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Immunosuppressive drugs and cancer risk

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Abstract The use of immunosuppressive medications is an area of interest for organ transplantation. These medications have been repurposed for the treatment of cancer in recent years. In the context of cancer therapy, the use of immunosuppressive medications such as cyclosporine, tacrolimus, sirolimus, mycophenolate acid mofetil (MMF), mycophenolate, and azathioprine is discussed. Treatment for cancer frequently includes methods designed to use the immune system to find and destroy cancer cells. Cancer cells can, however, avoid immune surveillance and eradication because the tumor microenvironment frequently has immune-suppressive components. Drugs that suppress the immune system, which were initially designed to avoid organ rejection, have demonstrated potential for obstructing these inhibitory pathways and boosting antitumour immune responses. Tacrolimus and cyclosporine, two immunosuppressive medications frequently used in transplantation, have potential anticancer effects. The immune system and stifling tumor-promoting inflammatory responses, can prevent tumor growth, angiogenesis, and metastasis. Another immunosuppressive drug, sirolimus, has shown anticancer effects by reducing angiogenesis and tumor cell growth while promoting immune-mediated tumors. Mycophenolate medicines, such as MMF and mycophenolate, have strong immunosuppressive properties. By inhibiting the enzymes responsible for purine production, these enzymes aim to inhibit lymphocyte proliferation. By altering immune cell function and reducing tumor growth, these medications have demonstrated promise in the treatment of cancer. Azathioprine, a medication that suppresses the immune system and is frequently used to treat autoimmune illnesses, has also been investigated as a possible cancer treatment. Although immunosuppressive medications have potential in the treatment of cancer, their usage needs to be carefully addressed due to potential side effects and the delicate balance between immune suppression and antitumour action. The immune system plays a crucial role in identifying and eliminating abnormal cells, including those associated with cancer.

Keywords: azathioprine, mycophenolate, sirolimus, tacrolimus, cyclosporine

1. Introduction and Background

The immune system's reaction is inhibited or weakened by a class of drugs known as immunosuppressants. The bulk of these medications were used to reduce the likelihood that the body may reject an organ donated by another person, such as the kidney, heart, or liver, in 1949, 1976, 1977, and 1987, respectively (Sprague, 1950; Borel et al., 1976). The immunosuppressive effects of cortisol, cyclosporine-A, sirolimus, tacrolimus, and everolimus were among the most popular and current immunosuppressive medications due to their structures (Chitty, 2017) Immunosuppressants are medications that block or reduce the severity of the immunological response in the body. Most of these drugs are employed in order to make the body less likely to refuse a transplanted organ. Immunosuppressive medications are required in solid organ transplantation for the activation of early-stage immunosuppression, the management of late-stage immunosuppression, and the maintenance of organ rejection. The emergence of innovative medicines and advancements in immunosuppressive regimens following transplantation are important reasons driving this progress. However, these treatments also increase the risk of infection, cancer, and unique adverse side effects specific to each agent in patients, particularly pregnant women, as well as fertility concerns. Clinical pharmacology and therapeutic usage of immunosuppressive medicines in rheumatology. Cyclophosphamide and azathioprine are cytostatic medicines that affect bone marrow progenitor cells, while cyclosporine, tacrolimus, and mycophenolate mofetil (MMF) target lymphocytes by blocking certain intracellular signaling pathways and/or proliferation. Their immune system effects are similar to those of classic disease-modifying antirheumatic medications such methotrexate, glucocorticoids, and biologics (Denman, 1982). The most regularly used immunosuppressive drugs, namely, cyclosporine, tacrolimus, azathioprine, and MMF, are described in more detail. Classification of different types of immunosuppressive drugs. Tacrolimus and cyclosporine are two agents that inhibit calcineurin. The anti-proliferative drugs used included mycophenolate acid mofetil, and azathioprine. mTOR inhibitor: sirolimus, everolimus (Sprague, 1950).

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1.1. Mechanism of action of immunosuppressive drugs

Tacrolimus and cyclosporine-A are calcineurin inhibitors that bind to immunophilins to mechanistically prevent calcineurin activity. Both sirolimus and everolimus work in similar ways. After subsequently interacting with tacrolimus binding protein (FK506) and mammalian target of rapamycin (mTOR), during the G1 phase of the cell cycle, Ca2+-based signaling is prevented. It blocks the mTOR and FK506 pathways, which are both independent and dependent on Ca2+-based activities. Sirolimus also prevents the release of the inflammatory mediators vascular endothelial growth factor and interleukin-6 by neutrophils. Sirolimus prevents T and B cells from differentiating and proliferating by inhibiting cyclin-dependent kinase (Chitty, 2017; Denman, 1982; Kemmner et al., 2020).

