Spring 2023

Benzimidazole Adjuvant Therapy: A Review of Efficacy and Safety in Patients with Cancer

Jared Mouw
University of North Dakota

Benzimidazole Adjuvant Therapy: A Review of Efficacy and Safety in Patients with Cancer

Jared Mouw PA-S | Contributing: Russell Kauffman, MPAS, PA-C
Department of Physician Assistant Studies, University of North Dakota School of Medicine & Health Sciences
Grand Forks, ND 58202-9037

Department of Physician Assistant Studies

UND School of Medicine & Health Sciences
University of North Dakota

Abstract

- The safety and toxicity profile of benzimidazoles will be assessed within a population of patients currently diagnosed with various types of cancer to determine if this class of medications could be implemented along with current cancer treatment regimens to increase efficacy and tolerance.
- Databases of CINAHL, ClinicalKey, and PubMed were searched with the keywords mentioned below. Studies include those after the year 2000, and those focusing on the use of benzimidazoles on human cancer cells and tissue, case studies, or all phases of clinical trials. Excluded were those using non-human study subjects, those before the year 2000, and those not applicable based on a population not being those with cancer resulting in 11 applicable studies available for this review.
- Benzimidazole's use in those with cancer is in its early stages of research. Many of these early-stage trials showed promise that benzimidazoles may have a place in these populations with possibly less severe side effects than conventional cancer treatments.
- Additionally, safety and toxicity properties among those with cancer appeared to be similar to their use in those with helminth infections. Larger-scale clinical trials will be necessary to further understand the role benzimidazoles may have as antineoplastic agents.
- Keywords: benzimidazoles, albendazole, mebendazole, flubendazole, adjuvant therapy, anticancer, antitumor, and drug repositioning.

Introduction

- According to the American Cancer Society, across the United States in 2022, over 1.9 million new cancer diagnoses are expected. This is an increase from previous years, contributing to approximately 610,000 expected cancer deaths in the United States alone (American Cancer Society, 2022).
- Although new therapies and drug classes are being researched, others have theorized that the answer may lie within our current formularies using a drug with a completely different current indication. The idea is that research should be focused on repurposing drugs that already have a known safety and toxicity profile, fast-tracking the process. Recently, benzimidazoles have been investigated as a practical adjuvant therapy for those with cancer who are receiving conventional therapies such as chemotherapy, radiation, and surgical intervention (National Center for Biotechnology Information, 2022).
- Due to the nature of how this works against parasites, those looking to repurpose this drug class recognized this mechanism of action (MOA) as having similar characteristics to other antineoplastic drugs, leading to the presumption of similar outcomes.
- This scholarly project aims to compile previous studies' data and explore the effects of benzimidazoles as adjuvant therapy and its relationship to a patient's cancer biomarkers, tumor progression, and quality of life. Additionally, we will attempt to identify the safety and toxicity profile of benzimidazoles in patients with cancer as a target population.

Statement of the Problem

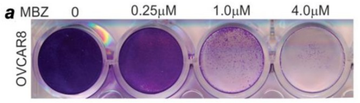
- While chemotherapy and radiation therapies have been widely studied and shown effective, many wonder what more can be done to improve efficacy of current treatment and quality of life measures as it is well known that traditional cancer treatments come with a significant amount of undesired and life altering side effects that remain even after remission of cancer.
- Recently, benzimidazoles have been investigated as a viable adjuvant therapy for those with cancer and receiving conventional therapies such as chemotherapy, radiation, and surgical intervention with hopes of reducing side effects and increase quality of life during treatment (American Cancer Society, 2022).

Research Question

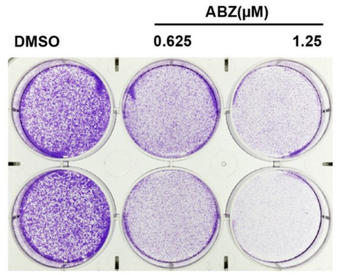
- In patients with cancer who have received conventional therapy, does the addition of adjuvant benzimidazoles versus those receiving conventional therapy or observation alone show improved safety and efficacy with increased antitumor tissue response, survival measures, and reduction in cancer biomarkers?

