Mebendazole and Triple Negative Breast Cancer brain metastases - Mebendazole selectively targets migrating tumor cells according to 2024 paper by Stanford authors

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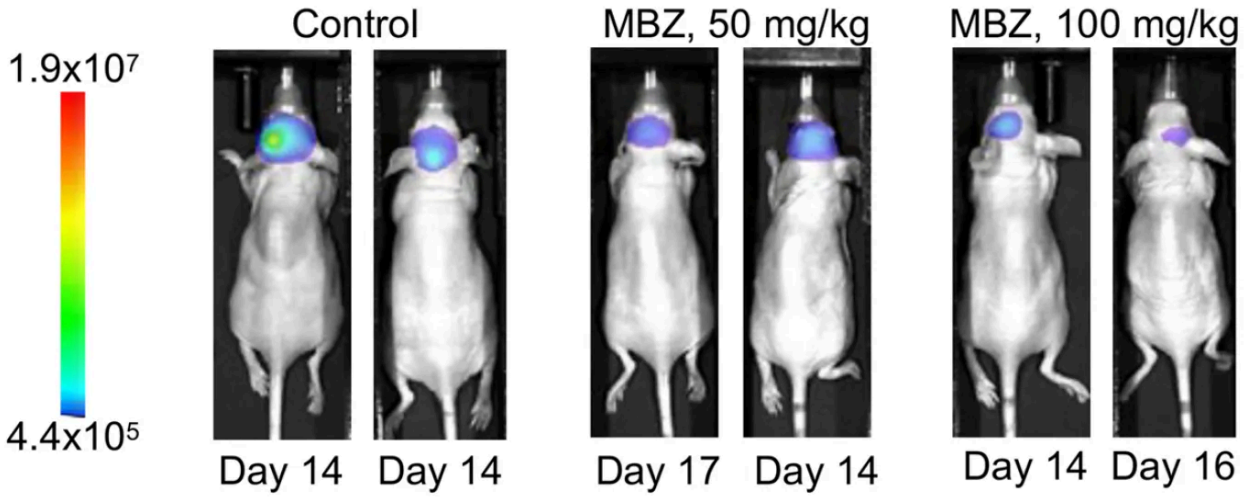

2024 (Rodrigues et al) - Repurposing mebendazole against triple-negative breast cancer CNS metastasis

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RESEARCH

Repurposing mebendazole against triple-negative breast cancer CNS metastasis

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Abstract

Purpose Triple-negative breast cancer (TNBC) often metastasizes to the central nervous system (CNS) and has the highest propensity among breast cancer subtypes to develop leptomeningeal disease (LMD). LMD is a spread of cancer into leptomeningeal space that speeds up the disease progression and severely aggravates the prognosis. LMD has limited treatment options. We sought to test whether the common anti-helminthic drug mebendazole (MBZ) may be effective against murine TNBC LMD.

Methods A small-molecule screen involving TNBC cell lines identified benzimidazoles as potential therapeutic agents for further study. *In vitro* migration assays were used to evaluate cell migration capacity and the effect of MBZ. For *in vivo* testing, CNS metastasis was introduced into BALB/c athymic nude mice through internal carotid artery injections of brain-tropic MDA-MB-231-BR or MCF7-BR cells. Tumor growth and spread was monitored by bioluminescence imaging and immunohistochemistry. MBZ was given orally at 50 and 100 mg/kg doses. MBZ bioavailability was assayed by mass spectrometry.

Results Bioinformatic analysis and migration assays revealed higher migratory capacity of TNBC compared to other breast cancer subtypes. MBZ effectively slowed down migration of TNBC cell line MDA-MB-231 and its brain tropic derivative MDA-MB-231-BR. In animal studies, MBZ reduced leptomeningeal spread, and extended survival in brain metastasis model produced by MDA-MB-231-BR cells. MBZ did not have an effect in the non-migratory MCF7-BR model.

Conclusions We demonstrated that MBZ is a safe and effective oral agent in an animal model of TNBC CNS metastasis. Our findings are concordant with previous efforts involving MBZ and CNS pathology and support the drug's potential utility to slow down leptomeningeal spread.