The active compound of mycophenolate, mycophenolic acid, inhibits the production of cytotoxic T cells and antibodies as well as T- and B-cell proliferation. The cell adhesion molecules MPA are glycosylated. It is possible to prevent lymphocyte and monocyte adherence to blood vessel endothelial cells, which is typically a component of inflammation. Moreover, it stops the de novo guanosine nucleotide route without interacting with deoxyribonucleic acid (DNA) by reversible and selective inhibition of inosine monophosphate dehydrogenase. because de novo purine synthesis is necessary for B and T-cell proliferation (Kemmner et al., 2020). These medications are critical for preventing organ rejection following transplantation as well as controlling autoimmune diseases such as rheumatoid arthritis and lupus. On the other hand, their immunosuppressive nature impairs the body's ability to recognize and kill aberrant cells, potentially leading to cancer growth. The risk of cancer is increased due to weakened immune surveillance, which allows cancer cells to avoid detection (Ross, 2007).

2. Review

2.1. Cyclosporine

Cyclo undeca peptide, which was isolated from Tolypocladium inflatum, exhibits highly hydrophobic characteristics. Its molecular mass is 1202.61 g/mol, and its chemical formula is C62H111N11O12 (Figure *1*). Cyclosporine, an immunosuppressive medication, is used to treat immunological disorders such as organ transplant rejection. It is a cyclic undecapeptide isolated from Tolypocladium inflatum, that is extremely hydrophobic. Inhibitors of calcineurin include cyclosporine (Chakkera et al., 2017). Three P-glycoprotein inhibitors, Pigment 450 (cytochrome P450 3A4) and calcineurin, constitute the mechanism of action of cyclosporin. However, interleukins require cyclosporine-A to block their synthesis, making it impossible for T cells to self-activate and differentiate. Cyclosporine is advantageous because it completely and permanently shuts down the cell cycle in the G0 and G1 phases. Inhibition of clusters of differentiation 4 (CD4+) and CD25+ TIGRs by cyclosporine (Laddicoat & Lavelle, 2019; Masi et al., 2019).

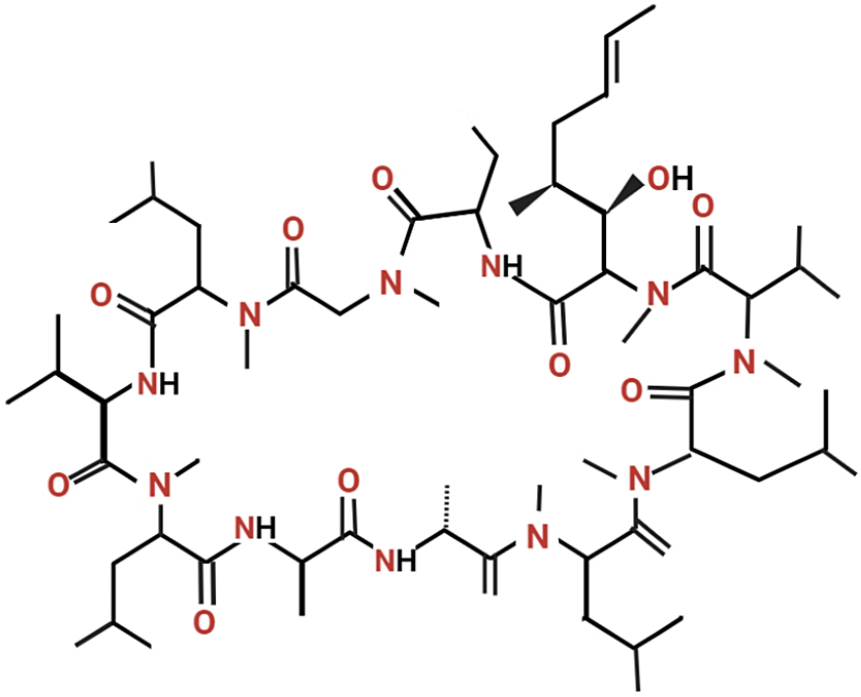

Figure 1 Chemical structure of cyclosporine.

