Review Article

Application of a widely-used tropical anti-worm agent, mebendazole, in modern oncology

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Abstract

Although clinical trials have not been completed, it has already been confirmed that mebendazole, a well-known anti-parasitic drug widely used in the tropical areas, inhibits cancer cell growth. Preclinical studies show that mebendazole notably impedes the growth of malignant and metastatic tumors such as osteosarcoma and soft tissue sarcoma, melanoma, carcinoma (lung, colorectal, breast, ovarian, hepatocellular and adrenocortical), acute myeloid leukaemia, glioblastoma multiforme and meduloblastoma. Mebendazole can induce the depolymerization of microtubules in neoplasms and newly formed vasculature, stopping tumor growth and neoangiogenesis, along with other proposed mechanisms of action.

Keywords: *Anthelmintic, Mebendazole, Cancer treatment, Antimicrotubullar effect, Anti-neoangiogenesis*

INTRODUCTION

Numerous early-stage laboratory experiments, clinical studies and epidemiological research have documented promising anticancer properties of many existing medications that millions of people take safely every day for other indications [1-3]. The Repurposing Drugs in Oncology (ReDO) Project [4], coordinated by the Anticancer Fund, has identified 70 agents for which there is evidence of anticancer properties. These include the de-worming drug mebendazole [5], the common analgesic aspirin [6], the diabetes drug metformin [7-9], cholesterol-lowering statins [10], the common antibiotic doxycycline [11], the antacid cimetidine [12], the anti-fungal itraconazole [13], the ACE inhibitor perindopril [14,15], the vasodilatator

nitroglycerin [16] and the immunotherapeutic agent levamisole [17,18]. These medications need to be tested and applied in oncology. Clinical trials are essential for determining whether repurposed drugs are applicable and better than the regular care, and for which patient groups. The goal is to find the best, safest and most reasonably priced forms of anticancer treatment [1-4].

Mebendazole is a benzimidazole anthelmintic with the chemical formula $C_{16}H_{13}N_3O_3$, molecular mass 295.293 g/mol and systematic (IUPAC) name methyl (5-benzoyl-1H-benzimidazol-2-yl) carbamate. It was introduced in the 1970s as an equivalent of formerly registered thiabendazole, but with the advantage of meaningfully abridged toxicity. The WHO listed mebendazole,

administered orally as an essential drug against roundworms, hookworms, pinworms, tapeworms and whipworms. Mebendazole paralyzes parasites in the alimentary canal. Mebendazole's low toxicity is ascribed to the small amount of the drug absorbed (5 - 10 % in all species, 17 - 22 % in humans) [19].

Fatty food improves the absorption of mebendazole [19]. The first-pass metabolism of almost all absorbed mebendazole occurs in the bowels and liver [19]. It is eliminated via urine and bile, mostly as metabolites. A large amount of it is eliminated unchanged via the feces, without absorption. In human circulation, mebendazole is 95 % protein bound [19]. Due to lipofility, mebendazole passes the blood-brain barrier [19]. The safety of mebendazole is not fully investigated in pregnancy (C category) and breastfeeding. Gastrointestinal pain, diarrhea and higher levels of liver enzymes are common side effects of mebendazole therapy. In rare cases, leukopenia, agranulocytosis and trombocitopenia may occur.

The combination with metronidazole may rarely cause Stevens–Johnson syndrome. Antiepileptics phenytoin and carbamazepine lower mebendazole plasma concentrations [20]. Interactions with cimetidine elevate the concentrations of mebendazole [20].

There are numerous findings that mebendazole, widely used to treat parasitic worm infestations, especially in endemic tropical regions, may prevent cancer cell proliferation and secondary tumours, although no clinical trials have been completed. In laboratory conditions, mebendazole has a good outcome for antitumor activity against various types of cancer: melanoma [21,22], lung [23], adrenocortical [24,25], colorectal [26-28], breast [29], ovarian [30] and hepatocellular [31] carcinoma; osteosarcoma and soft tissue sarcoma [26]; acute myeloid leukaemia [32,33]; glioblastoma multiforme [34] and meduloblastoma [35,36].

