REVIEW ARTICLE

Antiparasitic and Antifungal Medications for Targeting Cancer Cells Literature Review and Case Studies

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ABSTRACT

Context • Chronic inflammation is a new catch phrase for the explanation of all chronic degenerative diseases, from asthma, arthritis, heart disease, auto-immune disease, and irritable bowel disease to cancer. Occult infections from oncovirus, bacterial, and fungal infections as well as from lesser known parasitic infections are driving forces in the cellular evolution and degeneration of cancer cells. An approach using currently available medications that target both fungal and parasitic metabolism appears to interfere with the metabolic synergy that is associated with tumor growth and aggressiveness.

Objective • The review examined whether antiparasitic and antifungal medications that interfere with the metabolism of cancers, can be useful in cancer therapy by treating cancer as an infectious disease and as a metabolic parasite.

Design • The research team searched the National Center for Biotechnology Information (NCBI) PubMed database databases, using different keyword combinations, including repurposed drug, antifungal, antiparasitic, cancer, parasite, anti-cancer repurposed.

Setting • Prevention and Healing, St Louis, Mo, USA.

Results • The literature search identified a number of studies, including *in vitro*, *in vivo* and clinical, which support the use of antifungal and antiparasitic medication in the treatment of cancer. In the clinical area, the authors observed benefit from the use of antifungal and antiparasitic medication in the treatment of a variety of cancer cases.

Conclusions • Due to the complexity of the behavior and biology of cells, scientists' primary focus should be on detection and elimination of sources of inflammation. Antiparasitic medications, and also antiviral, antibiotic, and antifungal medications should be thought of as underrecognized, underappreciated, and forgotten medications that can be part of cancer therapy. The information offered in this review suggests scientists should think of cancer not only as a metabolic disease but also as a metabolic parasite and should consider using antiparasitic medications under a new understanding of the role of inflammation, infection, and mitochondrial dysfunction in the development of cancer cells. (*Altern Ther Health Med.* 2019;25(4):26-31).

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Unrecognized low-grade infection is a main cause of inflammation. The observation that cancers, like parasites, feed off of our bodies without returning a benefit has been known for some time, and early in the twentieth century, it was suggested that cancer is a parasite.[1] It has recently been shown that the metabolism of some parasites show a method of energy formation similar to that of cancer cells.[2]

In 2004, Houghton et al published a study relating to the formation of stomach cancer.[3] The researchers showed that stomach cancer originated from bone-marrow-derived cells and not from the stomach's lining cells as expected.

Bone-marrow-derived stem cells have cancer-like properties: unlimited growth, the ability to avoid programmed cell-death signals, and the capacity to develop into many tissue types. Chronic inflammation created by pre-existing bacterial or parasitic infections create a need for an influx of bone-marrow-derived stem cells into the stomach. After the stem cells are in the stomach, they are constantly under the negative-feedback influence of environmental toxins, heavy metals, synthetic hormones, hidden dental and fungal infections, endogenous biotoxins, electromagnetic fields, and unresolved emotional conflicts. These stressors cause the disrupted mitochondria and stem cells to transform into cancer cells rather than repairing the stomach cells. These effects are just beginning to be explored.[4]

Other causal associations between parasites and cancers have been established in humans and experimental animals, and a number of studies have demonstrated an association between parasites and malignancies.[5-7] The University of Manchester in England published a review in 2015, "Antibiotics that target mitochondria effectively eradicate cancer stem cells, across multiple tumor types: Treating cancer like an infectious disease".[8] The review proposed treating cancer as an infectious disease using FDA-approved antibiotics as anticancer therapies, across tumor types. Occult infections from oncovirus, bacterial, and fungal infections as well as from lesser known parasitic infections are driving forces in the cellular evolution and degeneration of cancer cells.

The similarities in the metabolism of parasites and cancer cells appear to allow them to survive in conditions with and without glucose. Glutamine has emerged as a critical amino-acid nutrient that supplies these cells with adenosine triphosphate (ATP) for energy, contributes carbon to cellular biomass, and provides a source of nitrogen for anabolic reactions, including nucleotide and hexosamine synthesis.[9-11]

These similarities suggest that therapeutic agents that are successful against parasites might also have lethal effects against cancers. A number of antiparasitic agents have shown anticancer qualities. It has been found that cancer metabolism is neither as homogenous nor as reproducible as initially suspected.