O (oxygen), N (nitrogen), H (hydrogen), OH (hydroxide), NH (nitrogen hydroxide)

After receiving a liver, kidney, liver graft, or heart, to prevent organ rejection and solid organ transplantation, cyclosporine is clinically utilized. In cases where the body has not responded appropriately to methotrexate, it is advised for rheumatoid arthritis sufferers. Amyotrophic lateral sclerosis patients can take cyclosporine to treat the disease and its variations. In addition, cyclosporine administered during nephrotic syndrome is used to treat glomerulonephritis with focal segmentation that is nonresponsive to corticosteroids (Pradier et al., 2019). Cyclosporin has many negative effects on a number of important organs. It can cause arrhythmia and hypertension, which are harmful consequences for the cardiovascular system. The glomerular filtration rate is decreased by cyclosporine because of the enhanced musculature of the glomerular afferent arteriole. As a result, there is a decrease in the amount of creatinine that is cleared from the body. The duration and dosage of drug therapy are linked to unfavorable effects. Endocrine and metabolic dyslipidemia, gynecomastia, hypertrichosis, hypomagnesemia, hyperkalemia, and hypomagnesemia are some of the side effects of cyclosporine. The neurotoxic side effects of cyclosporine have been noted to include convulsions, encephalopathy, anxiety, high-dose methylprednisolone, headache, and fever (Pal et al., 2019; Shin et al., 2019).

2.2. Tacrolimus

A macrolide immunosuppressant medication, tacrolimus (Figure *2*), was used. Its molecular mass is 804.02 g/mol, and its chemical formula is C44H69NO12. An immunosuppressive medication called tacrolimus is used to avert organ rejection following organ transplantation. Tacrolimus use is linked to the use of one or two other immunosuppressive medications. It can be used as a preventative measure or a treatment for some autoimmune diseases. The major metabolite of tacrolimus is produced by the enzymes cytochrome 3A4 (CYP3A4), CYP5, and P-glycoprotein, and the other 15 major breakdown products are 13-O-dimethyl tacrolimus (Yu et al., 2018). Tacrolimus is linked to FK506-binding proteins because it is a member of the calcineurin inhibitor class and ultimately prevents T-cell proliferation. Organ rejection is treated with tacrolimus and liver, heart, and kidney allogeneic transplants (Yoshikawa et al., 2020).

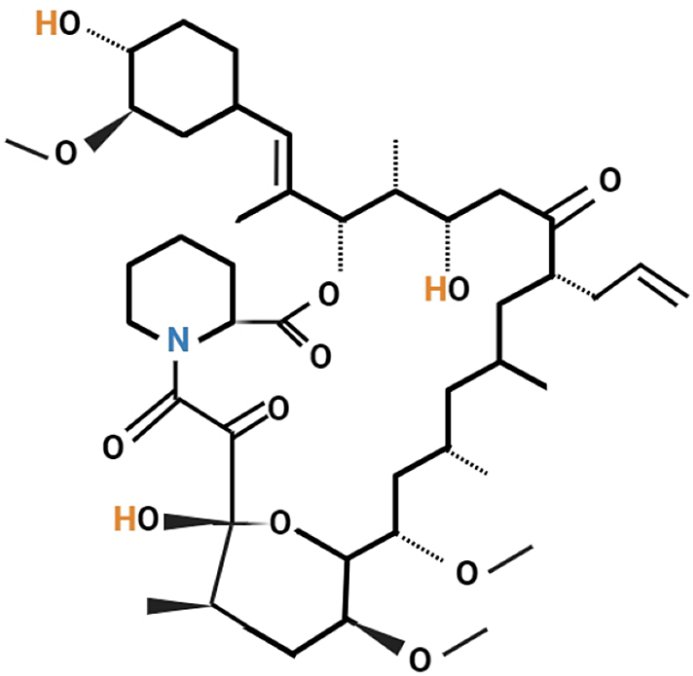

Figure 2 Chemical structure of tacrolimus.
O (oxygen), OH (hydroxide), N (nitrogen)

In stable organ transplantation, there is also an off-label use to shield patients from rejection who have undergone lung transplants. Other off-label indications include Crohn's disease and graft against host disease, myasthenia gravis, and rheumatoid arthritis (Kalt, 2017). In mild to severe atopic dermatitis, topical application and various off-label dermatologic disease states are other clinical applications of tacrolimus. Tacrolimus is also used as an antimetabolite when taken in kidney transplant situations (Dordal Culla et al., 2020). Immunosuppression can cause side effects such as infections caused by tacrolimus, which emphasizes the importance of tight management by lowering the intended doses to account for the potential for rejection. Tacrolimus is contraindicated in cases of hypersensitivity, and castor oil containing polyoxyl-60 is contraindicated (Fröhlich, 2019). Acute renal failure is usually a harmful side effect of tacrolimus. The use of urine, the glomerular filtration rate (GFR), the serum creatinine concentration, and the serum creatinine level is crucial for patients receiving tacrolimus. Toxicity

can also manifest as the occurrence of negative symptoms such as electrolyte imbalances, tremors, migraines, and increased serum creatinine (Jouve et al., 2019).