- **Triple-negative breast cancer (TNBC) is an aggressive breast cancer subtype that metastasizes to the central nervous system (CNS) in up to 50% of affected patients**
- **Once disseminated to CNS, TNBC carries poor prognosis, with limited treatment options, and a median survival of only 5 months**
- **Patient's prognosis is severely aggravated when cancer spreads to leptomeninges and cerebral spinal fluid (CSF), developing leptomeningeal disease (LMD)**
- **Among breast cancer subtypes, TNBC accounts for the shortest time between primary diagnosis and CNS metastasis**
- **Rapid metastatic dissemination of TNBC is likely based on its high migratory potential**
- **recent work has begun to focus on repurposing previously approved pharmaceutical agents**

- **In the study of CNS tumors, drug repurposing efforts have highlighted the benzimidazole anti-helminthic class, including mebendazole (MBZ), albendazole (ABZ), and fen-bendazole (FBZ)**
- **The effectiveness of MBZ in animal models of glioma and metastatic TNBC highlights both its potential as an alternative oncologic therapeutic and its potential utility against TNBC CNS metastasis.**
- **In the present study, we hypothesized that the tubulin-binding properties of MBZ would counter the migratory capacity of TNBC, reduce active metastatic dis-semination (LMD) and, therefore, delay mortality**