ANTICANCER ACTION OF MEBENDAZOLE IN PRECLINICAL STUDIES

Inhibition of microtubule synthesis

Mebendazole selectively inhibits microtubule synthesis in intestinal cells of parasitic worms, which blocks their uptake of sugar and other sustenance, producing paralysis and elimination of helminthes from the human body [19]. Mebendazole has been shown to induce the depolymerization of tubulin in various cancer models [21-36].

Microtubules are commonly accepted anticancer targets, because of their vital role in the cell life cycle. Drugs that target microtubules, such as Vinca alkaloids and taxanes, inhibit cell division, encouraging apoptosis. Microtubules in the lung cancer culture were effective targets for anticancer therapy with mebendazole. This therapy blocked mitosis, induced apoptosis of lung cancer cells, activated caspase and released cytochrome c [23].

Bcl-2, Bax and p53 proteins modulation

Bcl-2 and related proteins, encoded by the Bcl-2 oncogene, suppress or promote apoptosis [37]. The final apoptotic effect is dependent of the quantity of pro- and anti-apoptotic Bcl-2 proteins [37]. The impairment of the Bcl-2 gene induces cancers and resistance to oncological therapy [38].

Like other Bcl-2 proteins, Bax protein, coded by the Bax oncogene, suppresses or promotes apoptosis [37]. Bax protein forms a Bax-Bax homodimer that acts as an apoptosis inducer, while the heterodimer with Bcl-2 (Bcl-2-Bax) functions as an antiapoptotic regulator [37]. Bax opens the anion channel of mitochondria and liberates cytochrome c by decreasing the membrane potential [39]. The influence of Bax gene on apoptosis is dependent on tumor suppressor p53 [37]. Protein p53 and the related genes protect multicellular organisms from cancer appearance. This cancer suppressor is called the "genome guardian" because it prevents mutations. Bax can be activated due to the influence of Bcl-2, and also p53 [37] or Bif-1 proteins [40]. Contrariwise, Bax can be inactivated through interaction with mitochondrial outer-membrane protein VDAC2 (voltage-dependent anion channels) [41], Pin1 enzyme and IBRDC2, an IBR-type E3 ubiquitin ligase [42] (Figure 1).

Publications about mebendazole's effect on melanoma cells (via Bcl-2 inactivation plus other mechanisms) and melanocytes give more insight into the mebendazole's anticancer mechanism of action [21,22]. These studies have shown that mebendazole's anticancer effect on chemoresistant melanoma cells involves Bcl-2 regulated microtubular impairment. Bcl-2 protein, which is commonly expressed in human melanoma, enables the proliferation of mutated cells. It has been related to melanoma chemoresistance, through its antiapoptotic role [21,22].