2.3. Sirolimus

A macrolide immunosuppressant, sirolimus (Figure *3*). Its molecular mass is 914.18 g/mol, and its chemical formula is C51H79NO13. Sirolimus is a target of rapamycin inhibitor and immunosuppressive agents for mammals. P-glycoprotein, CYP2C8, CYP3A4, and CYP3A5 all metabolize sirolimus. The reactions of individual to sirolimus vary, which is attributable to the erratic expression of these enzymes. It has a 9 l/h clearance rate and a 63-hour terminal half-life. Sirolimus is mostly metabolized in the liver, and 92% of its metabolites are eliminated in bile as opposed to 1.2% in urine (Moes et al., 2015). During and after the G1 phase of the cell cycle, sirolimus inhibits calcium 2-independent or calcium 2-dependent processes. A protein that binds tacrolimus FK506 and mTOR. Vascular endothelial growth factor and interleukin are two other inflammatory mediators by which sirolimus stops the inhibition of leukocyte production. Sirolimus inhibits cyclin-dependent kinases, which in turn prevents T and B cells from differentiating and proliferating (Vitiello et al., 2015).

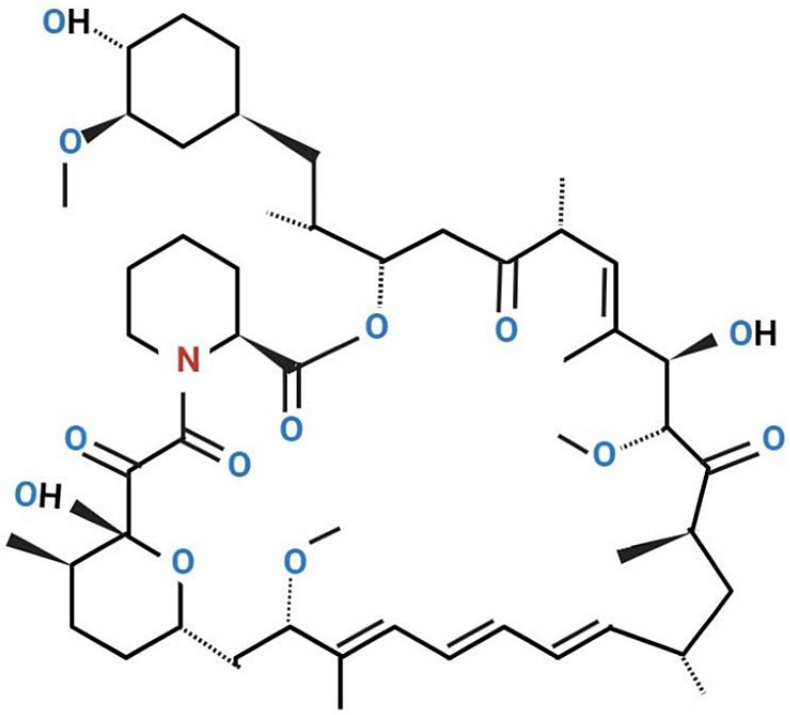

Figure 3 Chemical structure of sirolimus.
O (oxygen), N (nitrogen), OH (hydroxide)

In patients with renal allografts, sirolimus and corticosteroids are recommended to prevent transplant rejection. Pulmonary lymphangioleiomyomatosis is another condition for which it is utilized as a treatment. Moreover, it is used as a second medication (Yoon et al., 2018). Skin cancer in kidney transplant recipients is treated with sirolimus. The most common side effects of sirolimus are vaginal bleeding, irregular heartbeat, tremor, blurred vision, stomach cramps, nausea, vomiting, nasal congestion, burning when urinating, arthralgia, hypertension, and hypercholesterolemia. Other side effects included hypokalemia, acne, rashes, leucopenia, hyperlipidemia, diarrhea and arthralgia (Merkel et al., 2006). The problems include intolerance to medications, kidney damage, hepatic problems, hyperlipidemia, and slowed graft function. Sirolimus is not advised, and some of the drugs that interfere with treatment are mifepristone, posaconazole, posaconazole, rifampin, and diltiazem. Breastfeeding women should not take sirolimus because it falls under the pregnancy category. Health outcomes and drug-associated toxicity are related to the blood level of sirolimus. Moreover, sirolimus-infected individuals often do not have a greater risk of contracting proliferative illnesses before the initial six months after transplantation (Adams et al., 2016).