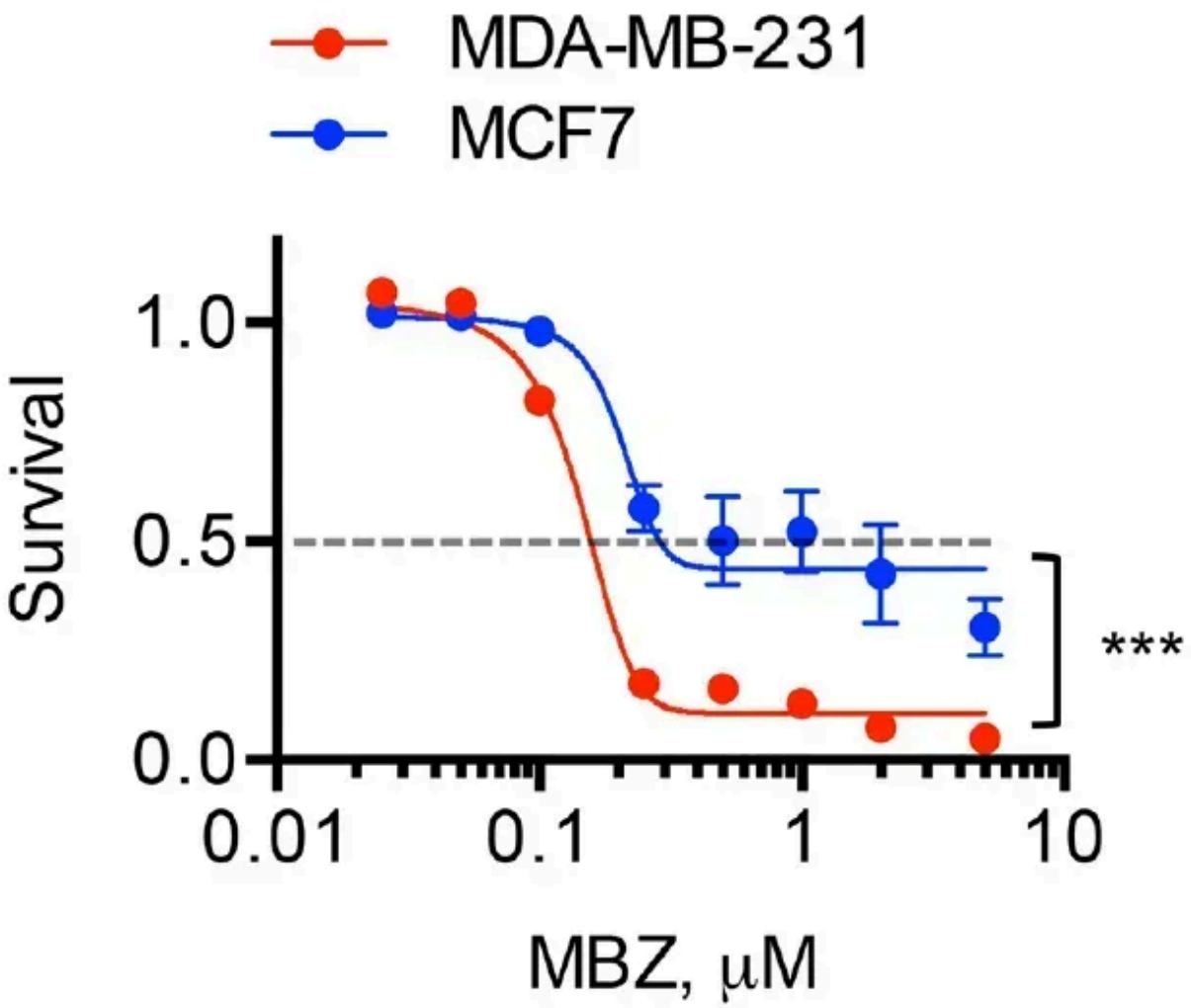
History of Mebendazole

- MBZ was developed in the 1960s to treat a range of gastrointestinal helminth infections, and it is still one of the most commonly used medications in the world
- **it can be taken safely in humans at doses as high as 200 mg/kg/day** and in rare cases, has been used in humans to treat CNS infections, including neurocysticer-cosis and echinococcus.
- **Indeed, its relatively small size and lipophilic properties render it an appropriate agent to be repurposed for CNS pathologies**
- Our study is the first effort to test the efficacy of the drug in the treatment of CNS metastasis. We were able to demonstrate that the oral administration of MBZ, at both 50 mg/kg and 100 mg/kg doses, **was able to slow tumor growth and increase survival** in an aggressive preclinical model of TNBC CNS metastasis.
- Importantly, our dosing protocol, in which mice voluntarily consumed MBZ in a mix of sesame oil and honey, reached therapeutic concentrations in the CSF, and **effectively reduced the leptomeningeal dissemination.**

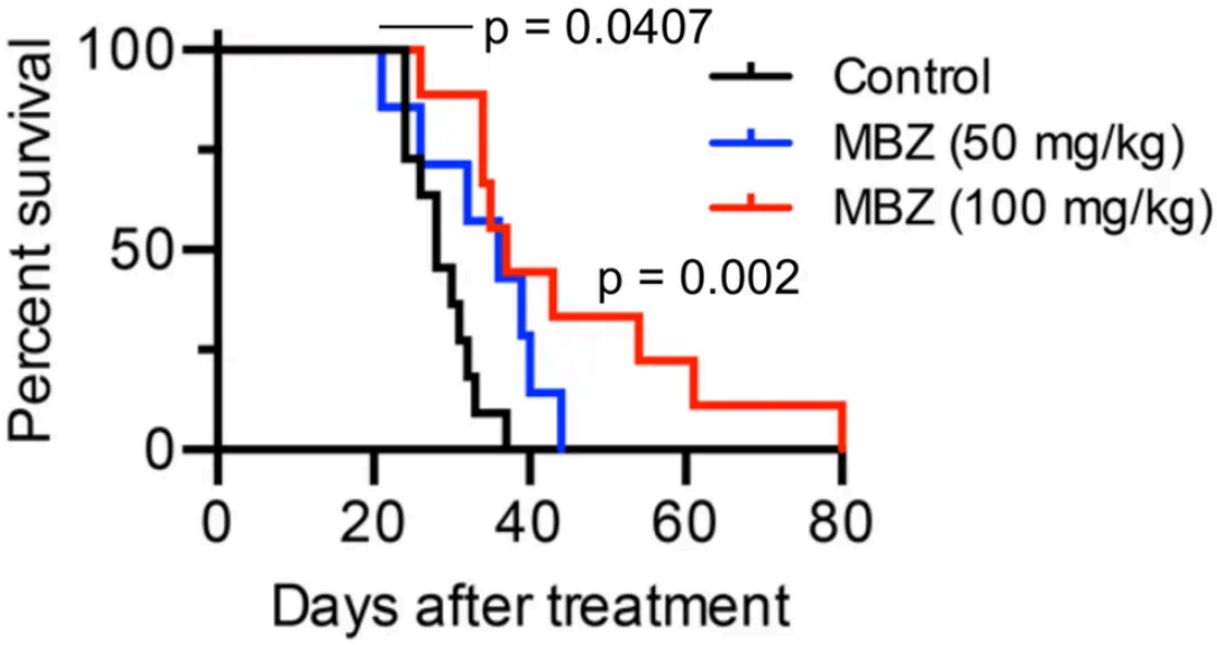
MBZ effect in mouse model of TNBC CNS metastasis

