Contribution of whey protein hydrolysate and medium-chain triglycerides on chemotherapy response in the Dark Agouti mammary adenocarcinoma model

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Introduction

- Optimizing chemotherapy efficacy while minimizing toxicity remains a critical part of advancing the treatment of cancer[1]
- We have previously shown that a diet rich in medium chain triglycerides (MCT) and extensively hydrolysed whey protein (WP) reduces methotrexate (MTX) toxicity in rats with breast cancer[2] and enhanced tumor clearance following a single dose of chemotherapy
- What has yet to be shown is if the same diet, or its components can improve response to multi-dose chemotherapy in the same model

AIMS

1. Determine the dietary effect on tumour control and survival

2. Determine the dietary component(s) responsible for the effect

Methods

- Dark Agouti rats, (female, N=32) bearing mammary adenocarcinoma (DAMA 2.0×10^7 cells/ml, s.c.) tumors were given *ad libitum* access to one of four diets; control (CD), MCT-rich (MCT), WP-rich (WP), or MCT and WP-rich (FD) (n=8/group) - researchers blinded to diets.
- MTX (2mg/kg intramuscular, MTX-1) was first administered when tumors reached ≥0.3%BW, and the second dose was administered after 6 days. – received two doses, a week apart
- Animal welfare was evaluated daily, including body weight and diarrhea assessments (Grade 0-3, no diarrhea to severe diarrhea).
- Tumor burden was calculated as tumor volume relative to body weight (%BW, cm^3/g).
- Rats were euthanized if tumors reached ≥10% BW or weight loss ≥15%; length of survival was the primary outcome measure.

Results

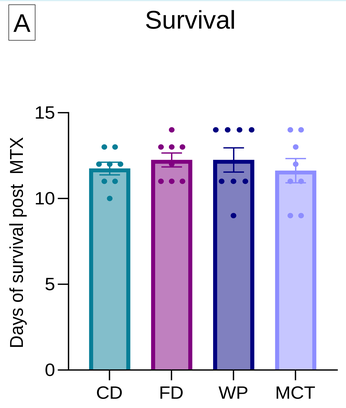

Figure A: Days of survival per group, mean±SEM. CD: 11.75±1.35 , FD: 12.25±1.25 , WP: 12.25±1.98, MCT: 11.63±1.99, no significant differences.

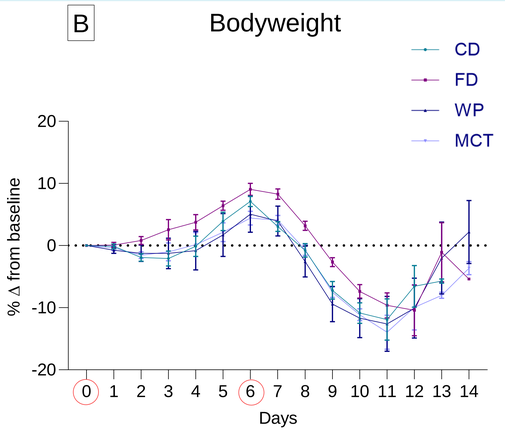

Figure B: Baseline-corrected bodyweight (grams). Day 0 = first day of MTX. Data shown as mean ±SEM.

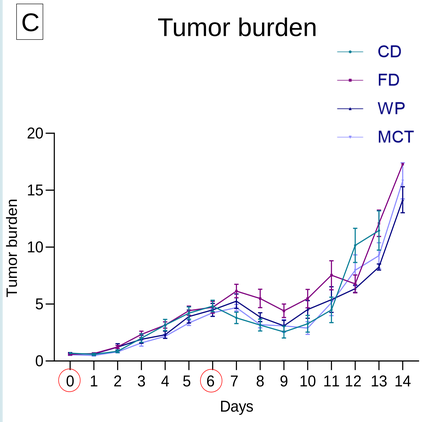

Figure C: Tumor burden (as %body weight) per group. Day 0 = first day of MTX. Data shown is expressed as mean±SEM with no significant difference between groups.

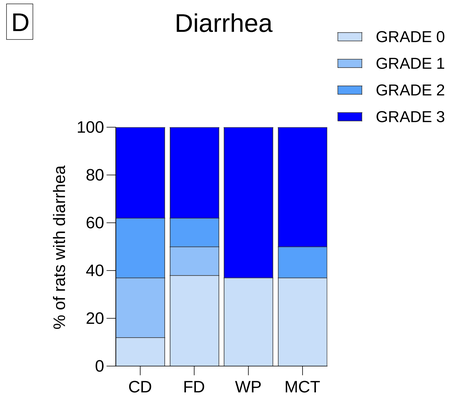

Figure D Diarrhea incidence and severity. Data shown is proportion of rats that experienced diarrhoea at each severity level measured during the study. FD, WP, & MCT significantly reduced the proportion of rats that experienced diarrhea compared to CD (P<0.0001,chi-square test).

Discussion

- Weekly dose of 2 mg/kg of MTX for two cycles, controlled tumor growth for up to 14 days without significant weight loss in most rats.
- The test diets significantly reduced the proportion of rats that experienced diarrhea compared to the control diet. This indicates that the test diets may be a useful intervention against MTX-induced diarrhea, warranting further exploration.
- No test diet significantly improved MTX efficacy in terms of survival, tumor burden, and body weight.
- This study highlights the importance of dosing frequency, with the 2 mg/kg MTX regimen over two cycles showing improved animal welfare evidenced by reduced toxicity and distress compared to the previous 0.7 mg/kg protocol over four cycles.
- Optimizing dosing schedules may not only enhance therapeutic efficacy but also contribute to better tolerability and ethical standards in preclinical models.

1. Burguin, A., Diorio, C., & Durocher, F. (2021). Breast cancer treatments: updates and new challenges. Journal of personalized medicine, 11(8), 808
2. Wardill, H. R., Da Silva Ferreira, A. R., Kumar, H., Bateman, E. H., Cross, C. B., Bowen, J. M., ... & Tissing, W. J. (2023). Whey-based diet containing medium chain triglycerides modulates the gut microbiota and protects the intestinal mucosa from chemotherapy while maintaining therapy efficacy. Cell Death & Disease, 14(5), 338.

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