2.4. Everolimus

A macrolide immunosuppressant, everolimus (Figure *4*). Its molecular mass is 958.24 g/mol, and its chemical formula is C53H83NO14. The immunosuppressive medication everolimus is a synthetic version of the natural macrolide rapamycin. However, its bioavailability is unstable due to its use as a substrate for p-glycoprotein and enzymes for metabolism. Everolimus is metabolized by the enzymes p-glycoprotein, CYP2C8, and CYP3A4/5, and 90% of its metabolites are eliminated by bile in the

liver, where it is mostly metabolized. Like sirolimus, everolimus works through the same mechanism. Upon subsequently interacting with FK506 and mTOR, Ca2+ is suppressed during the G1 phase of the cell cycle, and there are mechanisms that use Ca2+ that are either independent of or dependent on Ca2+ (mTOR; FK506, tacrolimus binding protein) (Moes et al., 2012). Inflammatory mediators including vascular endothelial growth factor and interleukins, are not released by neutrophils when sirolimus is present. By suppressing cyclin-dependent kinases, sirolimus prevents the maturation and expansion of T and B lymphocytes. For liver, kidney, and renal transplants, everolimus is advised. Breast cancer cells and renal cell carcinoma everolimus are also treated. In addition, it is appropriate for treating tuberous sclerosis complex, which includes subependymal giant cell astrocytoma and partial-onset seizures. Moreover, it is suggested for the management of advanced pancreatic neuroendocrine tumors. Everolimus should not be given until at least one month after the transplant because giving it sooner could cause the graft to fail or even cause death (Bilbao et al., 2015; Saliba et al., 2011).

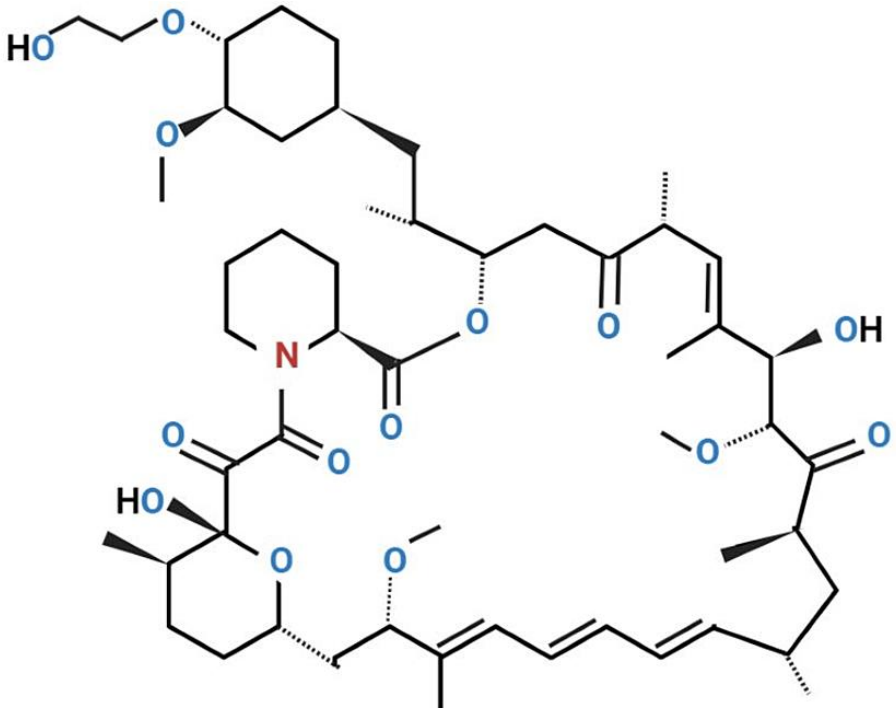

Figure 4 Chemical structure of everolimus.

