

# MEBENDAZOLE MONOTHERAPY AND LONG-TERM DISEASE CONTROL IN METASTATIC ADRENOCORTICAL CARCINOMA

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## ABSTRACT

**Objective:** To describe successful long-term tumor control in metastatic adrenocortical carcinoma, a relatively rare tumor with limited treatment options outside of surgery.

**Methods:** We present the clinical, radiologic, and pathologic findings in a patient with failure of or intolerance to conventional treatments for metastatic adrenocortical carcinoma.

**Results:** A 48-year-old man with adrenocortical carcinoma had disease progression with systemic therapies including mitotane, 5-fluorouracil, streptozotocin, bevacizumab, and external beam radiation therapy. Treatment with all chemotherapeutic drugs was ceased, and he was prescribed mebendazole, 100 mg twice daily, as a single agent. His metastases initially regressed and subsequently remained stable. While receiving mebendazole as a sole treatment for 19 months, his disease remained stable. He did not experience any clinically significant adverse effects, and his quality of life was satisfactory. His disease subsequently progressed after 24 months of mebendazole monotherapy.

**Conclusion:** Mebendazole may achieve long-term disease control of metastatic adrenocortical carcinoma. It is well tolerated and the associated adverse effects are minor. (*Endocr Pract.* 2011;17:e59-e62)

## Abbreviations:

ACC = adrenocortical carcinoma; CT = computed tomography

## INTRODUCTION

Adrenocortical carcinomas (ACCs) are rare tumors, with an incidence of 1 to 2 per million. The overall 5-year survival is limited, ranging from 16% to 44% (1). The treatment of early-stage disease is mostly surgical. Metastatic disease may respond to various combinations of mitotane, etoposide, doxorubicin, cisplatin, and streptozotocin, but the responses are generally short-lived. Mebendazole is a well-tolerated anthelmintic drug that has been in use since the early 1970s for gastrointestinal parasitic infections. It acts through inhibiting microtubule polymerization via binding to the growing end of the microtubules. Antitumor properties of mebendazole have been described in various human cancer cell lines in vitro and in vivo. This is the first report of using mebendazole as cancer treatment in a human patient.

## CASE REPORT

A 48-year-old man initially presented in 2002 with abdominal pain and a lump in his left subcostal area. Computed tomography (CT) revealed an adrenal mass, measuring 18 × 15 cm. CT-guided fine-needle aspiration biopsy of the mass revealed low-grade ACC, and it was staged as a T3NXMX tumor. The patient underwent complete resection of the mass with negative margins. He was observed with surveillance CT every 3 months, and 15 months later, a retroperitoneal recurrence of his ACC was detected on CT, which showed a mass at the level of the left

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diaphragmatic crus. The mass was surgically resected, and the surgical specimen had positive margins. The patient underwent adjuvant radiation therapy, followed by observation. Two years later, CT detected a growing, fluorodeoxyglucose-avid pelvic mass measuring  $2.2 \times 1.7$  cm. The mass was resected and was consistent with ACC; it had negative margins. The mass recurred 3 months later, and small, indeterminate lesions were identified in his liver. A biopsy specimen from one of the liver lesions was negative for tumor. The recurrent pelvic mass was resected, and it had negative margins, again revealing recurrence of ACC. One year later, another mass was found between the right kidney and right adrenal gland (interpreted as a metastatic focus abutting the right adrenal gland), and the liver lesions appeared to have increased in size. The mass was deemed surgically unresectable because of right kidney involvement and concern for liver metastases. Systemic cytotoxic chemotherapy was considered. The patient received mitotane in therapeutic doses, and initially his disease remained stable, but it progressed within 6 months. Mitotane was stopped, and he then received 4 cycles of 5-fluorouracil, streptozotocin, and bevacizumab. During this therapy, his tumor grew, and the patient reported severe nausea, vomiting, and right flank pain.

This patient's medical history was otherwise unremarkable. He took no medications, did not smoke cigarettes or use illicit drugs, and drank alcohol occasionally. His Eastern Cooperative Oncology Group (ECOG) performance status was 0-1, and he worked full time. His family history was positive for colon cancer in his grandmother and breast cancer in his great aunt. Physical examination findings were unremarkable, except for well-healed scars on his abdomen. His laboratory test results included the following: comprehensive metabolic panel, normal; complete blood cell count, normal; lactic dehydrogenase, normal; 24-hour urine cortisol, normal; random serum cortisol, at 12:00 PM, 4.7  $\mu\text{g/dL}$  (7.0-22.0  $\mu\text{g/dL}$ ), aldosterone, 11.6 ng/dL (4-31 ng/dL); renin, 2.8 ng/mL per h (0.5-4.0 ng/mL per h); corticotropin, 21 pg/mL (7-69 pg/mL);