Literature Review

- During the first cycle of the dose-escalation period of Mebendazole (MBZ) administration, no dose-limiting toxicities (DLTs) were noted among all dose ranges up to the max dose of 200mg/kg/day. With the study's multiple cycle administration design, repeat cycles of MBZ only resulted in DLT in 4 out of 24 patients and this occurred at the max dose of 200mg/kg/day. (Gallia et al., 2020).
- Following analysis of data, the most encountered significant adverse effects (AE) were gastrointestinal-related. Abdominal pain was the most reported AE with 13 patients compared to the control group with six reporting abdominal pain showing a significant increase over the control group (p=0.029). Diarrhea was the second most prevalent AE with 10 instances reported in contrast to the control group reporting three instances of diarrhea. (p=0.02) (Hegazy et al., 2022).
- The study monitored colony growth of cell lines treated with MBZ to sensitize them to cisplatin treatment and found there was a significant increase in cisplatin-based cellular toxicity compared to that of MBZ or cisplatin alone (p<0.01 – 0.05 dose-dependent and cell-line dependent) (Huang e

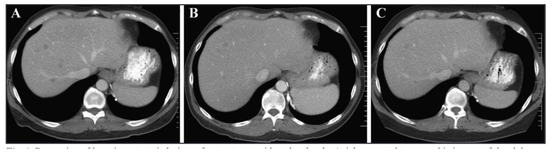


- Antineoplastic drugs showed the highest efficacy followed by antiparasitic, antiseptic/antibacterial, cardiovascular, antifungal, and central nervous system, respectively. As with known antineoplastics, such as anthracyclines and vinca alkaloids, benzimidazoles showed statistically significant effects on the cancer cell lines (correlation coefficient of 0.64 and considered statistically significant). (Nygren et al., 2013).
- The study found that as a single agent Albendazole (ABZ), at clinically achievable concentrations, was able to inhibit proliferation as a DNA damaging agent and microtubule destabilization in both multiple myeloma and squamous cell lung cancer cell lines with exposure to ABZ. (p <0.05). (Patel et al., 2011).
- Triple negative breast cancer (TNBC) cell lines were treated with a single dose of MBZ resulting in a reduction in viable breast cancer initiating cells (BCIC) along with reducing the ability to self-renew in two of the TNBC cell lines, with an overall reduction in BCICs in the TNBC cells (p <0.01). (Zhang et al., 2019).

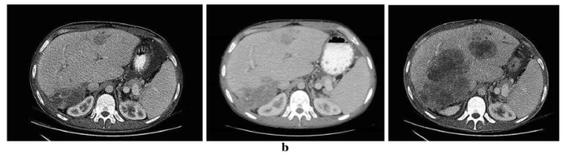


- Hepatic metastasis was defined as "stable" per RECIST criteria with a 17% to 42% decrease in the diameter of liver metastatic lesions. With continued monitoring and MBZ therapy, the patient's metastatic disease fluctuated without significant fluctuation to progression or regression for a total of 19 months. During these 19 months, the patient reported quality of life measures returning to that of pre-diagnosis levels. (Dobrosotskaya et al., 2011).

- Hepatic metastasis was defined as "stable" per RECIST criteria with a 17% to 42% decrease in the diameter of liver metastatic lesions. With continued monitoring and MBZ therapy, the patient's metastatic disease fluctuated without significant fluctuation to progression or regression for a total of 19 months. During these 19 months, the patient reported quality of life measures returning to that of pre-diagnosis levels. (Dobrosotskaya et al., 2011).