O (oxygen), N (nitrogen), OH (hydroxide)

Everolimus can cause heart failure, pyrexia, epistaxis, asthenia, stomatitis, anemia, nausea, dyspnea, vomiting, constipation, pruritis, headaches, weariness, and coughing. Contraindications to everolimus sensitivity were included. The adverse effects of everolimus are increased when ACE (angiotensin-converting enzyme) inhibitors are used at the same time. After administration, everolimus loses its therapeutic efficacy. The serum concentration of everolimus is increased by CYP3A4-inducing medications, while the serum concentration of everolimus is decreased by CYP3A4-inhibiting medications. Everolimus and live vaccines should not be used because immunosuppressants magnify the negative effects of live immunization. Immunosuppressants and live vaccine administration should be separated by at least 3 months (Casanovas et al., 2011).

2.5. Mycophenolate mofetil

Mycophenolate mofetil (Figure *5*) suppresses the immune system. Its molecular mass is 433.50 g/mol, and its chemical formula is C23H31NO7. Mycophenolic acid, an immunosuppressive medication intended to prevent transplant rejection, is used in pro-form, or mycophenolate mofetil, for improved oral absorption due to its poor solubility (Tönshoff et al., 2011). The active metabolite of mycophenolate, mycophenolic acid, inhibits T-cell and B-cell proliferation as well as the generation of cytotoxic T cells and antibodies. Leukocyte and monocyte adhesion to blood artery endothelial cells is typically a component of inflammation and is prevented by glycosylated cell adhesion molecules such as medroxyprogesterone acetate (MPA). It also hinders the de novo guanosine nucleotide pathway without interacting with DNA by selectively and reversibly inhibiting inosine monophosphate dehydrogenase. because de novo purine synthesis is necessary for the proliferation of both B and T cells (Park, 2011; Sagcal-Gironella et al., 2011).

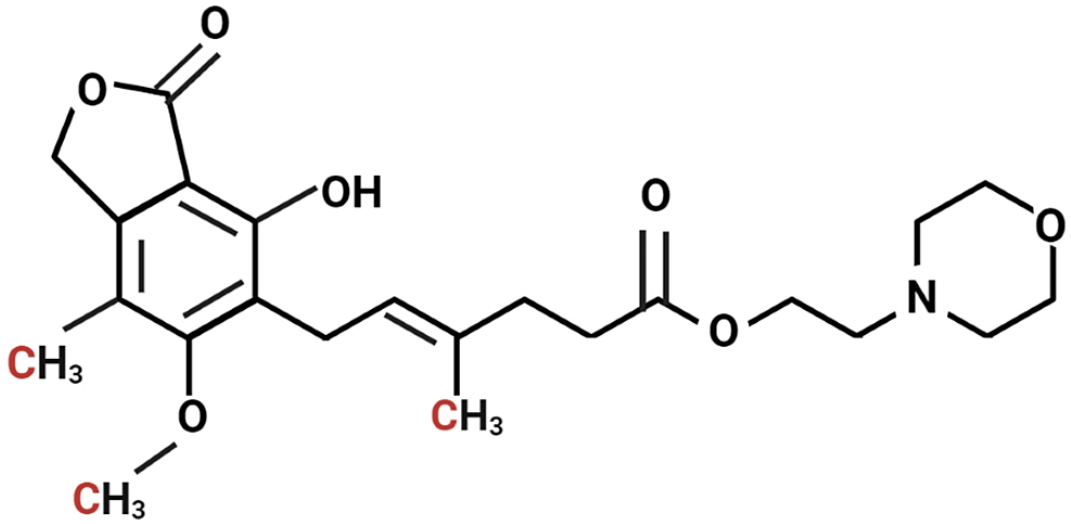

Figure 5 Chemical structure of mycophenolate mofetil.
O (oxygen), H (hydrogen), CH3 (methyl), N (nitrogen), OH (hydroxide)

Heart, kidney, and liver transplants are indications for its use. Steroids-resistant nephrotic syndrome is another condition for which it is indicated (Broen & van Laar, 2020). Rheumatology and autoimmune hepatitis are two additional conditions for which mycophenolate mofetil is prescribed. It is ingested along with tacrolimus or cyclosporine when used in organ transplant cases. Opportunistic fever, fever, headache, sepsis, necrosis, hypertension, leukopenia, hypochromic anemia, hemorrhage, vomiting, nausea, acne, and melanoma are among the more common adverse reactions (Kaltenborn & Schrem, 2013). In patients who have known hypersensitivity, mycophenolate mofetil is contraindicated. Receivers who have received Myco-Phenolate Mofetil are more likely to develop cancer and should stay out of the sun. Moreover, medication is not recommended for use in those with gastrointestinal conditions. The medication must be ingested on an empty stomach, and concurrent usage of multivalent ions is not advised (Dias-Polak et al., 2019).