Tumors consist of a heterogeneous mix of multiple, interacting cell types organized in a complex hierarchy, and the metabolic activity of cancer cells is a complex, heterogeneous, and nuanced process.[12] Recent research has revealed a metabolic synergy or coupling between glycolytic tumor stromal cells composed of different cell types, including fibroblast cells and oxidatively stressed cancer cells—the Warburg effect, which occurs in human cancers and promotes tumor growth.[13]

Decreasing the range of stressors on the tumor microenvironment appears to decrease the forces supporting cancer. Mohammadi-Bardbori and Rannug's study found that toxins can influence cell metabolism and that elimination of toxins such as mercury can play an important role in human-host survival.[14] Addressing the heterogeneous factors affecting metabolism available to tumors facilitates a reduction in tumor-cell survival.

Danish scientist Johannes Fibiger won the 1926 Nobel Prize in Medicine for the discovery that a roundworm caused stomach cancer in rats.[15] Controversy over the award emerged as subsequent studies showed that lesions similar to those Fibiger described could be formed in animals deficient in vitamin A, which may have occurred in Fibiger's study animals.[16] The observations reported in this study support the concept reported in Fibiger's award.

Work from the laboratory of M. Lisanti reveals in a 2010 study that cancer cells retain metabolism by oxidative metabolism and the metabolism of surrounding fibroblasts lose their mitochondrial function and become glycolytic, which supplies lactose as a fuel for the cancer cell mitochondria. The study shows cancer cells become "parasitic" and use oxidation stress as a "weapon" to extract nutrients from surrounding stromal cells.[17] Treating cancer like an infectious disease that has become a metabolic disease[18] and a metabolic parasite[17,19] may be of benefit.

The current review examined whether antifungal and antiparasitic medications would interfere with the metabolism of cancers. This approach has appeal due lack of severe side effects with the medications. The antiparasitic and antifungal medications discussed have been cleared for human use, and their safety has already been determined. The study presents published information suggesting these medications may be useful in cancer therapy.

METHODS

Procedures

The research team searched the searched the National Center for Biotechnology Information (NCBI) PubMed database databases, using different keyword combinations, including Repurposed drug, antifungal, antifungal repurposed for cancer, antiparasitic repurposed for cancer, parasite, anti-cancer The search was focused on the medications used by one of the authors, S.Y., over the last 25 years. F.G. searched the literature for articles with key words such as parasite and cancer, antiparasitic and cancer, antifungal and cancer. Studies relating medications known to have antiparasitic or antifungal properties and had been used or explored in cancer therapy were included.

RESULTS

The literature search identified a number of studies, including *in vitro*, *in vivo* and clinical, which support the use of antifungal and antiparasitic medication in the treatment of cancer. In the clinical area, the authors observed benefit from the use of antifungal and antiparasitic medication in the treatment of a variety of cancer cases.

Results: AntiParasiticals

Avermectins (AVMs). These drugs are a series of drugs used to treat parasitic worms and have been widely used in agriculture and animal husbandry on the basis of their broad

spectrum of effective anthelmintic activity and specificity against targets. They were introduced in 1981 and were welcomed as a potent new class of anthelmintic agents.[20]

AVMs are naturally occurring fermentation products elaborated by the morphologically distinct soil organism *Streptomyces avermitilis*, which presents as a macrocyclic lactone with 2 sugars that are needed for maximal function of the AVMs. The AVM synthetic derivative dihydroavermectin B1 is called ivermectin and displays characteristics of efficacy and safety.[20] The 2015 Nobel Prize in Medicine was awarded to William C. Campbell and Satoshi Ōmura for the discovery of AVM and its derivatives, which have revolutionized the treatment of devastating parasitic diseases, such as river blindness and lymphatic filariasis. AVMs also have shown efficacy against an expanding number of other parasitic diseases.[21]

Ivermectin works as an agonist of gamma-amino-butyric acid (GABA), which inhibits signals from the interneurons to the motor neurons in the ventral nerve cord of parasites. Arthropods use GABA as a neurotransmitter but tend to use it not between 2 sets of nerve cells as nematodes do but between nerve and muscle cells. Prolonged stimulation of GABA allows the effects of ivermectin to become sustained, and in most parasites, this results in irreversible neuromuscular blockade, paralysis, and death.[20] The drug has shown 93%+ efficacy against numerous parasite strains.[20]

