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(71) Applicant *(for all designated States except US)*: **PHARMACIA & UPJOHN COMPANY** [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **WARE, Joseph, Alan** [US/US]; Pfizer Global Research and Development, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105 (US).

(74) Agents: **FULLER, Grover, F., Jr.** et al.; c/o SIMPSON, Alison, Urquhart-Dykes & Lord LLP, 30 Welbeck Street, London W1G 8ER (GB).

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(54) Title: USE OF CFTR INHIBITORS FOR THE TREATMENT OF CHEMOTHERAPY-INDUCED DIARRHEA

(57) Abstract: The present invention provides a method for treating diarrhea caused by the interaction of a chemotherapeutic agent with a CFTR protein, which comprises administering sequentially, separately or simultaneously with said chemotherapeutic agent a therapeutically effective amount of a CFTR protein inhibitor to a patient in need of the treatment of such a diarrhea and a method for optimizing time and dosages of a diarrheagenic chemotherapeutic agent in a patient in need thereof, which comprises evaluating the sensitivity of said patients towards said agent through the detection of chloride levels in a biological sample of said patient and selecting a time and dosages of said agent based on the above chloride levels.

Title

USE OF CFTR INHIBITORS FOR THE TREATMENT OF CHEMOTHERAPY-INDUCED DIARRHEA

Field of the invention

The present invention relates to the treatment of diarrhea induced by pharmacologically active agents, in particular chemotherapeutic agents.

Description of the invention

Chemotherapy-induced diarrhea (CID) is a prevalent and severe toxicity associated with a variety of sole agents and combinations chemotherapy regimens used for the treatment of cancer. Not only does the occurrence of diarrhea reduce the quality of life of cancer patients, it may also strongly impact the clinical decision about chemotherapy regimens so that patients may undergo changes in treatments. These changes include dose reductions, delays in administration of subsequent drug cycles, and a total discontinuation of therapy. Acute or persistent diarrhea can often increase the cost of care when conventional treatment is unsuccessful and hospitalization is required.

Some chemotherapeutic drugs are more likely than others to cause diarrhea. Cisplatin and 5-fluorouracil, when administered alone, commonly cause diarrhea, as does irinotecan. About 8% of patients receiving 5-fluorouracil alone have severe or life-threatening diarrhea; the frequency increases to up to 25% when 5-fluorouracil is combined with leucovorin. Irinotecan causes severe diarrhea that may be life threatening. Irinotecan-induced diarrhea typically occurs 2 to 14 days after therapy. Several Phase II clinical studies report incidences of delayed CID as high as 80% with irinotecan and more than 18% of patients treated with CPT-11 required hospitalization because of diarrhea occurring alone or in combination with other gastrointestinal disturbances.

Although marked progress has been accomplished these last years, standardized and universally accepted methods for management of CID have not been developed. As a matter of fact, management of CID still represents a formidable challenge to the healthcare team and a substantial degree of further improvement is needed to ameliorate the effectiveness of specific treatments.

According to Kornblau et al. (J. of Pain and Symptom Management, Vol. 19, No. 2, Feb. 2000, pp 118-129), many factors contribute to diarrhea in the cancer patient, including damage to and maturational arrest of intestinal epithelium, inflammation, infection, and antibiotics. Although the pathophysiologic mechanisms for CID are not completely known, histopathologic evidence indicates that diarrhea is probably a multifactorial process that results in absorptive and secretory imbalance in the small bowel. Pathophysiologic mechanisms for cancer treatment–related diarrhea differ based on the causative factor.

According to Ippoliti (Am. J. of Health-System Pharm., Vol. 55(15), August 1, 1998, pp 1573-1580), diarrhea can be classified as osmotic, secretory, exudative, postresection, and motor. Osmotic diarrhea results from the ingestion of poorly absorbed substances that retard fluid absorption.

Both postresection and exudative diarrheas result from loss of functional intestinal mucosa: in exudative diarrhea, the mucosa is damaged by disease; in postresection diarrhea, some amount of functional mucosa is surgically removed.

Abnormally rapid transit time (causing reduced exposure of luminal contents to the intestinal wall) can result in motor diarrhea.

Inhibition of mucosal absorption or stimulation of secretion of fluid and electrolytes results in secretory diarrhea. Within the intestine, immature crypt cells secrete fluid into the lumen, and villi cells absorb fluid from the lumen. Secretory diarrhea can occur when either of these processes is disrupted and there is a net flow of fluid into the lumen. Movement of fluid across the crypt and villi cells is controlled chiefly by membrane-associated proteins involved in epithelial ion transport and smooth muscle contraction. These proteins, in turn, are regulated by secondary messengers, including cyclic nucleotides, elements of the phosphoinositide-diacylglycerol pathway, and free intracellular calcium.