2.6. Azathioprine

Azathioprine (Figure *6*) suppresses the immune system. Its molecular mass is 277.26 g/mol, and its chemical formula is C9H7N7O2S. Azathioprine, a 6-mercaptopurine prodrug, is used to inhibit the immune system. The oral use of azathioprine results in good absorption. Clinically, azathioprine has been suggested to prevent the rejection of heart, liver, and urinary system transplants, by decreasing the number of both T and B cells. Moreover, it is suggested for the treatment of inflammatory bowel diseases, connective tissue disorders, and vasculitis. Azathioprine is also prescribed for autoimmune hepatitis, myasthenia gravis, rheumatoid arthritis, lupus nephritis, and juvenile idiopathic arthritis (Horneff, 2015; Björnsson et al., 2017; Montante et al., 2019).

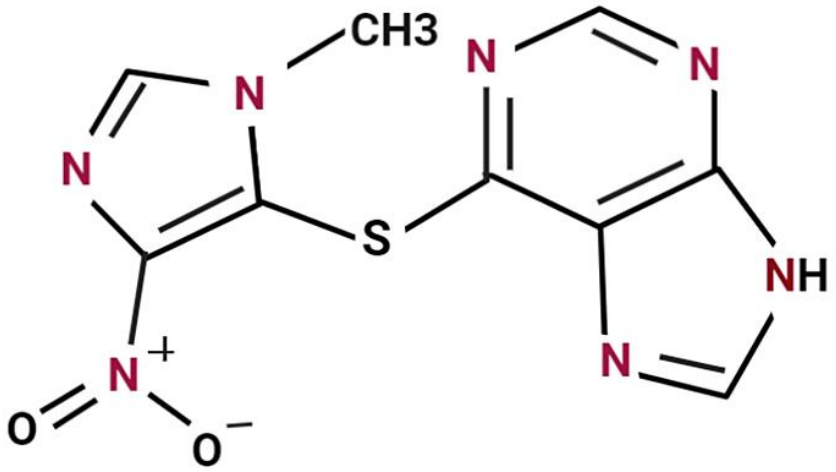

Figure 6 Chemical structure of azathioprine.
O (oxygen), H (hydrogen), CH3 (methyl), N (nitrogen), OH (hydroxide), S (sulfur)

The most common option is to steer clear patients with known azathioprine hypersensitivity. Drugs such as melphalan, cyclophosphamide, and chlorambucil are contraindicated when taken with azathioprine. Those who receive azathioprine while being treated with such medications have a greater risk of developing neoplasia. Due to the tight interaction between azathioprine and allopurinol, the dosage of azathioprine must be decreased when azathioprine is used in conjunction with allopurinol (Fuggle et al., 2015). Live vaccines should not be administered at the same time as azathioprine. Those who take too much azathioprine suffer from bleeding, infections, and bone marrow depression, which can be fatal (*Azathioprine-Induced Severe Bone Marrow Suppression | Case Reports in Clinical Practice*, n.d.).

2.7. How immunosuppressive drugs lead to câncer

The immune system of many organ transplant recipients is suppressed by medications, preventing the body from rejecting the donated organ. These "immunosuppressive" medications lessen the immune system's capacity to identify and eliminate cancer cells as well as combat infections that can cause cancer. There are numerous ways in which immunosuppressive medications might cause cancer. They impair immunity, reducing the body's ability to recognize diseases and likewise annihilating malignant cells (*Risk Factors*, 2015). Additionally, some immunosuppressive drugs can directly promote cancer development by activating certain signaling pathways or inhibiting tumor suppressor genes. Some immunosuppressive drugs can cause mutations in deoxyribonucleic acid (DNA), which can lead to cancer. This occurs because these drugs are converted into reactive metabolites that can damage DNA and cause mutations. Overall, the exact mechanisms by which immunosuppressive drugs lead to cancer are not fully understood and require further research (Setlai et al., 2022; Weaver, 2012). In terms of morbidity and mortality, cancer is one of the major causes of the numerous negative consequences of immunosuppressive medications. The most recent clinical data are the foundation of this review. Epidemiology studies and cancer registries have repeatedly indicated that transplant patients have a greater chance of developing malignancies, albeit the calculated risk (a 4- to 500-fold increase) varies significantly between studies, primarily because of variations in methodology and patient selection. The three most common cancers in these people are cancers, lymphomas, and Kaposi's sarcomas. Latent viral infections, the type of therapy, and the degree of immunosuppression are only a few of the risk factors that have been identified. To more clearly define the effects of mild-to-moderate immunosuppression, it is helpful to see how immunosuppressive medications are being used frequently in nontransplant patients (Vial & Descotes, 2003).

