Antiparasitics: Emerging Data in Cancer Treatment

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Overview:

Though the mechanisms for treating parasitic infections and managing cancer may seem to be unconnected, they actually share a complicated relationship. Some parasitic infections decrease the risk of cancer while other parasitic helminths are thought to be biologic carcinogens. The specific underlying mechanism of this carcinogenicity has not yet been fully elucidated, but antiparasitic drugs and antitumor drugs have some overlapping targets, including cyclin-dependent kinases (CDKs) and the tubulin/microtubule system.[1-3] Emerging data on some antiparasitic drugs, especially benzimidazoles like mebendazole or avermectins like ivermectin may play a role in cancer therapy due to antitumoral effects.

Macrolide Antiparasitic Drugs:

Avermectins are a class of macrolide antiparasitic agents including avermectin and ivermectin (a semisynthetic derivative of natural avermectin) among others.[1,4] The anticancer effect of ivermectin appears to vary depending on the type of cancer treated. A study in mice revealed that ivermectin increased intracellular influx of chloride ions leading to increased oxidative stress and death of leukemia cells without impacting healthy cells.

The mechanism of action for ivermectin as a treatment of colon and lung cancers differs and is thought to be related to Wnt-T cell factor. The Wnt/β-catenin pathway is inhibited by ivermectin. This pathway plays a major role in cell regulation including cell migration, cell proliferation, and apoptosis as well as being essential for embryonic development. Dysregulation of the Wnt/β-catenin pathway is a causative factor in a variety of

cancers including breast, colon, and skin cancer among others.[5] Ivermectin, which inhibits this pathway, has come under interest as a possible treatment for the cancers for which this pathway plays a pivotal role.[6]

Though in vitro and animal trial data regarding the utility of ivermectin for the treatment of various types of cancers is promising, data on human use for this indication is limited. A review of data on ivermectin for the management of tumors noted that studies showed more than a 50% reduction in tumor volumes with ivermectin treatment courses ranging from 10-42 days. These studies in mice evaluated dosing at an incredibly wide range (2.5-40mg/kg) with 5mg/kg being the median dose. Though testing is always needed before extrapolating animal dosing to human dosing, this 5mg/kg dose is approximately equivalent to 0.4mg/kg in humans based on human equivalent dose calculations provided by the FDA.[7,8]

Though safety and efficacy data is not yet available, an upcoming phase 1 study looking at ivermectin in patients with triple negative breast cancer (in combination with balstilimab, a chemotherapeutic agent) plans to evaluate dosing at 30, 45, or 60mg daily on days 1-2, 8-10, and 15-17 in a 21 day cycle until disease progression or intolerance.[9] One limited case series looking at 1mg/kg in pediatric patients with acute myeloid leukemia found no toxic effects and reported this treatment resulted in disease stabilization or clinical remission.[13,14]

In addition to its direct effects on cancer cells, evidence also exists to suggest that ivermectin may be a useful tool for mitigating multidrug resistance in cancer therapy. Some studies suggest that ivermectin can inhibit overexpression of P-glycoprotein, thereby reducing efflux of chemotherapy drugs from effected cells.[10] Data on the impact of ivermectin on multidrug resistance is mainly in animal studies, but benefit has been demonstrated with agents such as vincristine.[11,12]

Benzimidazoles:

Benzimidazoles are a class of antihelmintic drugs including albendazole, mebendazole, and fenbendazole among others. Data testing the impact of these benzimidazoles on cancer cell lines from pancreatic, paraganglioma, and colorectal cancer cells demonstrated mebendazole, albendazole, and fenbendazole to be highly active against these cancer cell lines.[15]

Though the mechanisms via which these drugs exert their anticancer effects are still being elucidated, benzimidazoles have been found to inhibit microtubule polymerization (a mechanism of some common cancer drugs such as paclitaxel), induce apoptosis, and inhibit angiogenesis. Unlike ivermectin, which does not penetrate the blood brain barrier well, some benzimidazoles such as mebendazole can penetrate this barrier, and therefore show promise for some cancers of the brain as well.[16]

While several benzimidazoles have been studied for potential anticancer activity, mebendazole has garnered particular interest. Among this class of drugs, though it is subject to first pass metabolism, mebendazole has relatively high oral bioavailability, allowing for oral rather than injectable dosing.[16,18] Some studies also suggest that mebendazole is less likely to cause oxidative stress than some other benzimidazoles such as albendazole.[17]

Although fenbendazole has also been studied for anticancer activity, unlike mebendazole it is currently only FDA approved in animals. This had led to more limited studies on fenbendazole, though, one case series of three patients with genitourinary malignancies found that all three patients had a complete response when fenbendazole 1 gram three times weekly was used or added on to their current chemotherapeutic regimen.[19]

Of the antiparasitic agents currently being studied as anticancer treatment, mebendazole has by far the most data in human populations for this indication. A phase 1 clinical trial evaluating mebendazole in conjunction with temozolomide treatment in patients (median age 49.8 years) with newly diagnosed high-grade gliomas compared escalating doses from 25 to 200mg/kg/day of oral mebendazole (polymorph C) divided into three doses given with meals. The study found 200mg/kg/day dosing to be tolerated by the majority of patients,

though, four out of 17 necessitated a lower dose due to hepatotoxicity (elevated AST and ALT liver enzymes). Some patients also had hematologic abnormalities, that while they did not necessitate discontinuation or a dose decrease, did cause the researchers to recommend monthly blood cell counts for safety purposes.