Mammals use GABA as a central neurotransmitter, but they aren't generally adversely affected by ivermectin. Lack of adverse reactions in humans is related to ivermectin being a macrolide of large molecular weight that doesn't readily cross the blood-brain barrier of the mammal to affect GABA within the central nervous system. Ivermectin has an excellent safety profile; adverse reactions called Mazzotti reactions are due to the efficacy of the drug, because the body's immunological system reacts to the release of inflammatory components upon the death of the microfilariae.[22] These reactions are in most cases mild to moderate and disappear within a few days without treatment.[23-25] Severe adverse reactions to ivermectin treatment can, however, occur in people heavily infected with the filarial parasites such as *Loa loa*.[26]

Ivermectin induces cytostatic autophagy in breast-cancer cells.[27] At least part of ivermectin's function relies on the inhibition of the protein kinase B-mechanistic target of rapamycin (AKT-mTOR) signaling pathway by promoting ubiquitination-mediated degradation of p21 (RAC1)-activated kinase 1 (PAK1), leading to increased autophagic flux.[27] This work begins to unravel the molecular mechanism underpinning ivermectin-induced cytostatic autophagy in breast cancer and characterizes ivermectin as a potential therapeutic option for breast-cancer treatment.

Benzimidazole-based compounds. These compounds are widely used antihelmintic drugs that show low mammalian toxicity and are highly effective against a wide range of helminth species.[28] While a wide spectrum of benzimidazoles are available for veterinary use, thiabendazole, albendazole (ABZ), and mebendazole (MBZ) have been registered as human medicine for several decades.[29,30] ABZ and MBZ were introduced in the 1970s and have proven to be well-tolerated and safe.[31]

The mechanism by which benzimidazoles exert their effects as anthelmintic and by which they induce cell death in malignant cells is still under investigation. Several cellular responses have been described. The molecular mechanism of action of benzimidazoles is based on specific binding to the microtubule subunit protein tubulin. Its effects result in the disruption of microtubule structure and function, causing interference with the microtubule-mediated transport of secretory vesicles in the absorptive tissues of helminths.[32,33] The low toxicity of benzimidazoles in mammals could be explained by the much stronger interaction of these drugs with helminth tubulin in comparison to the interaction with mammalian tubulin. Moreover, benzimidazoles have been shown to inhibit glucose uptake, deplete glycogen stores, and decrease the formation of ATP, leading to the death of the parasite.[34]

ABZ is a widely used anti-helminthic agent and has also shown promising efficacy against cancer cells *in vitro,* impairing microtubule formation. The antiproliferative effect of ABZ has been observed *in vitro* in hepatocellular and colorectal carcinoma cells[35] as well as *in vivo* in a xenograft mouse model of peritoneal carcinomatosis.[36] A dose-finding, Phase I clinical trial in patients with advanced malignancy showed that ABZ was well tolerated at 2400 mg per day (1200 BID).[37] Myelosuppression has been observed and could be a dose-limiting toxicity.[37]

MBZ's use in colon-cancer cell lines showed IC_{50}<5 μM, while the drug was largely inactive in nonmalignant cell-line models.[38] MBZ's antitumor activity has been described in lung[39] and adrenocortical carcinoma[40] and caused depolymerization of tubulin in a variety of cancer models.[41]

A case report on MBZ treatment of cancer recounts a patient with refractory metastatic colon cancer, who was treated with it at the standard anthelmintic dose of 100 mg twice daily. The patient experienced no subjective adverse effects from the drug, and a computerized tomography evaluation after 6 weeks of therapy showed near complete remission of the metastases in the lung and lymph nodes and a good partial remission in the liver.[38]

Praziquantel (PZQ) treatments and decreased biliary periductal fibrosis (PDF). Cholangiocarcinoma (CCA) is also known as bile-duct cancer arising along the intra- or extrahepatic biliary tree. It accounts for approximately 10–25% of all hepatobiliary malignancies worldwide[42] Liver flukes, Opisthorchis viverrini (OV), is distinct among helminth infections because it drives a chronic inflammatory response in the intrahepatic bile duct that progresses from advanced periductal fibrosis (APF) to cholangiocarcinoma (CCA),[43] which has one of the highest mortality rates of any cancer.[44] OV is a food-borne trematode that encysts as a metacercaria in the fins, skin, and musculature of cyprinid fish. Infection occurs when individuals ingest raw or uncooked fish infected with the metacercaria.

