Mebendazole, Fenbendazole and Albendazole in Osteosarcoma - Mebendazole superior in multiple anti-cancer pathways

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2013 (Joanna Schmit) - In Vitro anti-cancer effects on Benzimidazoles on the Canine Osteosarcoma D17 Cell Line

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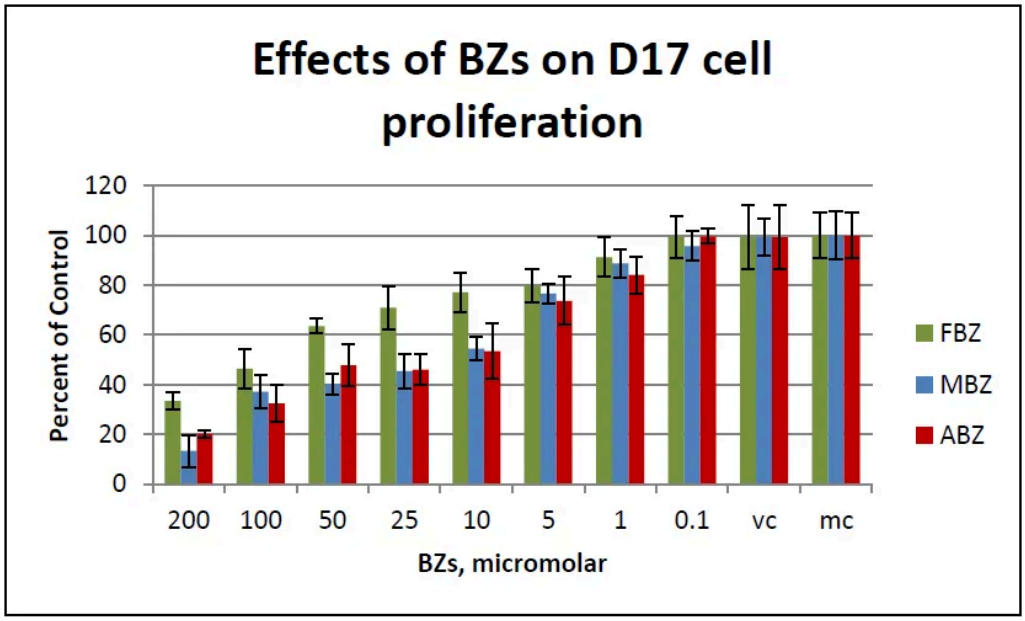
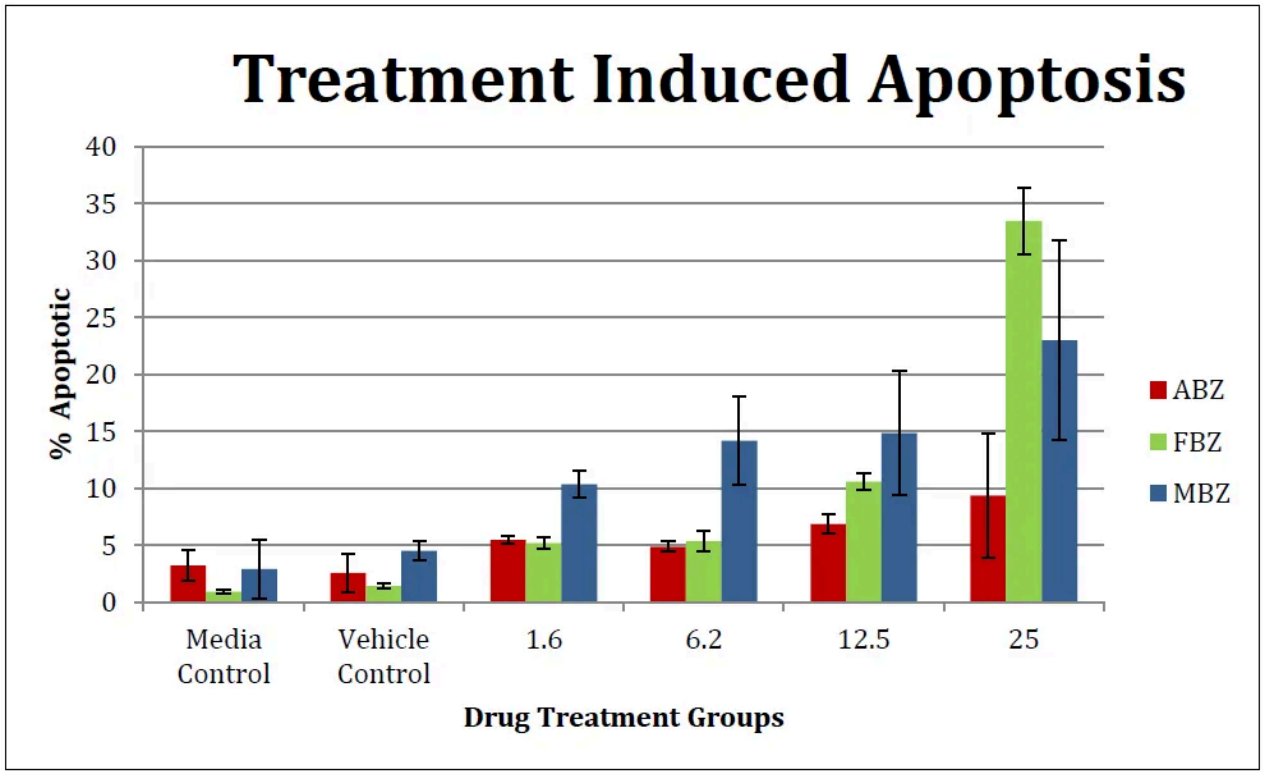
- “The high morbidity and mortality of canine osteosarcoma (OS) despite standard therapy warrants the need to investigate new treatment options“
- “**Benzimidazole (BZ) drugs are used routinely as effective anti-parasitics in both human and veterinary medicine. Their safety is well-established and side effects are minimal**”
- Safety has been described both with short-term high doses as well as long-term chronic dosing with minimal adverse effects
- “BZs have demonstrated in vitro and in vivo anti-cancer effects in both people and animal tumor models”
- **The mechanism of BZs is thought to be similar to the microtubule inhibitory actions of traditional chemotherapeutic drug classes such as taxanes and vinca alkaloids, leading to metaphase arrest (G2/M phase) and tumor cell apoptosis.**