- The 12-week control group overall response rate (ORR) showed 0 at complete response, 2 patients with partial response, 3 patients with stable disease, and 15 patients with progressive disease, respectively (p <0.001). The MBZ treatment group was found to have 2 patients with complete response, 11 patients with partial response, 4 patients with stable disease, and 3 patients with progressive disease (p =0.001). (Hegazy et al., 2022).
- Progression free survival (PFS) is reported with the control group showing a median PFS of 3 months while the MBZ group is found to have a PFS of 9.25 months, respectively (p <0.001). (Hegazy et al., 2022).
- After three months these biomarkers were analyzed again with a significant decrease noted within the MBZ group in both biomarkers vascular endothelial growth factor (VEGF) and carcinoembryonic antigen (CEA) (P<0.05). Within the control group, the data showed a significant increase of VEGF (p <0.01) and CEA (p <0.05) indicating MBZ does show an effect on cancer biomarkers (Hegazy et al., 2022).
- Four of these patients were further investigated for signs of hyperprogressive disease defined as the phenomenon of cancer drug-related treatment with continued tumor progression at similar or higher rates after cessation of drugs than prior to initial therapy (Mansoori et al, 2021). The study also found that the time to tumor progression (TTP) included a median of 162 days in the period prior to MBZ therapy and a median of 59 days while on the MBZ therapy, showing a quicker time to progression of tumor while receiving MBZ therapy. (Mansoori et al., 2021)



- Upon completion of the MBZ therapy, there was no report of adverse effects and near complete remission of lung and lymph node metastasis with partial remission of liver lesions, identified by follow-up and comparative CT scans. (Nygren & Larsson, 2014).

Discussion

- There appears to be evidence that suggests benzimidazoles as a class has moderate to high occurrence of AEs mostly related to the gastrointestinal tract, which does not appear to be severe across all studies.
- Benzimidazoles may have a safety profile and tolerance level that supports further large-scale clinical trials to determine their efficacy as an anticancer medication and confirm the initial safety and tolerability data.
- MOA being comparable to known effective antineoplastics and, if in-vitro studies are a good predictor of in-situ studies, this drug class has the potential to show high specificity to cancer cells resulting in a likely higher safety and tolerability profile.
- When considering benzimidazoles as a monotherapy, multiple in-vitro studies showed efficacy in reducing cancer cell viability indicating probable antineoplastic effects when employed as a single drug.
- Many anti-cancer pathways were found to have been affected by MBZ and ABZ administration. Hegazy et al. (2022) report findings within the clinical setting that would suggest these early antineoplastic presumptions have merit.
- Data suggesting that benzimidazole may have efficacy in altering RECIST criteria, especially early during the treatment period. There is some question as to whether treatment with benzimidazoles provided longer-term benefits to prevent the progression of disease as well as if some patients may have a hyperprogressive reaction to the therapy.

Applicability to Clinical Practice

- The information presented in this scholarly project could be considered highly specialized and not remotely applicable to clinical practice. That being said, there are a few key takeaways that should be highlighted from this review. First, understanding that our primary care patients may be working with oncology to work at irradicating cancer as well as being involved in trials like these. When seeing these patients, learning about their treatment and possible requirements of their trials is essential to making sure that we are able to help them without jeopardizing their current regimen. Second, remembering that many drugs we may be familiar with as one thing, could be repurposed off label or in a trial for a different purpose. Full questioning of any medication that does not have an apparent traditional reason for being prescribed should not be discontinued unless we determine who prescribed this and what for as it may be a essential part of another specialties regimen. Lastly and above all else, understanding that these are patients with cancer and their disease does not define them. Treat their cancer as any other disease.