Adult flukes can reside within the human host for over 10 years, feeding on the epithelial cells that line the intrahepatic bile ducts.[45] Extensive research shows that oxidative stress (OS) plays a critical role in the transition from chronic OV infection to CCA. In affected individuals, oxidative stress results in the excretion of increased amounts of a modified DNA lesion (8-oxodG) into urine compared to individuals without these pathologies. The level of 8-oxodG in urine can predict whether an individual presents with APF or CCA.[43] Elevated levels of interleukin 6 (IL-6) are a marker of chronic inflammation among OV-infected individuals and are significantly associated with the development of PDF.[44] Elevation of transforming growth factor-beta (TGF-beta) is reported to be associated with the response to excretory and secretory molecules from OV.[46]

Infection with OV can be eliminated by chemotherapy with praziquantel (PZQ).[43] A significant association exists between the number of PZQ treatments (>2 times) and a decreased PDF risk.[47] PZQ has been established as the anthelminthic drug of choice to treat OV infection due to its chemotherapy effects, its wide availability, and it provides a more than 90% cure rate.[48]

Results: Antifungals

An emerging body of *in vivo, in vitro,* and clinical evidence has been reviewed in two 2017 articles describing the repurposing of the antifungal agent itraconazole for treatment of cancer.[49,50] The articles offer extensive references that confirm that itraconazole possesses antineoplastic activity by itself and has a synergistic action when combined with other chemotherapeutic agents.[49,50] Itraconazole has been shown to be safe in humans.[49]

Results: Case Studies of Antiparasitical Therapy

Case study 1. A 72-year-old man with stage-4 lung cancer and metastasis to the bone was a poor candidate for chemotherapy or radiation. He responded to ivermectin, praziquantel, nitazoxanide (Alinia), MBZ, itraconazole, and fluconazole during the 12 months of treatment. The antiparasitic medications and dosages were selected by one of the authors based on an Acupuncture Meridian Assessment (AMA). The patient also received insulin potentiation therapy (IPT) with acyclovir, cefatriaxone, fluconazole, and metronidazole to cover viral, bacterial, fungal, and protozoal infections. Chemotherapy agents weren't used. PET scans completed 3 times in the 12 months after the end of the treatment have been all negative, and the patient is clinically cancer free.

Case study 2. A 46-year-old female with stage-4 multiple myeloma, metastasis to bones, four fractured bones, and elevated free kappa light chain micro-globulin over 4000—wasn't responding to chemotherapy agents and radiation therapy and had increasing bone pain. The antiparasitic medications and dosages were selected by one of the authors based on the AMA. The patient had multiple rounds of antiparasitic medications, including ivermectin, pyrantel pamoate, praziquantel, itraconazole, and fluconazole and IPT with acyclovir, ceftriaxone, fluconazole, and metronidazole. Her free kappa light chain dropped below 100, and she became free of bone pain. No chemotherapy agents were used. Dental operations were done several times by an oral surgeon to clean an infected jaw bone cavitation to remove the source of occult dental infection. Following the therapies, Her oncologist retired, and her new oncologist thought that the original diagnosis of multiple myeloma must have been wrong because he hadn't seen an advanced-stage multiple myeloma reverse and become asymptomatic.

Case study 3. A 32-year-old female with recurrent left-breast cancer was postmastectomy and had had radiation and chemotherapy. The antiparasitic medications and dosages were selected by one of the authors based on the AMA. The patient had a dental operation for cavitation; had 10 mercury-silver amalgams removed due to a documented, very high mercury level of 150 microgram/creatinine (normal range 0-3); received 2,3-Dimercapto-1-propanesulfonic acid (DMPS) IV chelation treatment; and also received ivermectin, pyrantel pamoate, levamisole, and tinidazole. The patient has been physically active and cancer free for 17 years since the end of treatment.