testosterone, 1.53 ng/mL (2.5-9.5 ng/mL); free testosterone, 5 pg/mL (10-30 pg/mL); and thyrotropin, 1.71 mIU/L (0.3-5.5 mIU/L). These test results were consistent with nonfunctioning ACC (2,3). Chemotherapy was stopped. The patient pointed to a report of mebendazole activity in ACC, as well as in other cancer cell lines. Considering its low toxicity and good safety profile, he inquired about a trial of mebendazole given lack of success with his other treatments and the overall poor prognosis. Because of these considerations, his treating physicians agreed, and he was prescribed single-agent mebendazole, 100 mg orally twice daily (a typical anthelmintic dosage). The patient also underwent palliative radiation to the right adrenal metastasis for pain control. The treatment was given using 16 MV photons, in a 3-dimensional conformal approach, at 1.8 Gy/fraction, to the total dose of 45 Gy; the liver was not targeted in the radiation field.

The patient tolerated mebendazole therapy well. His nausea abated, and his metastatic disease responded to this treatment (Fig. 1). On a follow-up visit 2 months later, the right flank metastatic mass had decreased in size, and this was attributed to the radiation therapy. CT demonstrated a decrease in the size and number of liver metastases on follow-up scans (Fig. 2 and Table 1). Two months after initiation of mebendazole, there was a 17% to 42% decrease in the diameter of the hepatic metastases (stable disease per response evaluation criteria in solid tumors [RECIST] criteria). On subsequent CT, the hepatic metastases fluctuated in their size without demonstrating consistent growth. Overall, the disease was stable.

The patient took mebendazole for 19 months as a single agent for his ACC. His disease remained stable during this period, and the patient tolerated mebendazole without adverse effects. His weight was stable, and his quality of life returned to his baseline before his initial surgery. His comprehensive metabolic panel and complete blood cell count remained within normal limits. However, his disease subsequently progressed, as evidenced by follow-up CT of the abdomen 24 months after single-agent mebendazole



**Fig. 1.** Regression of hepatic metastatic lesions after treatment with mebendazole. Axial computed tomographic images of the abdomen with contrast performed 1 month before (*Panel A*), 4 months after (*Panel B*), and 19 months after (*Panel C*) the initiation of mebendazole treatment.

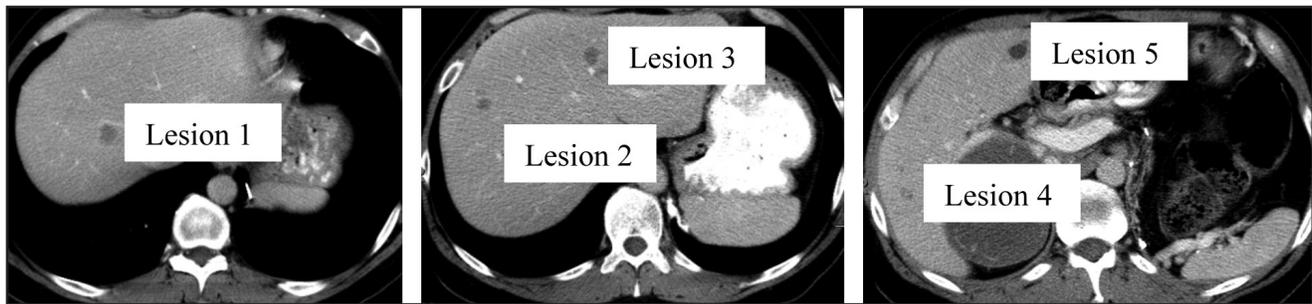


Fig. 2. Axial computed tomographic imaging, demonstrating change in size of liver metastases.

treatment was initiated. At that point, everolimus was added to his medication regimen. Unfortunately, this addition did not control his disease.

## DISCUSSION

The patient described in this report demonstrates prolonged tumor response to mebendazole after having shown progression with other chemotherapeutic approaches. In contrast to the morbidity observed with other treatments, mebendazole was very well tolerated and greatly improved the patient's quality of life.

Mebendazole is an anthelmintic drug that has been used since the early 1970s (4). Mebendazole is a benzimidazole, a class of chemical compounds that disrupts tubulin polymerization (5). Mebendazole interacts with both parasite and mammalian tubulin, attaching to the colchicine binding site (6). It binds to tubulin at a site different from other tubulin-binding agents, such as vinblastine or paclitaxel (7,8).

