 10 (7), e0130078. https://doi.org/10.1371/journal.pone.0130078.

Thorn, C.F., Oshiro, C., Marsh, S., Hernandez-Boussard, T., McLeod, H., Klein, T.E., Altman, R.B., 2011. Doxorubicin pathways: pharmacodynamics and adverse effects. Pharmacogenetics Genom. 21 (7), 440–446. https://doi.org/10.1097/FPC.0b013e32833ffb56.

Toyonaga, T., Nakano, K., Nagano, M., Zhao, G., Yamaguchi, K., Kuroki, S., Eguchi, T., Chijiiwa, K., Tsuneyoshi, M., Tanaka, M., 2003. Blockade of constitutively activated Janus kinase/signal transducer and activator of transcription-3 pathway inhibits growth of human pancreatic cancer. Cancer Lett. 201 (1), 107–116. https://doi.org/10.1016/s0304-3835(03)00482-8.

Trédan, O., Galmarini, C.M., Patel, K., Tannock, I.F., 2007. Drug resistance and the solid tumor microenvironment. J. Natl. Cancer Inst. 99 (19), 1441–1454. https://doi.org/10.1093/jnci/djm135.

Truong, N.T.H., Gargett, T., Brown, M.P., Ebert, L.M., 2021. Effects of chemotherapy agents on circulating leukocyte populations: potential implications for the success of CAR-T cell therapies. Cancers 13 (9), 2225. https://doi.org/10.3390/cancers13092225.

Verma, R., Foster, R.E., Horgan, K., Mounsey, K., Nixon, H., Smalle, N., Hughes, T.A., Carter, C.R., 2016. Lymphocyte depletion and repopulation after chemotherapy for primary breast cancer. Breast Cancer Res. 18 (1), 10. https://doi.org/10.1186/s13058-015-0669-x.

Vivanco, I., Sawyers, C.L., 2002. The phosphatidylinositol 3-Kinase AKT pathway in human cancer. Nat. Rev. Cancer 2 (7), 489–501. https://doi.org/10.1038/nrc839.

Waidhauser, J., Schuh, A., Trepel, M., Schmälter, A.K., Rank, A., 2020. Chemotherapy markedly reduces B cells but not T cells and NK cells in patients with cancer. Cancer Immunol., Immunother.: CII 69 (1), 147–157. https://doi.org/10.1007/s00262-019-02449-y.

Wang, X., Martindale, J.L., Holbrook, N.J., 2000. Requirement for ERK activation in cisplatin-induced apoptosis. J. Biol. Chem. 275 (50), 39435–39443. https://doi.org/10.1074/jbc.M004583200.

Wang, L., Zhou, D., Ren, H., Chen, Y., 2018. Effects of modified FOLFOX-6 chemotherapy on cellular immune function in patients with gastric cancer. Oncol. Lett. 15 (6), 8635–8640. https://doi.org/10.3892/ol.2018.8361.

Wang, L., Qin, W., Huo, Y.J., Li, X., Shi, Q., Rasko, J.E.J., Janin, A., Zhao, W.L., 2020. Advances in targeted therapy for malignant lymphoma. Signal Transduct. Targeted Ther. 5 (1), 15. https://doi.org/10.1038/s41392-020-0113-2.

Weaver, B.A., 2014. How Taxol/paclitaxel kills cancer cells. Mol. Biol. Cell 25 (18), 2677–2681. https://doi.org/10.1091/mbc.E14-04-0916.

Wijayahadi, N., Haron, M.R., Stanslas, J., Yusuf, Z., 2007. Changes in cellular immunity during chemotherapy for primary breast cancer with anthracycline regimens. J. Chemother. (Florence, Italy) 19 (6), 716–723. https://doi.org/10.1179/joc.2007.19.6.716.

Wyld, L., Audisio, R.A., Poston, G.J., 2015. The evolution of cancer surgery and future perspectives. Nat. Rev. Clin. Oncol. 12 (2), 115–124. https://doi.org/10.1038/nrclinonc.2014.191.

Xia, Y., Shen, S., Verma, I.M., 2014. NF-κB, an active player in human cancers. Cancer Immunol. Res. 2 (9), 823–830. https://doi.org/10.1158/2326-6066.CIR-14-0112.

Xia, L., Tan, S., Zhou, Y., Lin, J., Wang, H., Oyang, L., Tian, Y., Liu, L., Su, M., Wang, H., Cao, D., Liao, Q., 2018. Role of the NFκB-signaling pathway in cancer. OncoTargets Ther. 11, 2063–2073. https://doi.org/10.2147/OTT.S161109.

Yamamoto, Y., Gaynor, R.B., 2001. Therapeutic potential of inhibition of the NF-kappaB pathway in the treatment of inflammation and cancer. J. Clin. Invest. 107 (2), 135–142. https://doi.org/10.1172/JCI11914.

Yin, L., Duan, J.J., Bian, X.W., Yu, S.C., 2020. Triple-negative breast cancer molecular subtyping and treatment progress. Breast Cancer Res. 22 (1), 61. https://doi.org/10.1186/s13058-020-01296-5.

Yue, J., López, J.M., 2020. Understanding MAPK signaling pathways in apoptosis. Int. J. Mol. Sci. 21 (7), 2346. https://doi.org/10.3390/ijms21072346.

Zachariae, H., 1990. Methotrexate side-effects. Br. J. Dermatol. 122 (Suppl. 36), 127–133. https://doi.org/10.1111/j.1365-2133.1990.tb02890.x.

Zheng, H.C., 2017. The molecular mechanisms of chemoresistance in cancers. Oncotarget 8 (35), 59950–59964. https://doi.org/10.18632/oncotarget.19048.

Zhu, L., Chen, L., 2019. Progress in research on paclitaxel and tumor immunotherapy. Cell. Mol. Biol. Lett. 24, 40. https://doi.org/10.1186/s11658-019-0164-y.

Ziebart, A., Huber, U., Jeske, S., Laban, S., Doescher, J., Hoffmann, T.K., Brunner, C., Jackson, E.K., Schuler, P.J., 2017. The influence of chemotherapy on adenosine-producing B cells in patients with head and neck squamous cell carcinoma. Oncotarget 9 (5), 5834–5847. https://doi.org/10.18632/oncotarget.23533.

Zitvogel, L., Kepp, O., Kroemer, G., 2011. Immune parameters affecting the efficacy of chemotherapeutic regimens. Nat. Rev. Clin. Oncol. 8 (3), 151–160. https://doi.org/10.1038/nrclinonc.2010.223.

Zugazagoitia, J., Guedes, C., Ponce, S., Ferrer, I., Molina-Pinelo, S., Paz-Ares, L., 2016. Current challenges in cancer treatment. Clin. Therapeut. 38 (7), 1551–1566. https://doi.org/10.1016/j.clinthera.2016.03.026.