Several studies suggest that cystic fibrosis transmembrane conductance regulator (CFTR), a member of the ATP-binding Cassette (ABC), subfamily C member 7 (ABCC7) is the final common pathway for intestinal chloride (Cl^-) and thus fluid secretion into the lumen of the small and large intestine. Activation of CFTR (ABCC7) by pathogenic microorganisms is a major factor in enterotoxin-induced diarrhea (EID)

produced by many gut pathogens. In many examples, second messengers generated in response to an enterotoxin exposure have been shown to activate CFTR and thus Cl^- secretion. These second messengers include cAMP and cGMP protein kinase C, inflammatory mediators (such as tumor necrosis factor-α and interleukin 1 and 8), as well as prostaglandins that are known metabolites of arachidonic acid (such as PGE_2). Despite the complex nature of events leading to ultimate effect of EID, the role of CFTR has been established using *in-vitro* studies and in mice where CFTR has been selectively deleted from the mouse.

The interaction of chemotherapeutic agents with ABC transporters has been well established with the earliest research describing the role of ABCB1 also known as P-glycoprotein (P-gp) or multidrug resistance gene (MDR1) in the genesis of tumor drug resistance. Further research on acquired drug resistance in tumor cells identified other ABC proteins such as MRP1 (ABCC1), MRP5 (ABCC5), and BCRP/MXR/ABCP (ABCG2). Through the utilization of acquired drug resistance and through the expression of individual clones for these ABC transporters, prototypical substrates have been identified. However, it is important to recognize that there is much overlap in the ability of ABC transporters to interact with drugs or model investigative compounds. For instance, irinotecan has been shown to be a substrate of P-gp (ABCB1), MRP1 (ABCC1), MRP2 (ABCC2), and BCRP/MXR/ABCP (ABCG2). It is likely that interactions may occur between drugs and with other ABC proteins that are responsible for critical physiological functions.

Irinotecan [1,4'-Bipiperidine]-1'-carboxylic acid (4*S*)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-9-yl ester is a camptothecin analog and topoisomerase-I inhibitor derived from a compound, which occurs naturally in the Chinese tree, *Camptotheca acuminata.* Irinotecan can be prepared following the procedure disclosed in U.S. Pat. No. 4,604,463, European patent No. 835,257 or S. Sawada *et al.,* Chem. Pharm. Bull. 39, 1446 (1991). Irinotecan hydrochloride, clinically investigated as CPT-11, is a commercially available compound (CAMPTOSAR™, Pharmacia Corp.).

As used herein the term "irinotecan" encompasses all pharmaceutically acceptable salts of irinotecan, particularly the hydrochloride salt.

In a preferred aspect of the present invention, irinotecan is irinotecan hydrochloride, namely CPT-11.

Irinotecan is a prodrug extensively metabolized in the liver to various metabolites. It is cleaved enzymatically by carboxylesterases to form 7-ethyl-10-hydroxycamptothecin (SN-38), which has cytotoxic activity that is 100 to 1,000 times greater than that of the parent drug. SN-38 is further conjugated to an inactive glucuronide (SN-38G) by uridine diphosphate glucuronosyltransferases. Other CPT-11 metabolites identified are the major plasma metabolite 7-ethyl-10-[4-*N*-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecin (APC) and 7-ethyl-10-[4-amino-1-piperidino]-carbonyloxycamptothecin (NPC), resulting from a ring-opening oxidation of the terminal piperidine ring of CPT-11 mediated by cytochrome P450 3A4 enzymes. The major dose-limiting nonhematologic toxicity of irinotecan is diarrhea. Although the pharmacokinetic-pharmacodynamic relationship between exposure and toxicity has been widely studied, the results have been discrepant because of its complex and incompletely understood relationship and because of different study designs. Although most investigations have reported that area under the concentration-time curve (AUC) values for both irinotecan and SN-38 significantly correlated with the severity of diarrhea, others have detected that correlation only for irinotecan AUC. Similarly, although several studies have suggested that there is a correlation between the biliary index and diarrhea, other studies could not confirm that correlation. Finally, some trials failed to find any relationship between diarrhea and any of the studied pharmacokinetic parameters (Clinical Pharmacology and Therapeutics, Vol. 72(3), Sept. 2002, pp 265-275).

It has now been found that camptothecin derivatives, especially irinotecan and its active metabolite SN-38 would produce disturbances in colonic electrolyte transport by interacting with CFTR (ABCC7) in the colonic crypts, so contributing to diarrhea associated with the administration of said drug in a manner analogue to EID.

As an example, to determine the interaction of CPT-11, SN-38, and topotecan with CFTR (ABCC7), the effect of said substances on Cl^- conductance in CFTR (ABCC7)-transfected Xenopus laevis oocytes is evaluated via single voltage clamp conditions.

