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Race and Colorectal Cancer Stage in an Equal Access Medical System

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Background: Colorectal cancer (CRC) is the second leading cause of cancer deaths in the United States. In the past decade, there has been tremendous progress in reducing colorectal cancer incidence and death rates largely through prevention and early detection. Overall, colorectal cancer incidence and mortality rates are highest in black men and women. In general, blacks have also been diagnosed at a later stage compared to non-blacks. This disparity may be due to a number of factors, such as disproportionately limited access to medical care for blacks. The military health care system is unique in that equal access is available to all patients. Therefore, there is a difference in age and colorectal cancer stage at diagnosis between blacks and non-blacks in an equal access medical system. Methods: We conducted a retrospective cohort study examining data from patients diagnosed with colorectal cancer in an academic tertiary military health system from 2007-2012. Data including race, stage, and age at diagnosis were reviewed. Results: Data were available for 192 patients. The average patient age diagnosed with colorectal cancer was 60.5 years and the majority of patients were male (70%). Blacks comprised 8% of the total patient population diagnosed with CRC. The average age of CRC diagnosis was 71.4 years for non-blacks, 64.4 years, and 64.3 years for blacks (p=0.588). There was no significant difference in the stage of CRC at diagnosis between blacks and non-blacks (p=0.915). Furthermore, 47% of blacks were diagnosed at advanced CRC stage compared to 55% of non-blacks (p=0.14). Conclusion: In an equal access medical system, there was no difference between blacks and non-blacks with regard to patient age and stage at CRC diagnosis.

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Bile Acid Malabsorption is a Very Common Cause of Diarrhea Secondary to Different Cancer Therapies for a Whole Range of Different Cancer Types

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Introduction: In the UK, approximately 16,000 patients per year are left with a chronic change in bowel function due to gastrointestinal symptoms following treatment for cancer. This can have a significant impact upon quality of life and even compromise on-going cancer therapy. Previous small studies focusing on patients with gynaecological cancers suggest that bile acid malabsorption (BAM) may be an important cause of radiotherapy-induced diarrhoea. We retrospectively study aims to elucidate the true prevalence of BAM in patients referred to a specialist gastroenterology clinic which specialises in treating patients with consequences of cancer treatments. Methods: Patients referred to our clinic are managed using a peer reviewed algorithm. If they report diarrhoea, defined as Bristol Stool Charts type 6-7, a routine referral for a sHeCAT (75-selemant homocylcine acid taurocholate) test is made to diagnose possible BAM. BAM is diagnosed when the sHeCAT 7 day retention is <15% and is graded mild (10-15%), moderate (5-10%) and severe (<5%). Results: During a four year period between 2009-2013, 50 consecutive patients were referred for a sHeCAT scan. 35 patients (70%) were diagnosed with moderate (6.5%) or severe (33.5%) bile acid malabsorption. The graphs below show the proportion of patients with each type of cancer who have BAM, with mild, moderate and severe grades indicated accordingly. Conclusions: This study has several new and important findings, and the BAM is seen as being caused by a variety of reasons. Some of the stand-out findings include: 1) Cancers lower in the pelvis generally have much lower rates of BAM than those higher in the pelvis. This is likely due to reduced collateral damage to the terminal ileum. 2) Notwithstanding this, there are significantly lower rates of BAM in prostate cancer, which is treated with radiotherapy alone and may therefore lack a sensitising effect from chemotherapy. 3) The high rates of BAM and severe BAM after colon cancer treatment is associated with right hemicolectomy, which removes the terminal ileum. 4) The high rates of BAM and severe BAM after pancreatic cancer treatment is associated with the Whipple's procedure. Subsequent fat malabsorption likely interferes with bile acid reabsorption. 5) The high rates of BAM seen after myeloma treatment are exclusively caused by the use of lenalidomide. It is not the majority that have severe BAM. Overall, this landmark study with significant patient numbers establishes BAM as a very frequent cause of diarrhoea secondary to cancer treatments. Given the effectiveness of dietary fat manipulation combined with a new generation of bile acid sequestrants for BAM, sHeCAT scanning should be a first line investigation for patients with diarrhoea after cancer therapies.