References

- Society. (2022). Cancer Facts & Figures 2022. Retrieved from https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2022/2022-cancer-facts-and-figures.pdf
- American Cancer Society. (2019). Cancer Treatment & Survivorship Facts & Figures 2019-2021. Retrieved from https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-treatment-and-survivorship-facts-and-figures/cancer-treatment-and-survivorship-facts-and-figures-2019-2021.pdf
- Dobrosotskaya, I. Y., Hammer, G. D., Schteingart, D. E., Maturen, K. E., & Worden, F. P. (2011). Mebendazole monotherapy and long-term disease control in metastatic adrenocortical carcinoma. *Endocrine Practice*, *17*(3). https://doi.org/10.4158/ep10390.cr
- Gallia, G. L., Holdhoff, M., Brem, H., Joshi, A. D., Hann, C. L., Bai, R.-Y., Staedtke, V., Blakeley, J. O., Sengupta, S., Jarrell, T. C., Wollett, J., Szajna, K., Helie, N., Mattox, A. K., Ye, X., Rudek, M. A., & Riggins, G. J. (2020). Mebendazole and temozolomide in patients with newly diagnosed high-grade gliomas: Results of a phase 1 clinical trial. *Neuro-Oncology Advances*, *3*(1). https://doi.org/10.1093/noajnl/vdaa154
- Hegazy, S. K., El-Azab, G. A., Zakaria, F., Mostafa, M. F., & El-Ghoneimy, R. A. (2022). Mebendazole; from an anti-parasitic drug to a promising candidate for drug repurposing in colorectal cancer. *Life Sciences*, *299*, 120536. https://doi.org/10.1016/j.lfs.2022.120536
- Huang, L., Zhao, L., Zhang, J., He, F., Wang, H., Liu, Q., Shi, D., Ni, N., Wagstaff, W., Chen, C., Reid, R. R., Haydon, R. C., Luu, H. H., Shen, L., He, T.-C., & Tang, L. (2021). Antiparasitic mebendazole (MBZ) effectively overcomes cisplatin resistance in human ovarian cancer cells by inhibiting multiple cancer-associated signaling pathways. *Aging*, *13*(13), 17407–17427. https://doi.org/10.18632/aging.203232
- Mansoori, S., Fryknäs, M., Alvfors, C., Loskog, A., Larsson, R., & Nygren, P. (2021). A phase 2A clinical study on the safety and efficacy of individualized dosed mebendazole in patients with advanced gastrointestinal cancer. *Scientific Reports*, *11*(1). https://doi.org/10.1038/s41598-021-88433-y
- Morris, D. L., Jourdan, J.-L., & Pourgholami, M. H. (2001). Pilot study of albendazole in patients with advanced malignancy. *Oncology*, *61*(1), 42–46. https://doi.org/10.1159/000055351
- Nygren, P., Fryknäs, M., Ågerup, B., & Larsson, R (2013). Drug repositioning from bench to bedside: Tumour remission by the antihelmintic drug mebendazole in refractory metastatic colon cancer. *Acta Oncologica*, *53*(3), 427–428. https://doi.org/10.3109/0284186x.2013.844359
- Nygren, P., & Larsson, R. (2014). Repositioning of the anthelmintic drug mebendazole for the treatment for colon cancer. *Journal of Cancer Research and Clinical Oncology*, *139*(12), 2133–2140. https://doi.org/10.1007/s00432-013-1539-5
- Patel, K., Doudican, N. A., Schiff, P. B., & Orlow, S. J. (2011). Albendazole sensitizes cancer cells to ionizing radiation. *Radiation Oncology*, *6*(1). https://doi.org/10.1186/1748-717x-6-160
- Zhang, L., Bochkur Dratver, M., Yazal, T., Dong, K., Nguyen, A., Yu, G., Dao, A., Bochkur Dratver, M., Duhachek-Muggy, S., Bhat, K., Alli, C., Pajonk, F., & Vlashi, E. (2019). Mebendazole Potentiates Radiation Therapy in triple-negative breast cancer. *International Journal of Radiation Oncology*Biology*Physics*, *103*(1), 195–207. https://doi.org/10.1016/j.ijrobp.2018.08.046
- Zhu, L., Yang, Q., Hu, R., Li, Y., Peng, Y., Liu, H., Ye, M., Zhang, B., Zhang, P., Liu-Smith, F., Li, H., & Liu, J. (2022). Novel therapeutic strategy for melanoma based on Albendazole and the CDK4/6 inhibitor palbociclib. *Scientific Reports*, *12*(1). https://doi.org/10.1038/s41598-022-09592-0

Acknowledgements

Genuine thanks to all those involved. Thanks to my advisor Russel Kauffman and the topic committee for encouraging me to choose a topic outside of what was familiar. The challenge to study an unfamiliar area reaches further than this project and will allow me to be more capable of pursuing things outside of my comfort zone in the future. I would also like to thank Megan Denis, MLIS, and Dr. Marilyn Klug for helping me obtain studies and understand the data and its application to my topic. Laura Hofer PA-C with Avera Oncology was also instrumental in the development of this project with her knowledge of the current common practices and up-and-coming treatments in this field. Lastly, thanks to all my family, friends, and classmates for their continuous motivation and assistance with this project and the entire program.