The possible mechanism of mebendazole's antitumor effect is controversial. Mebendazole possesses activity against a variety of human tumor cell lines in vitro and in vivo, where it appears to induce apoptosis via interference with microtubule structure and function. Mukhopadhyay

et al showed that mebendazole causes depolymerization of tubulin in human tumor cells, inhibits normal mitotic spindle formation, and therefore induces mitotic arrest and apoptosis (9). In that study, mebendazole showed a tumor-specific proapoptotic effect in culture against non-small cell lung cancer cells, which was time- and dose-dependent. It also suppressed tumor growth and metastasis formation in nude mice, without significant host toxicities. This study also demonstrated reduced angiogenesis in the tumor treated by mebendazole, which may be a consequence of diminished tumor growth. The latter observation is in contrast to Martarelli et al's data, which did not show any difference in tumor angiogenesis (10).

Sasaki and colleagues also showed that mebendazole caused microtubule depolymerization with resultant apoptosis of non-small cell lung cancer cells in vitro (11). Mebendazole inhibited the growth of tumors derived from these cells in nude mice. The expression of *Trp53* (p53 protein) and *Cdkn1a* (p21 protein) was increased in the mebendazole-treated cells, thus implicating these genes in the proapoptotic effect of mebendazole. It also stimulated cleavage of caspase 3, 8, and 9, as well as release of cytochrome c, which are all well-known proapoptotic signals. Doudican et al demonstrated that mebendazole inhibits growth of a variety of melanoma cell lines by disrupting

Table 1  
Changes in Size of Liver Metastases on Computed Tomography<sup>a</sup>

Date of scan	Mass size, cm				
	Lesion 1	Lesion 2	Lesion 3	Lesion 4	Lesion 5
2/29/08	2.2 × 2.4	1.6 × 1.6	1.4 × 1.8	1.2 × 1.2	1.9 × 2.1
5/19/08	1.3 × 1.9	1.3 × 1.3	1.0 × 1.1	1.1 × 1.0	1.5 × 1.7
7/25/08	1.5 × 1.9	1.2 × 0.9	1.2 × 1.3	0.8 × 1.0	1.9 × 2.2
1/23/09	1.5 × 1.8	1.1 × 0.9	1.1 × 1.4	0.8 × 0.9	1.5 × 1.5
4/24/09	1.4 × 2.2	1.2 × 0.9	1.1 × 1.3	0.8 × 1.1	1.1 × 1.6
7/24/09	1.4 × 1.6	1.2 × 0.8	0.8 × 0.9	0.6 × 0.8	0.9 × 1.2
10/23/09	1.6 × 1.9	1.1 × 0.9	1.1 × 1.2	0.6 × 0.9	0.8 × 1.1

<sup>a</sup> All dimensions represent greatest orthogonal axial measurements.

tubulin polymerization with resultant Bcl-2 phosphorylation and induction of apoptosis (12). This effect was achieved at a clinically relevant, 1 mM concentration. Of note, Bcl-2 is not expressed in ACC (13), suggesting that this mechanism is probably not applicable for its action in ACC. Additionally, mebendazole is synergistic with a recombinant methioninase in inhibiting proliferation of neuroblastoma cells in culture (14).

Immunologic mechanisms of mebendazole's antitumor effect may also be relevant. Mebendazole belongs to the chemical class of benzimidazoles that have been shown to possess immunomodulatory effects. For instance, thiabendazole can affect maturation and function of macrophages, lymphocytes, and other hematopoietic cell lines (15). It restores delayed hypersensitivity impaired by radiation or doxorubicin treatment (16). Interestingly, other benzimidazoles also possess antitumor properties. Pourgholami and colleagues showed that albendazole inhibited hepatocellular carcinoma cell proliferation in culture, as well as in nude mice (17).

ACC cells may also be susceptible to the antitumor effect of mebendazole. Martarelli and colleagues showed that mebendazole selectively inhibited growth of the human ACC cell line H295R, but not growth of a control fibroblast cell line (10). The drug also inhibited the growth of these tumor cells in nude mice and reduced their invasive properties. These antitumor effects were achieved at least in part through stimulating apoptosis, as evident in a DNA fragmentation assay. The mechanism may involve induced expression of proapoptotic proteins procaspase-3 and procaspase-9 and the tumor suppressor protein p53.

## CONCLUSION

Our report is the first account of successful, long-term use of mebendazole in the treatment of metastatic ACC in a patient who demonstrated disease progression on mitotane and cytotoxic chemotherapy. Its excellent safety profile and good tolerability suggest that mebendazole is a drug that should be considered for further clinical investigation. The response of this patient's tumor to mebendazole may be unique, since the patient's ACC had a rather indolent course and had responded for a time to other treatments. The response that this low-grade malignant tumor had to mebendazole may not be reproducible in high-grade and more aggressive tumors. It is also not clear when in the course of therapy this drug is most effective or whether a combination of mebendazole with other cytotoxic drugs would have a synergistic effect. These possibilities call for randomized controlled clinical trials of mebendazole as a therapeutic option in patients with ACC.

## DISCLOSURE

The authors have no multiplicity of interest to disclose.

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