Case study 4. Patients with pancreatic, cholangio-carcinoma, and liver cancer were evaluated using the AMA by one of the authors and often responded to triple antiparasitic medications—ivermectin, pyrantel pamoate and praziquantel. It hasn't been uncommon to prolong their survival prognosis from 3-to-4 months to 2-or 3-years.

DICUSSION

Inflammation has a long history as a component leading to cancer. At the same time, the genetic and metabolic flexibility, both intrinsic (within the tumor) and extrinsic (the tumor microenvironment) is important to the progression of cancer.[51] Metabolic flexibility in tumors,[51] described by some authors as tumor heterogeneity, provide the basis for treatment resistance in cancers.[52] These tumor cell variations have led to a need for new anti-cancer drugs and "Since designing new anti-cancer therapies is both a long-term and costly endeavor, there is a lot of interest in repurposing "old" drugs to help speed up the fight against cancer".[51] If effective against cancer, antiparasitic and antifungal drugs have appeal due to their relative lack of side effects. The efficacy of some antifungal and antiparasitic drugs as part of cancer treatment is reviewed in this article.

One of the authors of this review had the opportunity to observe the effects of many of the antiparasitic drugs mentioned in this article while overseeing the antiparasitic treatment of thousands of individuals during an Army mission in Bolivia. Familiarity with the medications led to his use of these medications in his clinical practice. This review is intended to improve the understanding that these medications have benefits in the treatment of cancer as well as antiparasitic and antifungal application.

The drugs utilized in the study have been in human use, and their safety in clinical use has been observed and

documented in studies. The drug literature reviewed was limited to the drugs utilized in the clinical section of the study and is not intended to represent all the drugs that may have a duel function as antifungal or antiparasitic and anti-cancer effects.

It has been observed that chronic infection by *O. viverrini* enhances bacterial diversity in the liver and promotes *Helicobacter pylori* growth.[53] *H. pylori* was the first formally recognized bacterial carcinogen. *H. pylori* is a well-recognized causative factor of gastrointestinal diseases, and has been strongly linked to the development of gastric adenocarcinoma.[54] The association of *H. pylori* with *O. viverrini* stimulates consideration of the possibility that the parasite effect that led to Fibiger's 1926 Nobel Prize might have had alterations in the microbiome that were not appreciated at that time.[15]

The causal relationship between inflammation and cancer has gained acceptance and studies support the view that there is an association between microbial agents such as bacteria or viruses and cancer.[55] The role of fungus has been known for some time with the *Aspergillus* toxin aflatoxin B1, having been well-characterized to lead to the development of hepatocellular carcinoma (HCC) in humans and animals. Aflatoxin B1 has also been shown to suppress alveolar macrophage phagocytosis.[56] Ochratoxin A produced by *Aspergillus species* and *Penicillium* species is a potent renal carcinogen.[57] Studies now show the opportunistic fungus *Candida albicans* increases the risk of carcinogenesis and metastasis.[58] There has been controversy about the possibility that *C. albicans* can produce gliotoxin, which is also produced by *Aspergillus fumigatus* and has known immunosuppressive effects.[59]

A recent issue of *Frontiers in Medicine* is devoted to articles on parasite-associated malignancy.[60] The reader is referred to this collection for additional research into the origins and evolution of the relationship between parasites and cancer. One of the articles notes that chronic inflammation is proposed as a common pathway for cancer initiation and development as a mechanism that ties parasites to cancer.[61]

While our understanding of the relationship between fungal and parasite infection and the development of cancer is being increasingly explored, it is hoped that this review will stimulate not only research but also an increased use of antifungal and antiparasitic medications in the management of cancer.

CONCLUSIONS

Due to the complexity of the behavior and biology of cells undergoing transformation to cancer, scientists' primary focus should be on detection and elimination of sources of inflammation. Antiparasitic medications, and also antiviral, antibiotic, and antifungal medications should be thought of as underrecognized, underappreciated, and forgotten medications that can be part of cancer therapy. The information offered in this review suggests scientists should think of cancer not only as a metabolic disease but also as a metabolic parasite and should consider using antiparasitic medications under a new understanding of the role of inflammation, infection, and mitochondrial dysfunction in the development of cancer cells.

AUTHOR DISCLOSURE STATEMENT

Authors have no conflict of interest to disclose.

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