Keefe, D. *et al*. Semin Oncol Nurs 20: 38–47, 2004]. It is often a dose-related adverse effect and may be associated with other features of toxicity. CID appears to be a multifactorial process whereby acute damage to the intestinal mucosa (including loss of intestinal epithelium, superficial necrosis and inflammation of the bowel wall) causes an imbalance between absorption and secretion in the small bowel [Keefe, D. *et al*. Gut 47: 632–637, 2000; Keefe, D. Support Care Cancer 15: 483–490, 2007; Gibson, R. and Stringer, A., Curr Opin Support Palliat Care 3: 31–35, 2009].

[0005] Left untreated, life-threatening gastrointestinal syndrome is recognized by two National Cancer Institute-sponsored cooperative group trials as a serious complication. These trials reviewed early toxic deaths occurring in irinotecan plus high-dose fluorouracil and leucovorin for advanced colorectal cancer and highlighted the need for vigilant monitoring and aggressive therapy for this serious complication [Conti, J. *et al*. J Clin Oncol 14: 709–715, 1996; Arbuckle, R. *et al*. Oncologist 5: 250–259, 2000; Saltz L. *et al*. N Engl J Med 343: 905–914, 2000]. In addition, diarrhea can hinder chemotherapy and other treatments for cancer by causing dosing delays, reductions, or use of alternative agents which may have an ultimate impact on survival [Engelking, C. *et al*., Oncol Nurs Forum 25: 859–860 1998; Ippoliti, A., Am J Health Syst Pharm 55: 1573–1580, 1998].

[0006] Therefore, drug-related diarrhea in human subjects undergoing chemotherapy represents an important and unmet clinical need requiring more effective management. Currently prescribed therapies are only partially effective or are plagued by unacceptable side effects such as constipation and the potential for addiction. The development of a drug for the treatment of chemotherapy-associated diarrhea with a low potential for drug-drug interactions, effects on drug metabolism, or abuse potential would provide an important benefit for subjects undergoing chemotherapy.

SUMMARY

[0007] Disclosed herein are methods of preventing, ameliorating and/or treating diarrhea in human subjects being administered or having been administered a chemotherapy regimen. In one example, the methods presented herein prevent, ameliorate or treat chemotherapy-induced diarrhea (CID).

[0007a] In one aspect, provided herein is a use of crofelemer in the manufacture of a medicament for treating chemotherapy-induced diarrhea (CID) in a human subject undergoing chemotherapy for treatment of breast cancer and in need thereof, the medicament comprising an effective amount of crofelemer to treat CID, wherein the chemotherapy comprises a CDK (cyclin-dependent kinase) 4/6 inhibitor.

[0008] In one example, provided herein are methods of treating CID in a human subject undergoing chemotherapy, particularly for cancer treatment, comprising administering to a subject in need thereof a composition comprising an effective amount of a proanthocyanidin polymer composition from *C. lechleri*, preferably crofelemer, to treat, ameliorate or prevent CID. In certain examples, the crofelemer is an enterically protected formulation. In certain examples the chemotherapy is administered to treat, ameliorate, manage or prevent cancer.

[0009] According to certain examples, crofelemer may be administered in combination with other chemotherapy agents.

[0010] In one example, the crofelemer is administered at the same time as administration of chemotherapy to reduce or delay the onset of CID.

[0011] In certain examples, the subject exhibits Grade 1, Grade 2, Grade 3 or Grade 4 diarrhea in accordance with the Common Toxicity Criteria from the National Cancer Institute.

[0012] In one example, the crofelemer is administered before administration of chemotherapy to reduce or delay the onset of CID.

[0013] In one example, the crofelemer is administered after administration of chemotherapy to reduce the onset of or treat CID.

[0014] In certain examples, the crofelemer is administered to reduce the risk, incidence or severity of CID so that the human subject can tolerate a particular chemotherapy agent with CID as a side effect or a higher dose of a chemotherapy agent that has CID as a side effect.

[0015] In one example, the chemotherapy agent is selected from alkylating agents, anthracyclines, cytoskeletal disruptors (taxanes), epothilones, histone deacetylase inhibitors, inhibitors of topoisomerase I, inhibitors of topoisomerase II, kinase inhibitors, nucleotide analogs and precursor analogs, peptide antibiotics, platinum-based agents and retinoids.

[0016] In one example, the chemotherapy agent comprises one or more tyrosine kinase inhibitors. The tyrosine kinase inhibitor (TKI) have a target selected from epithelial growth factor receptor (EGFR), VEGFR (e.g, VEGFR-1, VEGFR-2, and/or VEGFR-3); AXL, RET, TYRO3, MER, KIT, TRKB, FLT-3, CSF-1R, anaplastic lymphoma kinase (ALK), ROS-1 (c-ros); hepatocyte growth factor receptor (HGFR), c-Met, RON, platelet derived growth factor

receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR1,2,3, or 4), KIT, Lck, Fms, Itk, BRAF, mutant BRAF, c-CRAF, BRK, EPHRs, and TIE-2, In one example, the chemotherapy agent comprises one or more EGFR TKIs. In one example, the chemotherapy agent comprises one or more a pan-ErbB receptor TKIs. In one example, the chemotherapy agent comprises EGFR TKI and a pan-ErbB receptor TKI.

