(Hadanny, et al., 2022). KMT is synergistic with HBOT and elicits a potent synergistic effect on suppressing tumor growth and metastatic spread in pre-clinical models of metastatic cancer and human case reports (Elsakka, et al., 2018; Poff, et al., 2015; Poff, et al., 2019).

PROPOSED HYBRID ORTHOMOLECULAR PROTOCOL

Based on our review of the scientific literature, the following protocol combining orthomolecules, drugs and additional therapies for targeting the MSCC in cancer treatment is proposed:

1 Intravenous Vitamin C

Intermediate- and high-grade cancers:
Dose of 1.5g/kg/day, 2-3x per week (Fan, et al., 2023). Established as a non-toxic dose for cancer patients (Wang, F., et al., 2019).

2 Oral Vitamin D

All cancer grades:
Dose of 50,000 IU/day for patients with a blood level ≤ 30ng/mL; 25,000 IU/day for levels 30-60ng/mL; and 5000 IU/day for levels 60-80ng/mL. Established as a non-toxic dose (Cannon, et al., 2016; Ghanaati, et al., 2020; McCullough, et al., 2019).

It is necessary to reach a blood level of 80 ng/mL of vitamin D (25-hydroxyvitamine D (25(OH) D) (Kennel, et al., 2010; Mohr, et al., 2014; Mohr, et al., 2015). This level is non-toxic (Holick, et al., 2011). Once this level is reached it must be maintained with a reduced daily dosage of ≈ 2000 IU/day (Ekwaru, et al., 2014). The vitamin D blood concentration should be measured every two weeks for high doses and monthly for lower doses.

3 Zinc

All cancer grades:
Dose of 1 mg/kg/day is established as a non-toxic dose for cancer patients (Hoppe, et al., 2021; Lin, et al., 2006).

The reference range for serum zinc concentration is 80 to 120 µg/dL (Mashhadi, et al., 2016; Yokokawa, et al., 2020). Once this level is reached it must be maintained with a reduced daily dosage of 5mg/day (Li, et al., 2022). The zinc blood concentration should be measured monthly.

4 Ivermectin

Low-grade cancers:
Dose of 0.5mg/kg, 3x per week (Guzzo, et al., 2002).

Intermediate-grade cancers:
Dose of 1mg/kg, 3x per week (Guzzo, et al., 2002).

High-grade cancers:
Dose from 1 mg/kg/day (de Castro, et al., 2020) to 2 mg/kg/day (Guzzo, et al., 2002).

All these doses have been established as tolerable for humans (Guzzo, et al., 2002).

5 Benzimidazoles and DON

Low-grade cancers:
Mebendazole: Dose of 200 mg/day (Dobrosotskaya, et al., 2011).

Intermediate-grade cancers:
Mebendazole: Dose of 400 mg/day (Chai, et al., 2021).

High-grade cancers:
Mebendazole dose of 1,500 mg/day (Son, et al., 2020) or Fenbendazole 1,000 mg 3x per week (Chiang, et al., 2021).

All these doses have been established as tolerable for humans (Chai, et al., 2021; Chiang, et al., 2021; Son, et al., 2020). Benzimidazoles can be replaced or combined with DON, administered without toxicity; intravenously or intramuscularly: 0.2 to 0.6 mg/kg once daily; or orally: 0.2 to 1.1 mg/kg once daily (Lemberg, et al., 2018; Rais, et al., 2022). Benzimidazole are much easier to obtain than DON. However, for metastatic cancers, which rely heavily on glutamine (Seyfried, et al., 2020), a combination of DON and Benzimidazoles should be considered (Mukherjee, et al., 2023).

6 Dietary Interventions

All cancer grades:
Ketogenic diet (low carbohydrate-high fat diet, 900 to 1500 kcal/day) (Weber, et al., 2020).