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Protective Effects of Betaxolol (94-123), a Bioactive Peptide Present in Fermented Milk, in Inflammation and Stress-Related Gastrointestinal Disorders

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Background : beta-CN (94-123) is a recently discovered casein-derived bioactive peptide found in yogurt, targeting goblet cells. Our aims were to determine whether this peptide was able to influence the expression of genes involved in models of epithelial mucosal breakdown: maternal neonatal deprivation (NMD) and indomethacin-induced intestinal inflammation (Indo). Methods: Male Wistar rats were subdivided to NMD three hours a day, from postnatal days 5 to 20. Beta-CN (94-123), or its vehicle, was administrated by gavage from day 10 to day 20, at the concentration of 0.01, 1 and 100 μM (10μg, of body weight).

Animals were thereafter euthanized either at day 24 or at 12 weeks-old. Portions of jejunum and colon were collected and (i) mounted in Ussing chambers to evaluate paracellular permeability; and (ii) fixed for next histology analysis. In a second study, adult male Wistar rats were orally treated with beta-CN (94-123) for 8 days, then injected twice with 10 mg/kg indomethacin (i.c.) to induce intestinal inflammation, and euthanized at day 12. Jejunum were collected to determine macroscopic and microscopic damage scores, cytokine expression, myeloperoxidase activity and Muc2 and mucus layer labeling. Finally, we determined whether the peptide was able to stimulate wound healing on HT29 cells. Results: beta-CN (94-123) abolished NMD-induced jejunal paracellular hyperpermeability (0.87 ± 0.16 vs 2.63 ± 0.51 [p<0.01] and 1.65 ± 0.13 vs 0.59 ± 0.20 mm h⁻¹ cm⁻¹ [p<0.01]) at day 24 and 6 weeks, respectively. Conclusion: Beta-CN (94-123) prevents inflammation and intestinal lesions caused by either maternal stress or chemical injury in vivo. The mechanism of action would include a CROr-dependent pathway. The peptide may represent a novel therapeutic approach for intestinal diseases.

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Lanreotide Autogel 120 mg As a Treatment for Chronic Idiopathic Refractory Diarrhea: A Multicenter Prospective Trial

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Introduction: Lanreotide has an inhibitory effect on gastrointestinal secretions and motility. To evaluate the prolonged-release somatostatin analogue Lanreotide Autogel 120 mg for the treatment of persistent idiopathic diarrhea in a multicenter, prospective, open label study. Materials & Methods: The study was performed in 10 centers between July 2009 and August 2012. The study protocol was approved by the Ethics Committee of UZ Leuven, Belgium (CIT/2008/96). The study was performed in 10 centers (11 investigators: 2 male vs 8 female patients; with a mean age of 34.1 years) with refractory diarrhea were studied. The mean age was 55.2 ± 16.4 years. Four weeks after the first injection (Day 28), 44.4% of patients were responders, which increased to 54.3% at Day 56. Response rates were higher in male patients (58.3%) compared to females (37.5%). Overall, the mean number of stools decreased significantly from 5 ± 2.3 at baseline to 3.6 ± 2.2 at Day 56 (p = 0.0007). In the responder subgroup at Day 56, this number decreased significantly from 3.5 ± 2.4 to 2.2 ± 0.8 (p = 0.0001). The median percentage of days per week with less than 3 stools/day increased from 7.1% at baseline to 57.1% at Day 56. At Day 56, the median cumulative stool frequency and consistence (Bristol Stool Form Scale) were +1.36. Similarly, the SF-36-QOL scores improved at Day 56, especially in the domains of social functioning (+4.0), physical role (+11.8) and mental health (+10.1). In the responder subgroup at Day 56, the mean stool consistency score dropped significantly from 4.6 ± 0.7 to 2.4 ± 0.7 (p = 0.0005). In total, 2373 emergent AEs were reported, of which the majority (79%) were mild to moderate and only 9% were serious. The most frequently reported AEs were gastrointestinal disorders (abdominal pain, 25% of patients; nausea, 11% and steatorrhoea, 8.3%), injection site reactions (16.7%) and asthma/atopic (11.4%). Conclusion: Lanreotide showed improvement in gastrointestinal symptoms, diarrhea, and rectal bleeding with lanreotide autogel 120 mg treatment, which it suggest is it effective for the management of persistent refractory idiopathic diarrhea. Confirmatory studies are needed.