It is therefore an object of the present invention a method for treating diarrhea caused by the interaction of a chemotherapeutic agent with a CFTR protein, which comprises administering sequentially, separately or simultaneously with said chemotherapeutic agent a therapeutically effective amount of a CFTR protein inhibitor to a patient in need of the treatment of such a diarrhea.

It is another object of the present invention a method for treating a cancer sensitive to a potential diarrheagenic chemotherapeutic agent, which comprises administering a therapeutically effective amount of a CFTR protein inhibitor for treating diarrhea occurring when said chemotherapeutic agent is administered to a patient.

According to the present invention the definition "chemotherapeutic agent" includes diarrheagenic chemotherapeutic agents, i.e. chemotherapeutic agents which may potentially induce diarrhea when administered to a patient in need thereof such as, for example, fluoropyrimidines, e.g. 5-fluorouracil (5-FU), platinum derivatives, e.g. cisplatin and oxaliplatin, thymidylate synthase inhibitors e.g. raltitrexed and camptothecin derivatives, e.g. irinotecan, SN-38, rubitecan and topotecan.
Preferred examples of diarrheagenic chemotherapeutic agents according to the invention are camptothecin derivatives, particularly irinotecan, SN-38 and topotecan.

According to the present invention, the term "CFTR inhibitor" includes small molecules such as glyburide (glibenclamide), thiazolidinones such as for example 3-[(3-trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone, flavinoids and/or monoclonal or polyclonal antibodies directed toward some part of CFTR (ABCC7).

In a particular aspect, the present invention provides a method for treating diarrhea which results from the interaction of a camptothecin derivative, particularly selected from the group consisting of irinotecan, SN-38 and topotecan, with a CFTR protein, which comprises administering sequentially, separately or simultaneously with said chemotherapeutic agent a therapeutically effective amount of a CFTR protein inhibitor to a patient in need of the treatment of such a diarrhea.

In a more particular aspect, the present invention provides a method for treating diarrhea which results from the interaction of irinotecan or SN-38, with a CFTR protein, which comprises administering sequentially, separately or simultaneously with said chemotherapeutic agent a therapeutically effective amount of a CFTR protein inhibitor to a patient in need of the treatment of such a diarrhea.

According to the present invention the term "treating" includes, unless otherwise specified, preventing, controlling, ameliorating, alleviating, decreasing, reducing and inhibiting.

As an example, the efficacy of a CFTR inhibitor for the treatment of diarrhea induced by the administration of a chemotherapeutic agent, such as for example irinotecan or SN-38, may be evaluated in CFTR knockout mice.
It is believed that the subject CFTR inhibitor would be found to be effective in the treatment of diarrhea induced by the administration of the selected diarrheagenic chemotherapeutic agent.

Standardized methods for assessing diarrhea in cancer patients are needed to better manage CID. The initial assessment and management of CID should include an initial comprehensive and accurate clinical assessment, subsequent targeted reassessment, and the administration of appropriate pharmacological therapies at the optimal time and dosages.

Since diarrhea can unbalance chloride levels in a patients undergoing diarrheagenic chemotherapy, monitoring alteration of chloride levels, for example by detecting chloride levels pre- and post- administration of the chemotherapeutic agent may help the physician to evaluate/predict the patient sensitivity to said diarrheagenic chemotherapeutic agents and hence optimizing time and dosages of the same.
Chloride levels can be monitored, for example, through the detection of chloride in a sweat sample of the patient.

It is therefore another aspect of the present invention a method for assessing diarrhea in a cancer patient undergoing a diarrheagenic chemotherapy, which comprises monitoring chloride levels in said patient, in particular by detecting chloride levels pre- and post-administration of a chemotherapeutic agent.

It is a still another aspect of the present invention a method for optimizing time and dosages of a diarrheagenic chemotherapeutic agent in a patient in need thereof, which comprises evaluating the sensitivity of said patients towards said agent through the detection of chloride levels in a biological sample of said patient and selecting a time and dosages of said agent based on the above chloride levels.

Detection of chloride levels in a biological sample of a patient may be obtained, for example, by detecting chloride in a sweat sample of the patient, following a procedure known in the art.

It is a further another aspect of the present invention a method for optimizing the administration of a diarrheagenic chemotherapeutic agent, which comprises:

(a) obtaining a sweat sample before and subsequently the administration of said chemotherapeutic agent to a patient in need thereof;

(b) detecting the amount of chloride in said samples; and

(c) selecting a therapeutically effective amount of said drug based on the above chloride levels.