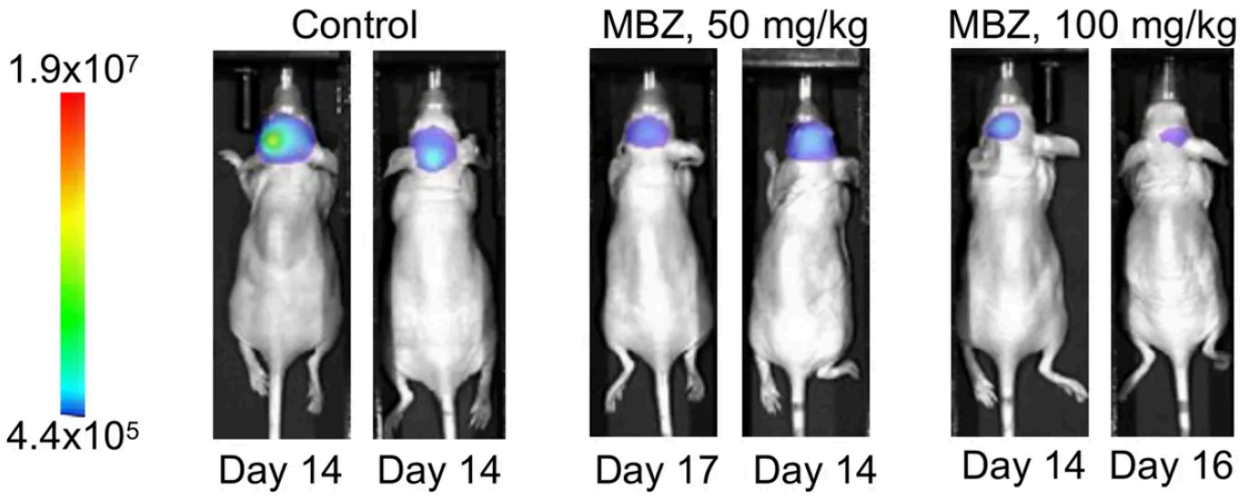
- strong inhibitory effect of MBZ on migration of the triple-negative MDA-MB-231-BR implied that **MBZ might be more effective against active metastatic dissemination.**

- **MBZ had a notable effect on the growth of MDA-MB-231-BR tumors at both 50 mg/kg and 100 mg/kg doses**
- **Compared to the control, MBZ treatment significantly extended survival in the MDA-MB-231 model**
- Histological examination of brain sections revealed that **MBZ effectively reduced metastatic dissemination** in the MDA-MB-231-BR model, **with a significant effect on single cell- and small metastasis populations**



Sensitivity to Mebendazole of TNBC cell line MDA-MB-231 and of hormone receptor positive Breast Cancer cell line MCF7.





CONCLUSIONS:

- Our data suggest that MBZ targets cancers with high migratory capacity & may be particularly effective when these cancers spread into leptomeningeal space
- Among breast cancer subtypes, the TNBCs had the highest migration potential
- Consistent with the strong inhibitory effect of MBZ on migration of TNBC MDA-MB-231-BR cells, MBZ extended survival of mice with TNBC LMD

- **MBZ was demonstrated to be a safe and effective oral agent in an aggressive animal model of TNBC CNS metastasis.**
- MBZ may function by **selectively targeting migrating tumor cells.**
- These findings support the **drug's potential utility to hamper leptomeningeal dissemination.**

MY TAKE...

Triple Negative Breast Cancer is going to be problematic over the coming years.

Pfizer and Moderna COVID-19 mRNA Vaccines complicate the picture because they cause Turbo Cancer, and in the top 3 most common Turbo Cancers are Breast cancers, vast majority of which are Triple Negative.

