The effects of a Ketogenic diet on markers of DNA Damage response and Cellular Senescence during chemotherapy, in Acute Myeloid Leukemia patients

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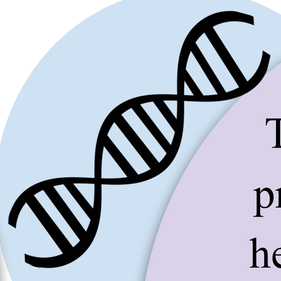
BACKGROUND:

- Chemotherapy non-selectively targets both malignant and rapidly proliferating healthy cells.
- Cellular damage to healthy tissues causes undesirable acute and chronic side effects.
- Preclinical data show a ketotic state protects healthy cells from chemotherapy without affecting toxicity to cancer cells, by inhibiting the insulin/IGF-1/mTOR pathway and inducing cellular repair pathways.

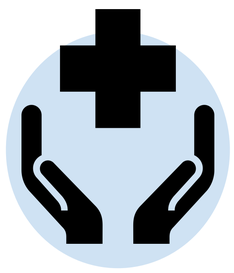
AIM

To analyse the effects of chemotherapy on healthy and leukemic cells in subjects with acute leukaemia randomised to either a ketogenic or control diet.



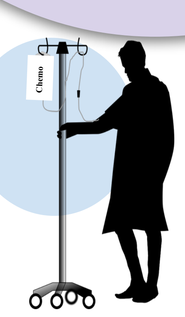
HYPOTHESIS

That metabolic ketosis will provide chemo-protection to healthy cells by upregulating DNA repair and inhibiting cellular senescence, while sensitising cancer cells to chemotherapy by depriving them of their main energy source, glucose.



METHODS

Changes in markers of DNA repair, cellular senescence and proliferation were analysed using flow cytometry in healthy and cancer cells from patients pre-, during, and post-chemotherapy treatment.



DNA DAMAGE MARKERS:

- y-H2AX
- p53
- Phospho-53BP1
- ATM
- ATR

SENESCENCE MARKERS:

- SA-β-galactosidase
- p21
- p16

Senescence: "process by which a cell ages and permanently stops dividing but does not die."

LEGEND:

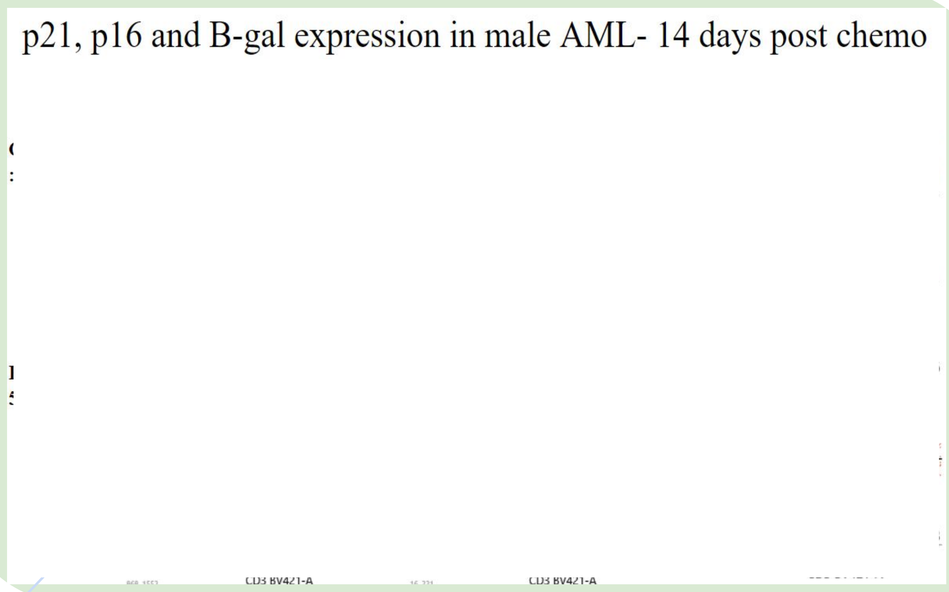
AML Blasts- Pink 

T cells (CD3+): Purple 

B cells (CD20+): Blue 

FIGURE 2

Non-leukaemic T-cells from ketogenic subjects' post-chemotherapy showed a decrease in the cellular senescence markers p16, p21 and SA β-galactosidase compared to control subjects



- ATM, 53BP1 and p53 were minimally altered in both study arms.

RESULTS SUMMARY:

Ketogenic Diet with Chemo

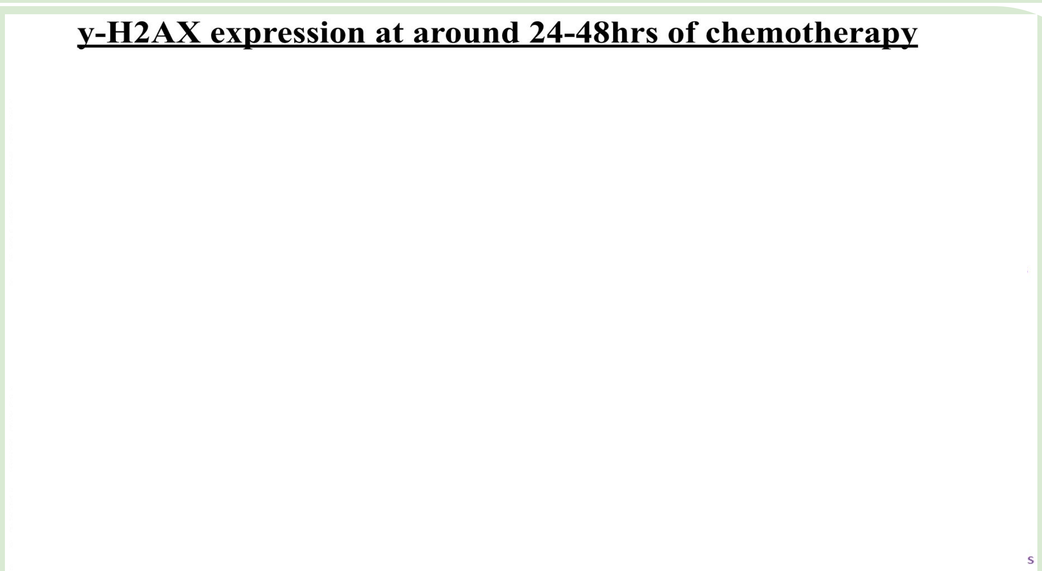
- ↑ DNA Damage to AML Blasts (Cancer)
- ↓ Cellular Senescence in Healthy T-cells

RESULTS

FIGURE 1

Preliminary data at 24 and 48 hrs of chemotherapy showed increased y-H2AX expression in leukemic cells in subjects receiving a ketogenic diet compared to the control diet.

y-H2AX expression at around 24-48hrs of chemotherapy



CONCLUSIONS & FUTURE DIRECTIONS:

- Preliminary data show that a ketogenic diet increases chemotherapy-induced DNA damage in leukaemic cells during chemotherapy
- The diet decreases cellular senescence markers in healthy lymphocytes post-treatment
- The results highlight the potential dual role of this diet as a first-line adjuvant and chemo-protective therapy.
- Although the results are promising, the effect of the variability of medication regimes between patients and patient heterogeneity is still unknown. Furthermore, the mechanisms and specifics of these DNA damage pathways in response to the diet are yet to be understood.
- Future experiments will explore mechanisms and additional markers of DNA damage repair, as well as inter-patient variability.

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