The calcineurin inhibitor (CNI) and mTORi suppress the immune system by acting on dendritic cells (DCs) and regulatory T cells (Tregs).). Immunosuppressive medications affect the Treg population in conflicting ways, both directly and indirectly. In DCs treated with CNI, the synthesis of IL-2 and IL-12, which are necessary to support Treg proliferation, is decreased. Furthermore, CNI directly suppresses T-cell production and reuptake of interleukin-2 (IL-2), which prevents Treg differentiation and proliferation. Additionally, mTORis can directly induce Tregs, improving tolerance to organ donation. rapamycin (RAPA)-DCs increase Treg production and can initiate the development of this subpopulation (Cangemi et al., 2019).

2.8. Molecular biology of immunosuppressive drugs and câncer

Drugs that suppress the immune system are commonly employed in the management of autoimmune disorders, aid in organ transplant procedures, and prevent rejection of transplanted organs. These medications function by dampening the immune response, rendering them beneficial in certain scenarios, yet they can also increase the likelihood of cancer (Reyes et al., 2023). The immune system plays a crucial role in identifying and eliminating abnormal cells, including those associated with cancer. Immunosuppressive drugs can weaken the immune system and decrease the effectiveness of identifying and eliminating cancer cells, which can increase the risk of cancer. Additionally, some immunosuppressive drugs can directly promote cancer development by activating certain signaling pathways or inhibiting tumor suppressor genes. For example, calcineurin inhibitors, which are commonly used in transplantation, can activate the nuclear factor of activated T cells (NFAT) pathway, which is involved in cancer development (Setlai et al., 2022). Molecularly, some immunosuppressive drugs, such as azathioprine, can cause mutations in DNA that can lead to cancer. This occurs because azathioprine is converted into a reactive metabolite that can damage DNA and cause mutations (*Risk Factors*, 2015). Cancer is a complex disease with multiple contributing factors, and the relationship between immunosuppressive drugs and cancer is not fully understood. It is important for patients who take immunosuppressive drugs to be closely monitored for signs of cancer and to work with their healthcare providers to minimize their risk of developing cancer (Setlai et al., 2022).

Cells within the cancerous microenvironment that suppress the immune system. Immune cells penetrate the tumor microenvironment, interact with tumor cells and other immune cells, and eventually develop an immunosuppressive phenotype that causes cancer cells to circumvent the body's defenses and spread the disease. Mast cells, Bregs, tumor-associated neutrophils (N2-TAMs), Tregs, myeloid-derived suppressor cells (MDSCs), M2- macrophages, and dendritic cells are some of these immunosuppressive cells. These cells release substances that negatively influence the immune system's response to cancer, remodel the extracellular matrix, and promote angiogenesis, including cytokines such as IL-2, IL-10, and transforming growth factor-β (TGF-β); growth factors such as vascular endothelial growth factor (VEGF); checkpoint ligands such as PD-L1; and checkpoints such as PD-1 and T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) on

Tregs. Due to the interaction of these immunosuppressive cells, an immunosuppressive milieu is created, which aids in the growth, evasion, and migration of cancer cells (Tie et al., 2022).

3. Conclusions

The risk of cancer in transplant recipients has been linked to immunosuppressive medications such as tacrolimus and cyclosporin, antiproliferative treatments such as mofetil mycophenolate and mycophenolate sodium, and the mTOR inhibitor sirolimus. These medications impair the immune system, which impairs the body's capacity to detect and destroy cancer cells and may actively promote the growth of cancer through a number of methods. Although these medications are essential for preventing organ rejection, they also increase the risk of some cancers, including Kaposi's sarcoma, lymphoma, and skin cancer. To reduce the risk of malignancy while preserving acceptable organ function, regular monitoring and individualized immunosuppressive therapy are crucial for transplant patients. To discover alternative medicines with a lower risk of cancer and to fully understand the precise processes by which these drugs cause cancer, additional studies are needed.

Ethical consideration

Not applicable.

Conflict of Interest

The authors declare no conflicts of interest.

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