- **BZs also demonstrate indirect anti-cancer activity by vascular disruption of endothelial cells and reduction in cancer cell secretion of the angiogenic cytokine vascular endothelial growth factor (VEGF).**
- In human Osterosarcoma (OS), mitotic spindle inhibitors are routinely used as an adjuvant chemotherapy agent, and similarly mitotic spindle inhibitors demonstrate effect for canine OS
- BZs may possess indirect anti-angiogenic effects in canine OS, including modulation of VEGF. **In human OS, increased VEGF expression is a negative prognostic factor and a strong predictor of metastasis and poor survival.**
- The aims of this study were to assess the in vitro effects of the clinically-used veterinary benzimidazoles [**mebendazole (MBZ), fenbendazole (FBZ), and albendazole (ABZ)] on a canine OS cell line.**
- Our findings demonstrate that the **clinically used veterinary BZs (ABZ, FBZ, and MBZ) possess anti-neoplastic activity** in an OS cell line.
    - In addition to direct effects on tubulin polymerization, cell cycle, proliferation, and cytotoxicity, BZs demonstrate indirect activity through modulation of a key pro-angiogenic cytokine.
    - These findings are similar to what we would expect with a traditional mitotic spindle inhibitor such as a vinca alkaloid.
    - In vitro effects are apparent at drug doses achievable in vivo with minimal expected adverse effects.