[0017] In one example, the tyrosine kinase inhibitor is selected from lapatinib, sunitinib, sorafenib, erlotinib, gefitinib, axitinib, imatinib, nilotinib, dasatinib, cabozantinib, ruxolitinib, neratinib, bosutinib, pazopanib, afatninib, lenvatinib, tucatinib, vandetanib, ceritinib, crizotinib, dacomitinib, and valatinib.

[0018] In one example, the chemotherapy is a phosphoinositide 3-kinase inhibitor, such as alpelisib.

[0019] In one example, the chemotherapy is a CDK (cyclin-dependent kinase) 4/6/ inhibitor, optionally, abemaciclib.

[0020] In one example, the chemotherapy comprises one or more HER of hEGFR (Human epidermal growth factor receptor) inhibitors.

[0021] In one example, the HER inhibitor is selected from RG7116, RG1273 (pertuzumab, Perjeta®), RG3502 (trastuzumab emantasine, T-DMI), RG597 (trastuzumab, HERCEPTIN), RGA201 (RG7160), erlotinib (Tarceva®), dacomitinib (PF-00299804), PF-05280014 (Pfizer's biosimilar mAB to RG597).

[0022] In various examples, the chemotherapy regiment comprises two or more HER inhibitors, such as trastuzumab and pertuzumab, and one or more chemotherapy agents, such as, a taxane like docetaxel or paclitaxel. In various examples, the chemotherapy regiment further comprises a platinum-based antineoplastic such as carboplatin.

[0023] In various examples, the chemotherapy regiment comprises a HER inhibitors, such as trastuzumab or pertuzumab, a tyrosine kinase inhibitor, such as neratinib, and a taxane, such as, docetaxel or paclitaxel. In various examples, the chemotherapy regiment further comprises a platinum-based antineoplastic such as carboplatin.

[0024] In various examples, the chemotherapy regiment is administered once every three weeks.

[0025] In various examples, the crofelemer is administered after a subject begins to exhibit symptoms of CID.

[0026] In certain examples, the crofelemer is administered for the duration of treatment with the chemotherapy.

[0027] In certain examples, the subject is undergoing chemotherapy to treat one or more forms of cancer, such as breast cancer.

[0028] In certain examples, the crofelemer is administered until symptoms of CID are ameliorated and then crofelemer is discontinued.

[0029] In various examples, the administration comprises: administering about 250 mg to about 1000 mg per day; administering about 250 mg per day; administering about 500 mg per day; administering about 1000 mg per day; administering about 125 mg two times per day; administering about 250 mg two times per day; or administering about 500 mg two times per day of crofelemer, particularly, enterically protected crofelemer formulated as a tablet for oral administration, to a subject in need thereof. In other examples, the crofelemer is formulated for oral administration but is not enterically protected, e.g., does not have an enteric coating. In other examples, the dosage of the proanthocyanidin polymer composition is bioequivalent to about 250 mg to about 1000 mg per day; about 250 mg per day; about 500 mg per day; about 1000 mg per day; about 125 mg two times per day; about 250 mg two times per day; or about 500 mg two times per day of an oral dosage form of crofelemer that enterically protected.

[0030] In one example, presented herein are methods of treating stool consistency in a subject undergoing chemotherapy, comprising: administering about 250 mg to about 1000 mg per day; administering about 250 mg per day; administering about 500 mg per day; administering about 1000 mg per day; administering about 125 mg two times per day; administering about 250 mg two times per day; or administering about 500 mg two times per day of crofelemer, particularly, enterically protected crofelemer formulated as a tablet for oral administration, to a subject in need thereof (or is a dosage of a proanthocyanidin polymer composition that is bioequivalent to the dosage of an enteric protected formulation of crofelemer).

[0031] In one example, presented herein are methods of improving stool consistency in a subject undergoing chemotherapy, comprising: administering about 250 mg to about 1000 mg per day; administering about 250 mg per day; administering about 500 mg per day; administering about 1000 mg per day; administering about 125 mg two times per day; administering about 250 mg two times per day; or administering about 500 mg two times per day of crofelemer, particularly, enterically protected crofelemer formulated as a tablet for oral administration, to a subject in need thereof (or is a dosage of a proanthocyanidin polymer composition that is bioequivalent to the dosage of an enteric protected formulation of crofelemer).