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Diamine Oxidase Activity As A Serum Biomarker For Intestinal Mucosal Damage: Consequences Of Diarrhea And Anticancer Drug Treatment


Aim: Intestinal mucosal damage due to anticancer drugs which induces QOL impairment and malnutrition is one of major problems for cancer treatment. However, there is no method to evaluate objectively the degree of intestinal mucosal damage and anticancer drug. Diamine oxidase (DAO) is an enzyme which exists specifically in villi tips of enterocytes of the small intestine. Since DAO activity decreases as intestinal mucosa is damaged, it is expected that DAO activity is a good indicator which reflects sharply damage of small intestinal mucosa. The aim of this study is to investigate whether DAO activity is useful as an indicative marker for intestinal mucosal damage, appearance of diarrhea and malnutrition in patients with chemotherapy. Method: The subjects are 20 patients with unselectable advanced gastric cancer who received doxetaxel, CDPD and 5-CDs combination chemotherapy (Yamagata et al, Br J Cancer 2000) as a first line chemotherapy. DCS therapy is a modified regimen of doxetaxel, CDPD and 5-FU combination chemotherapy, in which 5-FU was replaced by S-1. DAO activity was measured according to the methods of Takagi et al (Clin Chim Acta 1994), before, during and after chemotherapy. Mucosal atrophy is characterized by diminished intestinal function as well as morphological changes including decreased villous height, surface area(Shaw et al, World J Gastroenterol, 2012) and reduction in the number of goblet cells(Chang et al, World J Gastroenterol, 2005). Therefore, damage...
of small intestinal mucosa was evaluated by villous height, villous surface area and the number of goblet cells by endoscopic duodenum biopsies before and during chemotherapy. Degree of diarrhea was evaluated by NCI-CTC V4.0. Nutrition was evaluated by serum albumin and serum total protein activities decreased significantly during chemotherapy and recovered significantly after drug holiday. DAO activities (±SD) in 20 patients were 4.88±2.06U/L before chemotherapy, 2.96±1.62U/L after drug holiday (day 21). The DAO activity decreased significantly during chemotherapy and recovered significantly after drug holiday. Diarrhea (Grade-1) appeared in 19 patients in the 10 to 18 day after administration of antitumor drugs and followed decrease in DAO activity. Villos height, villous surface area, number of goblet cells were all significantly reduced by antitumor drugs and followed decrease in DAO activity. Serum albumin and serum total protein were significantly reduced by antitumor drugs and significantly increased after drug holiday. The DAO activity reduction rate between day 1 and day 14 was significantly correlated with albumin and total protein reduction rate between day 1 and day 21. Conclusion. Our results suggested that the DAO activity is a good marker for intestinal mucosal damage, appearance of diarrhea and malnutrition in patients with chemotherapy.

322 Ocludin Limits Epithelial Survival by Inducing Caspase-3 Expression
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BACKGROUND & AIMS: Knockout (KO) of the tight junction protein ocludin (occludin) has been reported to have no impact on intestinal barrier function ex vivo. However, in vivo and in vitro studies have implicated ocludin in cytokine-induced paracellular barrier loss. Further, ocludin expression is downregulated in human and experimental inflammatory bowel disease (IBD). Thus, ocludin function remains enigmatic. Our aim was to define the contributions, if any, of ocludin to intestinal epithelial homeostasis and apoptosis.

