Inflammatory mediators are reduced 2 days after a radical cystectomy in bladder cancer patients consuming immune modulating drinks

Bechtel M1, Yanke T1, Atchison S1, Holzbeierlein JM1, Lee EK1, Mirza M1, Chalise P1, George KE1, Hamilton-Reeves JM1

1Department of Dietetics & Nutrition, University of Kansas Medical Center, Kansas City, Kansas, USA; 2Department of Microbiology, Molecular Genetics, & Immunology, University of Kansas Medical Center, Kansas City, Kansas, USA; 3Department of Urology, University of Kansas Medical Center, Kansas City, Kansas, USA; 4Department of Biostatistics, University of Kansas Medical Center, Kansas City, Kansas, USA;

Abstract

Background: Immune modulating drinks (IMD) containing arginine, nucleotides, and fish oil may reduce the catabolic inflammatory response to surgery. To explore the effects of IMD in muscle invasive bladder cancer patients undergoing radical cystectomy (RC), we examined pathways that define helper T cell differentiation and surgery-induced cachexia.

Methods: Six men undergoing RC were enrolled in a single-blinded, randomized pilot study at the University of Kansas Medical Center. Men received IMD (n=3) or placebo drinks (n=3) to consume 5 days before and after surgery. Two days after RC surgery, CD4+ T cells were isolated from blood, stimulated with anti-CD3 and anti-CD28, and analyzed by Illumina Next Gen DNA Sequencing. Differences in mRNA levels were assessed using the Exact Test based on the negative binomial distribution. Multiple testing adjustments were applied using the Benjamini and Hochberg method.

Results: Compared to placebo, 46 mRNA transcripts were down regulated and 175 mRNA transcripts were up-regulated in the IMD group. The mRNA encoding for inflammatory cytokines IL-1β, IL-6, IL-17, and IL-31 were decreased in cells in the IMD group, as compared to placebo (FDR < 0.05). Furthermore, mRNA levels for IL-4 and IL-5 trended downward in the treatment group (FDR < 0.11).

RNA Sequencing: Compared to placebo, 46 mRNA transcripts were down regulated and 175 mRNA transcripts were up regulated in the IMD group. The mRNA encoding for inflammatory cytokines IL-1β, IL-6, IL-17, and IL-31 were decreased in cells in the IMD group, as compared to placebo (FDR < 0.05). Furthermoe, mRNA levels for IL-4 and IL-5 trended downward in the treatment group (FDR < 0.11).

Pathway Analysis: Gene Transcripts with large effect sizes (FDR < 0.05) were mapped to molecular pathways for biological interpretation using Ingenuity Pathway Analysis software (Ingenuity Systems®, www.ingenuity.com). Pathway analysis indicated cells from the IMD group had lower NF-κB activity than placebo.

Conclusions: IMD intake before and after RC surgery led to a reduction in mRNA levels of cytokines associated with helper T cell activity, particularly the pro-inflammatory cytokines. Thus, IMD may reduce the inflammatory environment after surgery, and reduce postoperative complications.

References


Support

Research relating to this article was funded by American Cancer Society grant (IRG-09-062-05), awarded to the University of Kansas Medical Center, Nestle Healthcare Nutrition Research Grant, Frontiers: The Heart Institute for Clinical and Translational Research which is supported by a CTSA grant to the University of Kansas Medical Center from the National Center for Advancing Translational Sciences (NCATS; grant # UL1TR000001); by the Kansas Intellectual and Developmental Disabilities Research Center (HD002528); and by Illumina, and the KL2 Scholars Award (KL2 TR000119-04).

Trial Registration: ClinicalTrials.gov NCT01868087.

Jill Hamilton-Reeves, PhD, RD, LD, School of Health Professions, Dept. of Dietetics & Nutrition 3901 Rainbow Blvd, Mail Stop 4013 Kansas City, KS 66160 PH: 913-588-7650 Email: jhamilton-reeves@kumc.edu