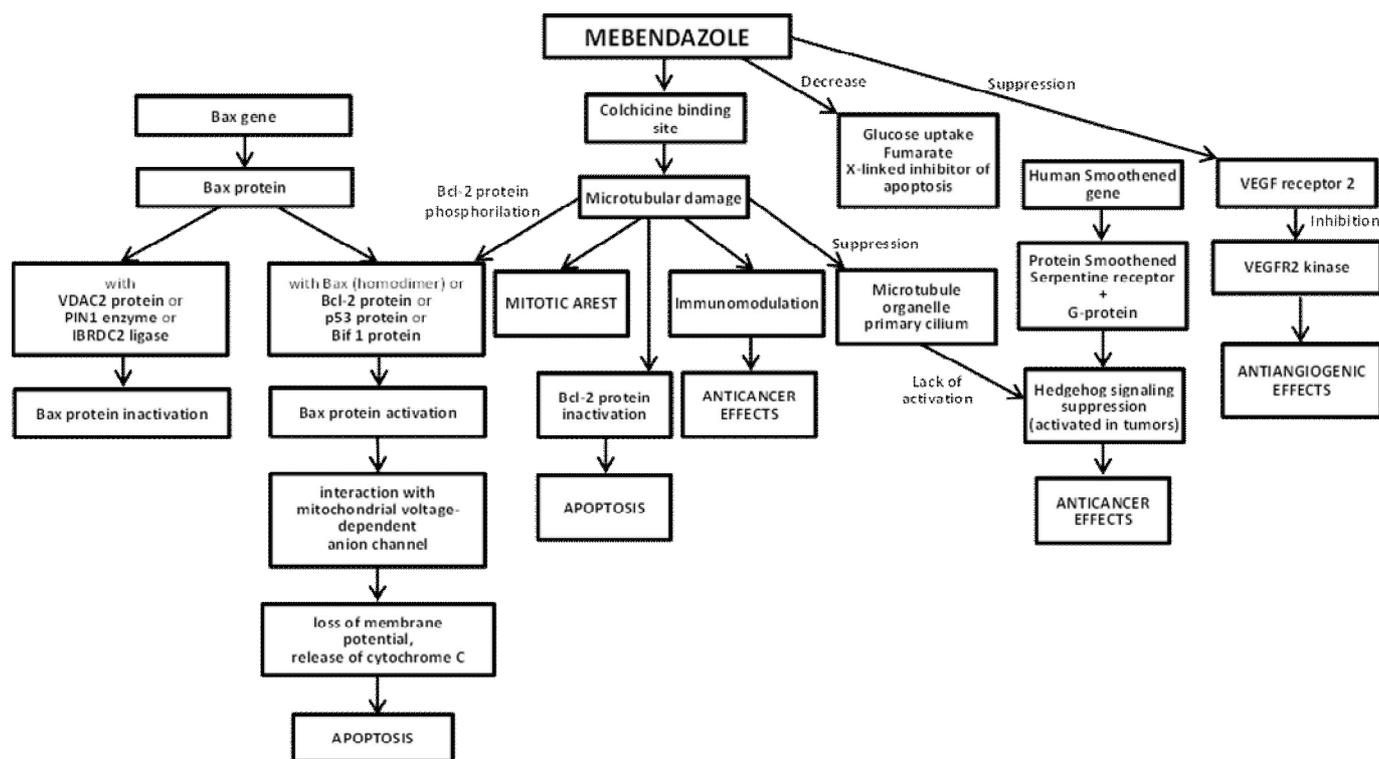In many cases, melanoma with metastases is resistant to standard microtubule-focused

Figure 1: Schematic presentation of proposed mebendazole anticancer mechanisms of action in various preclinical investigations

chemotherapeutics vinblastine and paclitaxel [21]. The mechanism of mebendazole's action involves a colchicine-binding site, which is different from vinblastine or paclitaxel binding sites [21,43]. Furthermore, mebendazole has a nucleotide-like structure [21], which permits interactions with wide range of biomolecules. Accordingly, mebendazole's anticancer actions encompass other effects, different from the microtubule damage, such as decreased fumarate and reduced uptake of glucose [21].

Oblimersen, a Bcl-2 antisense oligodeoxynucleotide, selectively aims at Bcl-2 mRNA, decreasing the production of Bcl-2 protein, which enables cancer cell proliferation and cancer development [44]. The use of oblimersen as a targeted anti Bcl-2 therapy against malignant melanoma has been examined [45].

The combination of oblimersen and dacarbazine gives significantly better clinical results in the treatment of advanced melanoma than dacabarzine alone [45]. It is important that mebendazole, like oblimersen, also causes melanoma cell apoptosis through Bcl-2 [21]. Oblimersen is administered by intravenous infusion, and is therefore difficult to manage. By contrast, mebendazole is easy for dosage, since it can be given orally. In melanocyte cultures and

melanoma cell lines, Bcl-2 small interfering RNA (siRNA) preparations show a moderate effect on mitoses [46].

