



www.sciencetranslationalmedicine.org/cgi/content/full/7/271/271ps1/DC1

Supplementary Materials for

Cancer and the gut microbiota: An unexpected link

Laurence Zitvogel,* Lorenzo Galluzzi, Sophie Viaud, Marie Vétizou, Romain Daillère,
Miriam Merad, Guido Kroemer

*Corresponding author. E-mail: laurence.zitvogel@gustaveroussy.fr

Published 21 January 2015, *Sci. Transl. Med.* **7**, 271ps1 (2015)
DOI: 10.1126/scitranslmed.3010743

This PDF file includes:

Table S1. Links between the gastrointestinal side effects of common anticancer regimens and the gut microbiota.

Supplementary Table 1. Links between the gastrointestinal side effects of common anticancer regimens and the gut microbiota

Therapeutic agent(s)	Main indication(s)	Macroscopic abnormalities	Histopathological changes	Molecular and microbial correlates	Preventive measures
<i>Conventional anticancer agents</i>					
5-fluorouracil	Breast carcinoma Head and neck cancer Colorectal carcinoma	Mucositis Diarrhea Weight loss	Degeneration of villi and crypts Apoptosis/necrosis among IECs Immune infiltration in the LP	TP53/BAX axis TNF α /NF- κ B/iNOS IL-1 β /IL-1RA, IL-4 Dihydropyrimidine dehydrogenase deficiency Increase in <i>Staphylococcus spp.</i> , <i>Clostridium spp.</i> , <i>E. coli</i> , and facultative anaerobes Decrease in <i>Lactobacillus spp.</i> and <i>Bacteroides spp.</i> Modifications in <i>Clostridium</i> cluster IV, XI and XIVa (when combined with irinotecan)	Opioid agonists Oxycodone R-Spondin 1 TLR5 agonists IL-1RA GLP2 iNOS/COX2 inhibitors Curcumin FGF7 Butyrate
Cisplatin	Testicular cancer NSCLC Ovarian carcinoma	Diarrhea Weight loss	Degeneration of villi and crypts Goblet cell depletion Apoptosis/necrosis among IECs and endothelial cells Edema	TP53/BAX axis acid sphingomyelinase Diarrhea-dependent depletion of the gut microbiota	TNF α antagonists Sodium selenosulfate
Cyclophosphamide	Leukemia Lymphoma Brain cancer	Mucositis (mice) Diarrhea (mice, patients) Weight loss (mice) Stomatitis (patients)	Shortening of villi Immune infiltration in the LP Edema Increased proliferation of Paneth and goblet cells	ABCC4 Diarrhea-dependent depletion of the gut microbiota	IL-1RA Enteral alanyl-glutamine

Docetaxel	Breast carcinoma NSCLC Prostate carcinoma	Neutropenic enterocolitis Diarrhea Colitis	Severe erosive esophago- gastroduodenitis	Diarrhea-dependent depletion of the gut microbiota	Loperamide
Paclitaxel	Breast carcinoma NSCLC Ovarian carcinoma	Weight loss (mice) GI symptoms (patients) Oral candidiasis (patients)	Reduction of villi depth (mice) Apoptosis in crypts (mice) Mitotic arrest and apoptosis/ necrosis among IECs (patients)	Diarrhea-dependent depletion of the gut microbiota	Dairy milk products
Doxorubicin	Leukemia Hodgkin's lymphoma Multiple solid tumors	Mucositis	Degeneration of villi and crypts Massive enterocyte apoptosis Immune infiltration in the LP	BMP4 TLR2/GSK-3 β TLR9	GSK-3 β inhibitors Dexrazoxane
Ifosfamide	Testicular cancer Breast carcinoma Lymphoma	GI symptoms (patients)	Reduction of villi depth Mitotic arrest and apoptosis/ necrosis among IECs	Diarrhea-dependent depletion of the gut microbiota	MESNA
Irinotecan	Colorectal carcinoma	Delayed diarrhea Severe mucositis Weight loss Mortality	Degeneration of villi and crypts Goblet cell depletion Mucin hypersecretion and malabsorption Extensive intestinal inflammation and apoptosis	TNF α /NF- κ B/iNOS IL-1 β /IL-18, IL-6 Bacterial β -glucuronidase Increase in <i>E. coli</i> and <i>Staphylococcus spp.</i> Decrease in <i>Lactobacillus spp.</i> Modifications in <i>Clostridium</i> cluster IV, XI and XIVa (when combined with 5-FU)	RDP58 Broad-spectrum antibiotics Loperamide Probiotic VSL#3 PHY906 Thalidomide Pentoxifylline Inhibition of IL-18
Melphalan	Multiple myeloma Ovarian carcinoma HSCT conditioning	Mucositis (mice, patients) Severe diarrhea (mice, patients)	Degeneration of villi and crypts Necrosis among IECs	SLC7A5 Diarrhea-dependent depletion of the gut microbiota	Amifostine
Methotrexate	Breast carcinoma Leukemia Lymphoma Osteosarcoma	Diarrhea Stomatitis Weight loss	Mitotic arrest and apoptosis/ necrosis among IECs Structural alterations of Paneth and goblet cells Immune infiltration in the LP	BAX/BCL2 system Diarrhea-dependent depletion of the gut microbiota	Dietary TGF β 2 supplementation Calcium folinate plus amifostine Oral glutamine (?)

