Contribution of whey protein hydrolysate and medium-chain triglycerides on chemotherapy response: interim results from the Dark Agouti mammary adenocarcinoma model

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Introduction

- Optimising chemotherapy efficacy while minimising 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 (HWP) reduces methotrexate (MTX) toxicity in rats with breast cancer and enhanced tumour clearance following a single dose[2].
- What has yet to be shown is if the same diet, or its components can improve response to multi-dose chemotherapy in the 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=64) bearing mammary adenocarcinoma (DAMA 2.0×10^7 cells/ml, s.c.) tumours were given *ad libitum* access to one of four diets; control, MCT-rich, HWP-rich, or MCT and HWP-rich (A-D, n=16) - researchers blinded to diets.
- MTX (0.75mg/kg intramuscular, MTX-1) was first administered when tumours reached ≥0.5%BW), thereafter a personalised MTX schedule (*determined by change in tumour burden and welfare of each rat*) was followed, ranging from injections every 3-5 days.
- Animal welfare was evaluated daily, including body weight and diarrhoea assessments.
- Tumour burden was calculated as tumour volume relative to body weight (%BW, cm^3/g).
- Rats were euthanised if tumours reached ≥10% BW or weight loss ≥15%; length of survival was the primary outcome measure.

Results

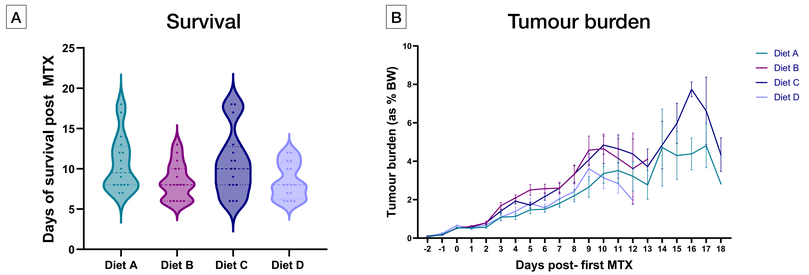

Figure 1. A. Length of survival per group. Data expressed as days post first MTX injection. Diet A: 10.63±3.46, Diet B: 8.44±2.25, Diet C: 10.69±4.05, Diet D: 8.50±2.19 (Mean±SD). **B.** Tumour burden per group with Day 0 as first day of MTX. Data expressed as Mean±SEM.

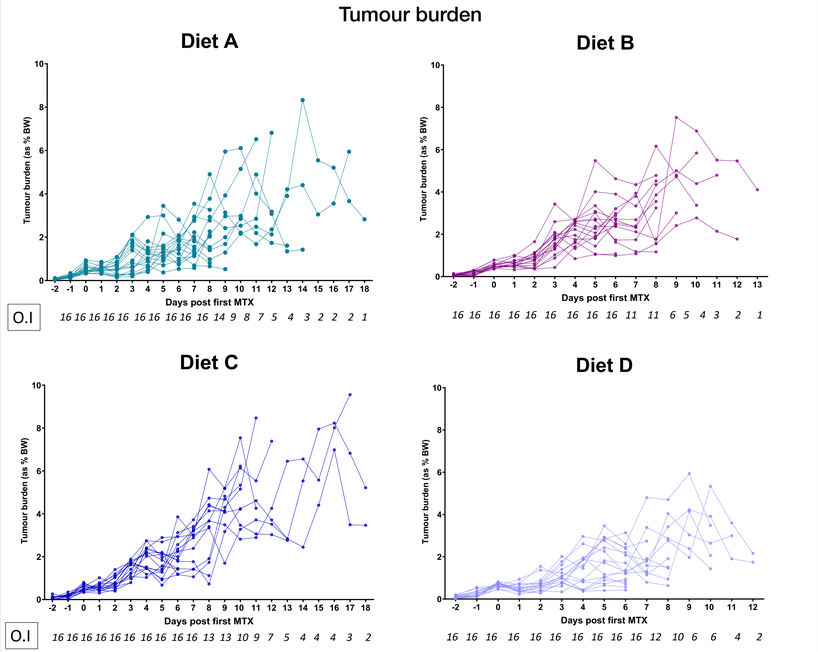

Figure 2: Tumour burden for each diet group showing individual animals. Day 0 indicates first day of MTX. Observable incidents (O.I) – Group number per day.

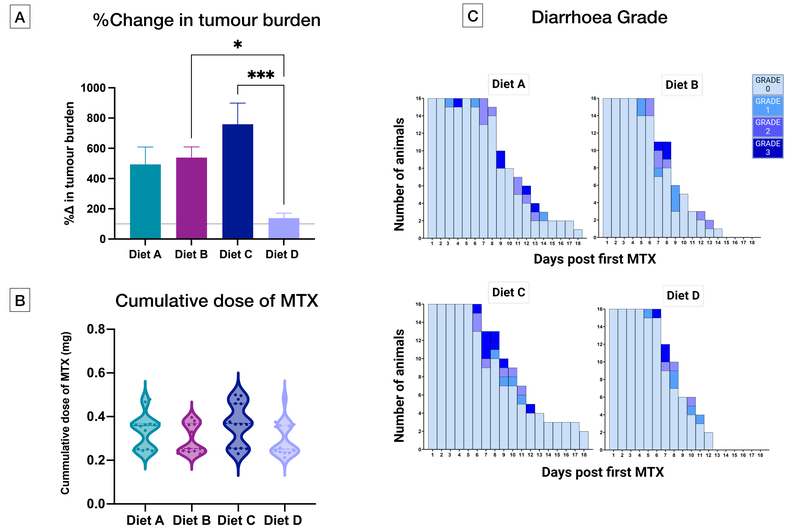

Figure 3A. Tumour growth as % change in tumour burden from the day of first MTX administration to cull day in each diet group. Data expressed as Mean±SEM, *P=0.0312, ***P=0.0002 (one-way ANOVA). B. Cumulative dose of MTX per diet group shown in mg: Diet A: 0.33±0.019, Diet B: 0.29±0.016, Diet C: 0.3±0.023, Diet D: 0.29±0.019 (Mean±SEM). C Diarrhoea incidence per group. Diarrhoea grades: 0 = none, 1 = mild, 2 = moderate, 3 = severe.

Conclusions

- Length of survival was similar across groups, however, Diet D sensitised DAMA tumours to MTX, suggesting therapeutic potential.
- Balancing welfare and tumour outcomes continues to be challenging in pre-clinical models.
- Due to anorexia induced by MTX treatment (food intake data not shown), future studies could explore feeding strategies to maximise diet intake and efficacy.

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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Let's Connect!!