Previous studies recognize the post-translationally phosphorylated Bcl-2 protein as a regulator of cell reaction to mebendazole in melanoma cells and melanocytes [21]. It was only in melanoma cells that mebendazole caused rapid phosphorylation of Bcl-2 protein [21]. Bcl-2 phosphorylation blocks its interaction with the mediator for apoptosis Bax (prevention of Bcl-2-Bax antiapoptotic heterodimer formation), thereby promoting selective apoptosis in melanoma cells [21]. There is also evidence that the treatment of mebendazole-resistant melanocytes with Bcl-2 siRNA decreases the levels of Bcl-2 and increases cell sensitivity to mebendazole's antiproliferative effects [21]. The second work on melanoma xenografts [22] confirmed mebendazole's inhibition of melanoma growth by the phosphorilation of Bcl-2 and documented that mebendazole diminished the concentrations of the X-linked apoptosis inhibitor.

In non–small cell lung carcinoma cells Bcl-2 phosphorylation was not a necessary event for mebendazole-induced apoptosis, based on the observation that Bcl-2 phosphorylation occurred in proapoptotic response to mebendazole treatment in H460 cells, but not in A549 cells

[23]. In two examined non–small cell lung carcinoma cell lines, A549 and H460, the phosphorylation of Bcl-2 protein caused by mebendazole supports apoptosis only in the H460 culture [23].

Hedgehog signalling pathway inhibition

The Hedgehog (Hh) signalling track is extensively stimulated in the brain tumor, medulloblastoma and some other aggressive human cancers. The Hh signaling blocker, vismodegib, has shown encouraging anticancer effects. Therefore, the Hh signalling pathway has become a new inviting and fascinating target for the investigation of potentially oncologic drugs. Mebendazole strongly suppressed Hh signalling and decreased the proliferation of Hh-controlled medulloblastoma human cell lines at concentrations achievable in clinical conditions [47]. The mutational status of Hh signalling genes in the tumor after disease progression, such as the mutated serpentine receptor Smoothened, caused resistance to vismodegib anticancer therapy. Protein Smoothened, a receptor connected with G protein, is a part of the Hedgehog signalling pathway and is conserved from flies to humans. Smoothened is encoded by the SMO gene and forms a serpentine protein involved in Hh-track. Mebendazole in human cell lines inhibits the genesis of the primary cilium, a microtubular cell organelle that has a role of a signalling junction for Hh pathway stimulation [47]. Mebendazole effectively inhibited Hh signalling, even in cell clones that became resistant to vismodegib due to the mutated gene which encodes Smoothened protein [47]. The mebendazole and vismodegib combination has an additive inhibitory effect on Hh signalling [47].

Inhibition of neoangiogenesis and immune-modulation

Some antimicrotubular drugs, such as mebendazole, can induce the depolymerization of microtubules in tumor blood vessels and as such target vasculature to decrease neoangiogenesis and the nutrient provision of neoplasms [35]. Bai *et al* [35] recently demonstrated preclinical evidence for using mebendazole for the treatment of various forms of medulloblastoma. Mebendazole inhibits VEGFR2 (Vascular Endothelial Growth Factor Receptor 2), the main receptor controlling the action of VEGF [35]. In a preclinical experiment on mice with medulloblastoma, it was shown that mebendazole blocks neoangiogenesis, which is necessary for tumor growth [35]. The

microvascular density was greatly reduced within treated tumors in mice, compared with the untreated tumors. The immunohistochemistry of tumors treated with mebendazole implies the inhibition of VEGFR2 kinase. Therefore, mebendazole is an antiangiogenic agent which decreases the development of tumor neovasculature by blocking the activity of VEGFR2 [35].

The effect of mebendazole on the immune system of organisms with cancer is still unknown. Nevertheless, it has been shown that albendazole can stimulate cellular immunity in mice with echinococcosis [5]. There is evidence that enhanced immune mechanisms can be connected with the dynamics of microtubules, and that this may also contribute to antitumor actions of medications which impair microtubules [5].