Radiation therapy Total body irradiation	Leukemia Lymphoma Solid tumors	Proctitis (patients) Fistula (patients) Enteritis (patients) Diarrhea (patients) Mucositis (mice) Ulcers (mice)	Mitotic arrest and massive apoptosis/necrosis among IECs Edema Increased proliferation of goblet cells	TP53/BAX axis Increase in <i>Actinobacteria</i> <i>spp.</i> and <i>Bacillus spp.</i> Decrease in <i>Clostridium spp.</i>	Loperamide Supportive care Tempol Glutamine (?) Probiotics
<i>Targeted anticancer agents</i>					
EGFR and ERBB2 inhibitors (erlotinib, gefitinib, lapatinib)	Breast carcinoma NSCLC Pancreatic carcinoma	Stomatitis Mucositis Diarrhea	Degeneration of villi and crypts (mice) Increased proliferation rate among IECs and goblet cells in the jejunum (rat)	Diarrhea-dependent depletion of the gut microbiota	Supportive care Dose reduction Discontinuation GLP2
MEK inhibitors (RO49876559)	Melanoma Solid tumors	Stomatitis Diarrhea	Not described	Diarrhea-dependent depletion of the gut microbiota	Dose reduction Discontinuation
MTOR inhibitors (everolimus, sirolimus)	Renal cell carcinoma Pancreatic carcinoma Breast carcinoma	Stomatitis Oral ulcers Mucositis Diarrhea	Degeneration of crypts (mice)	Diarrhea-dependent depletion of the gut microbiota	Supportive care Dose reduction

For additional information please see Refs (1) and (13). ABCC4, ATP-binding cassette, sub-family C (CFTR/MRP), member 4; BAX, BCL2-associated X protein; BMP4, bone morphogenetic protein 4; COX2, cyclooxygenase 2; EGFR, epidermal growth factor receptor; ERBB2, *v-erb-b2* avian erythroblastic leukemia viral oncogene homolog 2; FGF7, fibroblast growth factor 7; GI, gastrointestinal; GLP2, glucagon-like peptide 2; GSK-3 β , glycogen synthase kinase 3 β ; IEC; intestinal epithelial cell; IL, interleukin; IL-1RA, IL-1 receptor antagonist; iNOS, inducible nitric oxide synthase; LP, lamina propria; MEK, MAPK/ERK kinase; MESNA, 2-mercaptoethane sulfonate; MTOR, mechanistic target of rapamycin; NSCLC, non-small cell lung carcinoma; SLC7A5, solute carrier family 7 (amino acid transporter light chain, L system), member 5; TGF β 2, transforming growth factor β 2; TLR, Toll-like receptor; TNF α , tumor necrosis factor α ; TP53, tumor protein p53.