Given high pill burden and some adverse effects, the researchers proposed 75-100mg/kg/day as a reasonable dose for future trials evaluating mebendazole in various cancers. Though the intent of the study was to find the safe maximum dose of mebendazole, a survey of progression free survival in those who received greater than one month of mebendazole found that those who did had 13.1 months progression free survival, compared to 9.2 months progression free survival for those who received less than one month of mebendazole treatment.[20]

Another phase 1 study on mebendazole (also polymorph C) in pediatric patients at 50, 100, or 200mg/kg/day (divided into two doses) evaluated this treatment in conjunction with bevacizumab and irinotecan for management of high-grade gliomas. This small study was aimed at finding a safe dose and noted that doses up to 200mg/kg/day were well tolerated. Though efficacy was not the goal of this study, researchers reported a 33% overall response rate with 2/10 patients achieving a partial response and 1/10 demonstrating a complete response that was sustained for 10 months.[21]

Though this data and preclinical data on mebendazole is promising, not all small trials in human patients have noted benefit. A Phase 2a study evaluating mebendazole (polymorphism C) in patients with advanced gastrointestinal cancer treated patients with up to 4g/day mebendazole with a target serum concentration of 300ng/mL. In this study only eight patients were treated for the full 8 weeks, and only five actually reached the target serum concentration. The study noted that patients on mebendazole did continue to experience rapid disease progression both on treatment and after mebendazole had been discontinued.[22]

In addition to these phase 1 and phase 2 trials, there have been some case studies on mebendazole for cancer as well. One case study of a 48-year-old man with adrenocortical carcinoma with disease refractory to mitotane, 5-fluoruracil, streptozotocin, bevacizumab and radiation therapy stopped all chemotherapeutic drugs and was subsequently treated with mebendazole 100mg twice daily as monotherapy for 19 months. Researchers noted that metastases regressed, and disease remained stable with treatment. The patient did experience disease progression again after 24 months of monotherapy.[22,23]

A second trial of a 74-year-old man with advanced metastatic colon cancer refractory to chemotherapy also evaluated a relatively low dose of 100mg twice daily for six weeks and the patient experienced complete remission of metastases in the lungs and lymph nodes and partial remission of metastasis in the liver. Though the impact of treatment on the patient's cancer was good, the patient's liver enzymes were elevated and so treatment dose was lowered to 50mg twice daily. This decrease in dose improved liver enzyme levels and researchers noted that the disease remained stable even with this dose reduction.[22,24]

These doses are much lower than those evaluated in the phase 1 trials for high-grade gliomas. Though treatment with mebendazole at a range of doses appears to be safe in most cases, further data on appropriate dosing for various types of cancers and larger scale clinical trials are needed to determine the future role of mebendazole and other benzimidazoles in the treatment of cancer.

A note on polymorphisms:

Polymorphism refers to the phenomenon in which a drug can exist in different crystalline phases. These different polymorphs can have significant differences in solubility or chemical or physical stability among other characteristics. Changes in these characteristics can result in subsequent differences in drug efficacy, bioavailability, and toxicity.[25] Polymorphism is a common phenomenon, with some estimating that more than 50% of active pharmaceutical ingredients have more than one polymorphic form.[25]

Mebendazole has three different polymorphic forms (A,B, and C). Polymorph A is the most thermodynamically stable, however, it has the lowest solubility between forms and also has poor anthelmintic activity. Polymorph

C is more stable than polymorph B, has superior solubility to polymorph A, and is considered to be the preferred polymorphic form for pharmaceutical use. Polymorph B is the most soluble form and may be associated with greater toxicity than Polymorphs A or C.

Studies have demonstrated that polymorph C has superior absorption from the gut and is superior to other forms in terms of blood brain barrier penetration as well, making it the ideal form for potential future study in brain cancers.[20,29] Mebendazole may reconfigure from polymorph C to polymorph A under high humidity and temperature, though, one study looking at storage at 30C and 75% relative humidity did not note significant conversion over a 48-month period.[26-28]

Though there was an FDA approved chewable tablet that contained only polymorph C (discontinued for 'commercial reasons' and not currently available in the US) a study reviewing polymorphic forms in tablets from Teva, Janssen, Aurochem, and Medley found that polymorph C was the predominant form, but Teva and Aurochem tablets that had been stored for 2 years at room temperature showed mainly the A polymorph.[29] While the potential of conversion between forms is concerning, some studies have noted that conversion to polymorph A primarily occurs at temperatures exceeding 180°C.[30]

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