Here is how Triple Negative Breast Cancer survival compares to other breast cancers:

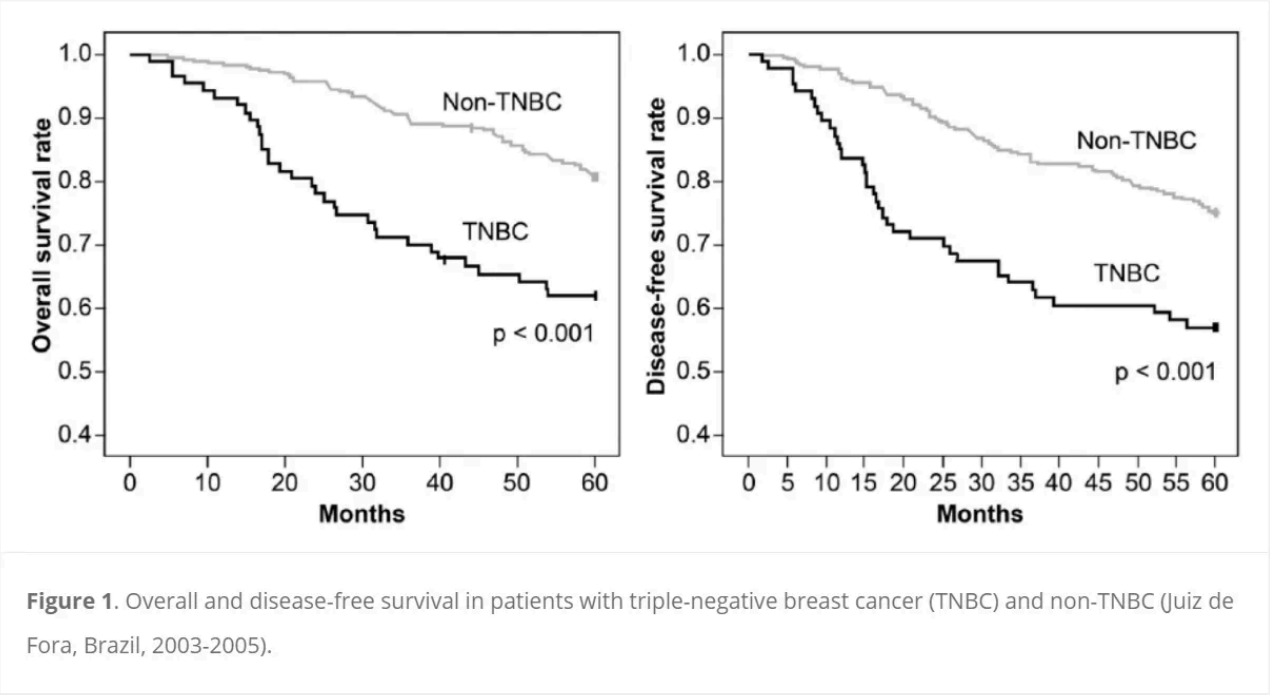


Figure 1. Overall and disease-free survival in patients with triple-negative breast cancer (TNBC) and non-TNBC (Juiz de Fora, Brazil, 2003-2005).

Source: (2018 Golcalves et al)

This is the prognosis BEFORE COVID-19 mRNA Vaccines were rolled out.

TNBC in a COVID-19 mRNA Vaccinated individual has a much worse prognosis.

The anti-parasitic Mebendazole (a relative of Fenbendazole) is going to be a key anti-TNBC drug going forward, especially the 500mg generic tablets.

98 Likes · 12 Restacks

Discussion about this post

Comments Restacks

Write a comment...

Mourits M. Joensen Aug 20

Mebendazole/Ivermectin: Are there points of similarity and differences between Mebendazole and Ivermectin, in the use in general, as well as when used for cancer treatments?

Would it be beneficial to be able to use a combination of Mebendazole and Ivermectin in the treatment of a certain form of cancer?

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Kate Kate's Newsletter Aug 20

Thank you for all the work you do. 🙏I am Living in Europe (Denmark DK) where everything is on prescription. (even melatonin. We can buy melatonin in other EU countries where we don't need a prescription)

My question is: what about Niclosamide , is it something you can recommend.? We can buy that I Europe, without prescription.

I have bought Niclosamide, stored in a cabinet waiting for the next plandemic 😅 (even though I haven't had covid at anytime the last 4 years, I tried hard though, eating saliva from 2 different people with symptoms) nothing happened.) and no injections either.

Regarding the Niclosamide i am thinking of my parents who both got 3. Jabs with Pfizer. My mom got sideefects. (seizures, blurred vision, brain fog, lost a lot of kilos .) I have persuaded her to take probiotics. She does that now everyday, and she says she feels better. Sorry for the long message, my entire question is regarding the niclosamide .