[0032] In one example, presented herein are methods of alleviating watery diarrhea in a subject undergoing chemotherapy, comprising: administering about 250 mg to about 1000 mg per day; administering about 250 mg per day; administering about 500 mg per day; administering about 1000 mg per day; administering about 125 mg two times per day; administering about 250 mg two times per day; or administering about 500 mg two times per day of crofelemer, particularly, enterically protected crofelemer formulated as a tablet for oral administration, to a subject in need thereof (or is a dosage of a proanthocyanidin polymer composition that is bioequivalent to the dosage of an enteric protected formulation of crofelemer).

[0033] In one example, presented herein are methods of decreasing the number of bowel movements per day in a subject undergoing chemotherapy, comprising: administering about 250 mg to about 1000 mg per day; administering about 250 mg per day; administering about 500 mg per day; administering about 1000 mg per day; administering about 125 mg two times per day; administering about 250 mg two times per day; or administering about 500 mg two times per day of crofelemer, particularly, enterically protected crofelemer formulated as a tablet for oral administration, to a subject in need thereof (or is a dosage of a proanthocyanidin polymer composition that is bioequivalent to the dosage of an enteric protected formulation of crofelemer).

[0034] The dosages may be the amount of a composition containing a proanthocyanidin polymer composition from *C. lechleri* that is bioequivalent to the dose of an enteric protected formulation of crofelemer.

[0035] In one example, a human subject is considered treated if the subject demonstrates one or more of a decrease in the number of bowel movements per day, a decrease in the number of watery bowel movements per day, an improvement in the daily or weekly abdominal score for pain or discomfort, an improvement in the score for daily stool consistency, a decrease in stool consistency score (from watery to formed), a decrease in the number of days per week that subjects experienced urgency, a decrease in the number of days per week that the subject experienced fecal incontinence.

[0036] In one example, a human subject is considered treated if the subject demonstrates an improvement in the score for daily stool consistency.

[0037] In one example, a human subject is considered treated if the subject demonstrates a decrease in stool consistency.

[0038] In one example, a human subject is considered treated if the subject demonstrates a decrease in the number of watery bowel movements per day.

[0039] In one example, a human subject is considered treated if the subject demonstrates a decrease in the number of bowel movements per day.

[0040] In one example, symptoms increased or decreased are measured from a baseline.

[0041] In one example, the administering is for the duration of the chemotherapy.

[0042] In one example, the administering occurs for about 1 to about 6 weeks longer than the chemotherapy cycle.

[0043] In one example, the administering occurs for about 3 to 12 weeks.

[0044] Other examples are disclosed below.

DETAILED DESCRIPTION

[0045] Certain chemotherapies may cause chemotherapy-induced diarrhea (CID) is a human subject that may cause distress, adversely impact the subject's health and wellbeing, make the chemotherapy difficult to tolerate such that the subject has to take a lower dose or go off of the chemotherapeutic agent or switch to a different treatment regimen that may be, but for the CID, more effective for the treatment of cancer. Proanthocyanidin polymer

What is claimed is:

1. Use of crofelemer in the manufacture of a medicament for treating chemotherapy-induced diarrhea (CID) in a human subject undergoing chemotherapy for treatment of breast cancer and in need thereof, the medicament comprising an effective amount of crofelemer to treat CID, wherein the chemotherapy comprises a CDK (cyclin-dependent kinase) 4/6 inhibitor.

2. The use of claim 1, wherein the crofelemer is to be administered in combination with the chemotherapy.

3. The use of claim 1, wherein the crofelemer is to be administered at the same time as the chemotherapy to reduce or delay the onset of CID.

4. The use of claim 1, wherein the crofelemer is to be administered before chemotherapy.

5. The use of claim 1, wherein the crofelemer is to be administered after chemotherapy.

6. The use of claim 1, wherein the CDK (cyclin-dependent kinase) 4/6 inhibitor is abemaciclib.

7. The use of claim 1, wherein the crofelemer is to be administered for the duration of treatment with the chemotherapy.

8. The use of claim 1, wherein the medicament comprises an amount suitable for administration of 250 mg two times per day or administration of about 500 mg two times per day.

9. The use of claim 1, wherein the crofelemer is to be administered as an enteric coated oral dosage form.

10. The use of claim 1, wherein the subject can tolerate the chemotherapy that the subject could not tolerate without the administration of crofelemer or can tolerate a higher dosage of chemotherapy than the subject could tolerate without administration of crofelemer.

11. The use of claim 1, wherein a subject is considered treated if the subject demonstrates one or more of a decrease in the number of bowel movements per day, a decrease in the number of watery bowel movements per day, an improvement in the daily abdominal score for pain or discomfort, an improvement in the score for daily stool consistency, a decrease in stool consistency, a decrease in the number of days per week that subjects experienced urgency, a

decrease in the number of days per week that subjects experienced fecal incontinence, or a decrease in the unscheduled visit for a significant worsening of diarrhea.

12. The use of claim 1, wherein administration of the medicament results in a decrease in 1, 2 or 3 Grades of the Grade of diarrhea according to the Common Toxicity Criteria.

13. The use of claim 1, wherein the medicament is the only anti-diarrheal to be administered to the human subject.