- This data supports the continued investigation into the use of BZs as an adjunctive therapy for canine osteosarcoma.

Figure 10. Comparison of albendazole, fenbendazole and mebendazole on inhibition of cell proliferation of D17 cell line.

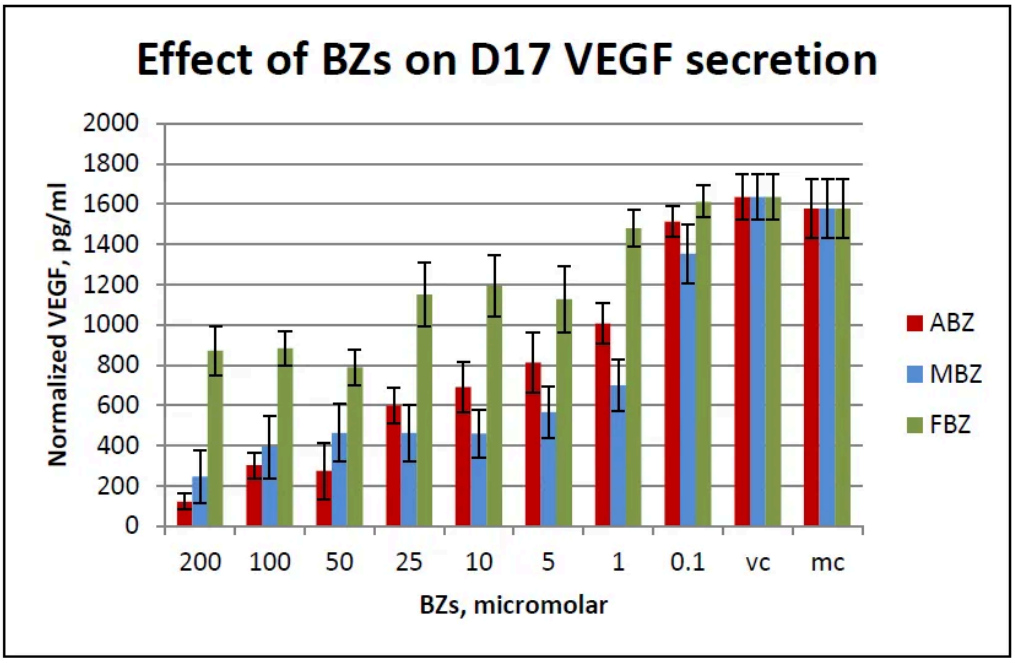


When it comes to inhibition of sarcoma proliferation, Mebendazole is the best.



When it comes to treatment induced apoptosis of cancer cells, Mebendazole is the best over most doses, although at highest dose, Fenbendazole takes over.

Figure 23. Comparison of albendazole, fenbendazole and mebendazole inhibition of VEGF secretion at doses from 0-200µM.



When it comes to inhibition of VEGF (angiogenic factor), Mebendazole is best over most doses, although Albendazole is best at higher doses.

CONCLUSION:

- "**Bone marrow toxicity is less frequent with fenbendazole** (FBZ) compared to Albendazole"
- Acute oral toxicity has been investigated in twelve animal species and mebendazole was well tolerated by all species
- In the early 1950s the anti-cancer potential of the BZs were first discovered when they were added to other compounds such as nitrogen mustard and showed inhibition of carcinoma, mammary adenocarcinoma and **sarcoma in mice**
- In the 1980s further work with various benzimidazole alkylating agents in combination with nitrogen mustard derivatives and benzothiazole alkylating agents showed efficacy against lymphocytic leukemias

- It was noted incidentally that **FBZ routinely administered in rat food inhibited tumor growth of human xenograft lymphoma** when combined with dietary vitamin supplementation

> **Overall Mebendazole shows superior inhibition of proliferation, apoptosis, and inhibition of VEGF secretion.**

My Take...

Interestingly, this is a Master's Degree Thesis, not a peer reviewed paper.

What I love about this research project is it shows that these anti-parasitic drugs can attack cancer cells in multiple ways.

In this paper, the osteosarcoma cancer cells were attacked in 3 ways:

1. **Inhibition of cell proliferation**
2. **Treatment induced apoptosis (cancer cell death)**
3. **Inhibition of VEGF secretion (inhibition of angiogenesis)**

This paper also showed that each anti-parasitic will have their strengths and weaknesses when it comes to the different mechanisms of anti-cancer action.

In OSTEOSARCOMA, Mebendazole seems to outperform both Albendazole and Fenbendazole. Whether these findings can be applied to ALL SARCOMAS isn't obvious at this time.

Extremely aggressive sarcomas are showing up in the COVID-19 mRNA Vaccinated. These are Turbo Cancer Sarcomas. They tend to be rare types: angiosarcoma for example.

The danger I currently see, is COVID-19 mRNA Vaccinated children coming down with SARCOMAS. These are extremely aggressive and difficult to treat. And at this time, no one wants to talk about it.

I'm talking about: Osteosarcomas, Ewing Sarcomas, Angiosarcomas and Rhabdomyosarcomas. I'm starting to see them.