VERIFICATION OF MEBENDAZOLE'S ANTI-CANCER EFFECT IN CLINICAL STUDIES

Investigations of mebendazole's anticancer effects in clinical conditions are not yet finalized [4]. Not more than two papers presenting case reports with completed research results have been published so far: treatment of a patient with metastatic adrenocortical cancer [25] and treatment of a patient with metastatic colon cancer [28].

Ideal cancer medications are 'target' cures, directed at specific targets exclusive to cancer cells. However, a lot of available anticancer medications known as "dirty" aim at several targets, distressing more than one protein or signalling pathway in cancer and normal cells at a time. The use of nontoxic repurposed drugs in arrangement with other medication should be effective against cancer, with decreased toxicity. A good course of action would be to experiment with combinations of low-toxic anticancer treatments (Table 1.) [5-16,21-36]. Mebendazole treatment could provide the following advantages: oral treatment (no need for infusion), lower toxicity (no special equipment for toxicities required), less frequent visits, potentially fewer blood tests and a low cost - so less cost for the patient and better compliance.

CONCLUSION

Clinicians and patients can choose anticancer therapy from assorted registered and/or even unconventional medications for cancer.

Table 1: Possible combinations of mebendazole with other drugs for the clinical treatment of specific neoplasms based on published results of preclinical investigations

Neoplasm	Reasonable therapeutic combination with mebendazole	Therapeutic strategies
Malignant melanoma	Hydroxychloroquine, Diclofenac or Celecoxib, Oral cyclophosphamide	microtubule disruption, inhibition of authophagy, anti-angiogenic and immunomodulation
Non-small cell lung cancer	Metformin, Intraconazole, Diclofenac or Celecoxib	microtubule disruption, AMPK activation, mTOR signalling, COX-2 inhibition, Hedgehog signalling
Adrenocortical carcinoma	Intraconazole, Oral cyclophosphamide	microtubule disruption, anti-angiogenic, Hedgehog signalling
Colorectal carcinoma	Metformin, Cimetidine, Diclofenac Oral vinorelbine	microtubule disruption, AMPK activation, mTOR signalling, immunomodulation, anti- histamine, COX -2
Breast cancer	Metformin, Oral cyclophosphamide, or Oral vinorelbine	microtubule disruption, AMPK activation, mTOR signalling, anti-angiogenic
Ovarian carcinoma	Metformin, Diclofenac, Intraconazole	microtubule disruption, AMPK activation, mTOR signalling, anti-angiogenic
Hepatocellular carcinoma	Albendazole	microtubule disruption, anti-angiogenic, Hedgehog pathway inhibition
Osteosarcoma	Metformin, Losartan, Oral cyclophosphamide	microtubule disruption, Hedgehog pathway inhibition, AMPK activation, mTOR signalling, IGF-I, anti-angiogenic
Soft tissue sarcoma	Metformin, Losartan, Oral cyclophosphamide	microtubule disruption, Hedgehog pathway inhibition, AMPK activation, mTOR signalling, IGF-I, anti-angiogenic
Fibrosarcoma	Hydroxychloroquine, Intraconazole	microtubule disruption, anti-angiogenic, Hedgehog pathway inhibition
Acute Myeloid Leukaemia	Albendazole or oral vinorelbine, Diclofenac	microtubule disruption, induction of apoptosis COX -2
Glioblastoma multiforme	Hydroxychloroquine, Intraconazole	inhibition of authophagy, microtubule disruption, anti-angiogenic, Hedgehog pathway inhibition
Meduloblastoma	Hydroxychloroquine, Intraconazole	microtubule disruption, anti-angiogenic, Hedgehog pathway inhibition

As a result, experiments and clinical studies must always be recommended in order to find and provide, by any means necessary, the attainable, adequate, physically most endurable and least expensive cure. Based on the existing preclinical studies, mebendazole is a good example.

Nonetheless, mebendazole deserves clinical investigation as an antineoplastic agent since it has potentials for enriched anticancer effectiveness and an outstanding safety profile.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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