Ketone metabolic therapy consists of approximately 60-80% fat, 15-25% protein and 5-10% fibrous carbohydrates. Adequate hydration and single-ingredient whole food ketogenic meals are necessary to achieve a glucose ketone index (GKI) score of 2.0 or below (Meidenbauer, et al., 2015; Seyfried, Shivane, et al., 2021). GKI should be

measured 2–3 hours postprandial, twice a day if possible (Meidenbauer, et al., 2015; Seyfried, Shivane, et al., 2021).
Intermediate- and high-grade cancers:
The ketogenic diet should be coupled with a water fast for 3 to 7 consecutive days in advanced cancers (Phillips, et al., 2022; Arora, et al., 2023). The water fast should be repeated several times (≈ every 3-4 weeks) throughout the treatment (Nencioni, et al., 2018), but fasting needs to be undertaken cautiously in individuals using certain drugs and those with < 20 BMI, to prevent loss of lean body mass. For patients who can not fast, the Fasting-Mimicking Diet (300 to 1,100 kcal/day of broths, soups, juices, nut bars, and herbal teas) can be used (Nencioni, et al., 2018).

7 **Additional Therapeutics**

All cancer grades:
Moderate physical activity, 3x per week. Increased heart and respiratory rate for a period of 45 to 75 minutes (Bull, et al., 2020) with activities such as cycling, running, swimming, etc.

Intermediate- and high-grade cancers or individuals who are unable to engage in physical activity:
Hyperbaric oxygen therapy, 1.5 to 2.5 ATA for 45 to 60 minutes 2-3x per week (Gonzalez, et al., 2018; Poff, et al., 2015).

The protocol should be followed for an average duration of 12 weeks, regardless of cancer type. The analysis of the interactions between each of the molecules revealed no contraindications to the combination of these substances (ANSM, 2023; CRAT, 2024; Lemberg, et al., 2018; Vidal, 2024). The treatment dosage and duration can be adjusted by the physician according to the individual patient, their ability to obtain the various molecules, and the treatment results. Adaptation of the protocol to include additional molecules to restore health, could be considered by the physician. These may include: vitamin K2 (Xv, et al., 2018), vitamin E (Abraham, et al., 2019), coenzyme Q10 (Liaghat, et al., 2024), methylene blue (da Veiga Moreira, et al., 2024), niacinamide (Yousef, et al., 2022), riboflavin (Suwannasom, et al., 2020), Artemisinin + 5-aminolevulinic acid (to cause porphyrin accumulation) (Adapa, et al., 2024), melatonin (Mocayar, et al., 2020), NADH (Medjdoub, et al., 2016), and magnesium (Ashique, et al., 2023), as examples. However, antioxidant dosages should be avoided.

This additive and synergistic effect of this combination of orthomolecules, drugs, and additional therapies targets the MSCC by increasing OxPhos activity in healthy mitochondria, offering protective action for these cells. However, in cancer cells, both CSCs and non-CSCs, the pro-oxidant effect of the combination induces apoptosis. Additionally, this protocol specifically targets fermentable fuels, CSCs and macrophages, and thus metastases. In brief, the key points of the MSCC. Therefore, comparative studies need to be conducted in both animals and humans to evaluate the effectiveness and safety of this hybrid protocol against standard therapies.

CONCLUSION

The mitochondrial-stem cell connection could be a key element in the therapeutic approach to cancer. In light of current knowledge, we have selected and propose the use of specific orthomolecules, drugs and other therapies for their potential to revive cellular OxPhos activity, and target CSCs, glycolysis and glutaminolysis. These are also aimed at addressing metastases created by fusion hybridization between cancer stem cells and macrophages. Numerous experiments in cells, animals, and humans support the role of targeting the MSCC in both the prevention and treatment of cancer.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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This manuscript is dedicated in memory of our colleague and friend Dr. Michael J. Gonzalez. He left a lasting impact on orthomolecular medicine, and we will strive to honor him through the publication of what will be one of his final contributions.

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