METHODOLOGY: Ocludin KO and transgenic mice, caspase-3-/- mice, ocludin knockdown (KD) Caco-2 cells, and human biopsy samples were studied. RESULTS: Ocludin KO mice were resistant to DSS-induced mucosal damage and colitis relative to wild type (WT) mice (weight loss WT 9±4%, KO 1x0±4%, p=0.017). Disease severity could be blocked by specific ocludin expression in ocludin KO mice (weight loss increased to 7x±2%, P001 vs ocludin KO), showing the importance of epithelial ocludin in promoting DSS colitis. Further analyses showed that, while epithelial proliferation was not affected, epithelial apoptosis was markedly reduced in ocludin KO mice relative to WT mice (6.5±0.9% vs 3.8±0.9% of keratin 14 positive cells). These results were also protected from intestinal epithelial apoptosis induced by 5-fluorouracil (5-FU) or tumor necrosis factor-0 (TNF), indicating that ocludin promotes both intrinsic and extrinsic pathways of apoptosis. TNF-induced caspase-8 and -9 activation were unaffected by ocludin KO, but caspase-3 activation was reduced. Consistent with this, cytochrome C and dATP failed to efficiently activate caspase-3 in cytosolic extracts of Ocludin KD Caco-2 cells. Moreover, caspase-3 protein and mRNA expression were reduced in ocludin KO colonocytes (to 47±9% and 40±6% of WT colonocytes, respectively) and ocludin KD Caco-2 cells, and caspase-3 promoter activity was decreased in ocludin KD Caco-2 cells (to 45±7% of control), indicating that ocludin promotes caspase-3 transcription. Similar to ocludin KO mice, DSS- or 5-FU-induced intestinal epithelial apoptotic were reduced in caspase-3-/- mice (caspase-3 expression decreased to 6x±6% of WT) relative to WT mice, suggesting that caspase-3 expression decrease is responsible for the protection afforded by ocludin KO. Analysis of colon biopsies from ulcerative colitis patients and control subjects showed a direct correlation between ocludin and caspase-3 expression, indicating ocludin downregulation may promote epithelial survival to limit IBD disease progression. CONCLUSION: Ocludin expression enhances caspase-3 promoter activity and sensitivity to intrinsic and extrinsic apoptotic stimuli. Conversely, reduced ocludin expression increases epithelial survival. Thus, in addition to reducing paracellular barrier function, decreased ocludin expression in colitis may limit intestinal epithelial apoptosis, reduce damage, and promote mucosal homeostasis.

323 Chemotherapy Induced Diarrhea in Colorectal Cancer: A Retrospective Analysis of Clinico-Pathological and Radiological Features
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Background Chemotherapy induced diarrhea (CID) is a common and debilitating side effect of cancer treatment. Aims and Methods The aim was to ascertain the incidence of CID in chemotherapy. Analysis of Clinico-Pathological and Radiological Features

METHODS: Ocln KO and transgenic mice, caspase-3-/- mice, ocludin knockdown (KD) Caco-2 cells, and human biopsy samples were studied. RESULTS: Ocludin KO mice were resistant to DSS-induced mucosal damage and colitis relative to wild type (WT) mice (weight loss WT 9±4%, KO 1x0±4%, p=0.017). Disease severity could be blocked by specific ocludin expression in ocludin KO mice (weight loss increased to 7x±2%, P001 vs ocludin KO), showing the importance of epithelial ocludin in promoting DSS colitis. Further analyses showed that, while epithelial proliferation was not affected, epithelial apoptosis was markedly reduced in ocludin KO mice relative to WT mice (6.5±0.9% vs 3.8±0.9% of keratin 14 positive cells). These results were also protected from intestinal epithelial apoptosis induced by 5-fluorouracil (5-FU) or tumor necrosis factor-0 (TNF), indicating that ocludin promotes both intrinsic and extrinsic pathways of apoptosis. TNF-induced caspase-8 and -9 activation were unaffected by ocludin KO, but caspase-3 activation was reduced. Consistent with this, cytochrome C and dATP failed to efficiently activate caspase-3 in cytosolic extracts of Ocludin KD Caco-2 cells. Moreover, caspase-3 protein and mRNA expression were reduced in ocludin KO colonocytes (to 47±9% and 40±6% of WT colonocytes, respectively) and ocludin KD Caco-2 cells, and caspase-3 promoter activity was decreased in ocludin KD Caco-2 cells (to 45±7% of control), indicating that ocludin promotes caspase-3 transcription. Similar to ocludin KO mice, DSS- or 5-FU-induced intestinal epithelial apoptotic were reduced in caspase-3-/- mice (caspase-3 expression decreased to 6x±6% of WT) relative to WT mice, suggesting that caspase-3 expression decrease is responsible for the protection afforded by ocludin KO. Analysis of colon biopsies from ulcerative colitis patients and control subjects showed a direct correlation between ocludin and caspase-3 expression, indicating ocludin downregulation may promote epithelial survival to limit IBD disease progression. CONCLUSION: Ocludin expression enhances caspase-3 promoter activity and sensitivity to intrinsic and extrinsic apoptotic stimuli. Conversely, reduced ocludin expression increases epithelial survival. Thus, in addition to reducing paracellular barrier function, decreased ocludin expression in colitis may limit intestinal epithelial apoptosis, reduce damage, and promote mucosal homeostasis.

AGA Abstracts