It is a still further aspect of the present invention a method for treating a cancer sensitive to a diarrheagenic chemotherapeutic agent, which comprises:

(d) obtaining a sweat sample before and subsequently the administration of said chemotherapeutic agent to a patient in need thereof;

(e) detecting the amount of chloride in said samples; and

(f) selecting a therapeutically effective amount of said drug based on the above chloride levels.

Claims

1. A method for treating diarrhea caused by the interaction of a diarrheagenic chemotherapeutic agent with a CFTR protein, which comprises administering sequentially, separately or simultaneously with said chemotherapeutic agent a therapeutically effective amount of a CFTR protein inhibitor to a patient in need of the treatment of such a diarrhea.

2. The method of claim 1, wherein the chemotherapeutic agent is selected from the group consisting of fluoropyrimidines, platinum derivatives, thymidylate synthase inhibitors and camptothecin derivatives.

3. The method of claim 2, wherein the camptothecin derivative is selected from the group consisting of irinotecan, SN-38, rubitecan and topotecan.

4. The method of claim 3 wherein the camptothecin derivative is irinotecan.

5. A method for treating a cancer sensitive to a potential diarrheagenic chemotherapeutic agent, which comprises administering a therapeutically effective amount of a CFTR protein inhibitor for treating diarrhea occurring when said chemotherapeutic agent is administered to a patient.

6. The method of claim 5, wherein the chemotherapeutic agent is selected from the group consisting of fluoropyrimidines, platinum derivatives, thymidylate synthase inhibitors and camptothecin derivatives.

7. The method of claim 6, wherein the camptothecin derivative is selected from the group consisting of irinotecan, SN-38, rubitecan and topotecan.

8. The method of claim 7 wherein the camptothecin derivative is irinotecan.

9. A method for assessing diarrhea in a cancer patient undergoing a diarrheagenic chemotherapy, which comprises monitoring chloride levels in said patient, in particular by detecting chloride levels pre- and post- administration of a chemotherapeutic agent.

10. A method for optimizing time and dosages of a diarrheagenic chemotherapeutic agent in a patient in need thereof, which comprises evaluating the sensitivity of said patients towards said agent through the detection of chloride levels in a biological sample of said patient and selecting a time and dosages of said agent based on the above chloride levels.

11. A method for optimizing the administration of a diarrheagenic chemotherapeutic agent, which comprises:

(a) obtaining a sweat sample before and subsequently the administration of said chemotherapeutic agent to a patient in need thereof;

(b) detecting the amount of chloride in said samples; and

(c) selecting a therapeutically effective amount of said drug based on the above chloride levels.

12. A method for treating a cancer sensitive to a diarrheagenic chemotherapeutic agent, which comprises:

(d) obtaining a sweat sample before and subsequently the administration of said chemotherapeutic agent to a patient in need thereof;

(e) detecting the amount of chloride in said samples; and

(f) selecting a therapeutically effective amount of said drug based on the above chloride levels.

INTERNATIONAL SEARCH REPORT

International Application No
/IB2004/001660

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4745 A61K31/64 A61K31/426 A61P1/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, PHARMAPROJECTS, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BLEIBERG H ET AL: "Characterisation and clinical management of CPT-11 (Irinotecan)-induced adverse events: The European perspective" EUROPEAN JOURNAL OF CANCER, vol. 32A, no. SUPPL. 3, 1996, pages S18-S23, XP002291899 ISSN: 0959-8049 page S22, column 1, paragraphs 3,5 -----	1-12
Y	DATABASE PHAR 'Online! PJB PUBLICATIONS LTD.; 1995, "Tiorfan" XP002291900 retrieved from STN Database accession no. AN:4659 PHAR abstract ----- -/--	1-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2004	02/09/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Giacobbe, S

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 234 922 A (WELSH MICHAEL J ET AL) 10 August 1993 (1993-08-10) the whole document	1-12
Y	US 6 281 240 B1 (SCHULTZ BRUCE D) 28 August 2001 (2001-08-28) the whole document	1-12
Y	WO 02/05794 A (SHEPPARD DAVID NOEL ; CAI ZHIWEI (GB); UNIV BRISTOL (GB)) 24 January 2002 (2002-01-24) page 1, paragraphs 1,2 abstract	1-12
Y	WO 01/52828 A (SAVARESE DIANE ; UNIV MASSACHUSETTS (US)) 26 July 2001 (2001-07-26) page 1, paragraph 3	1-12
A	DATABASE WPI Section Ch, Week 200112 Derwent Publications Ltd., London, GB; Class B03, AN 2001-112385 XP002291901 & WO 01/00217 A1 (MEIJI SEIKA KAISHA LTD) 4 January 2001 (2001-01-04) abstract	1-12
A	WO 01/49299 A (MICHAEL MICHAEL ; MOORE MALCOLM J (CA)) 12 July 2001 (2001-07-12) abstract	1-12
Y	ABIGERGES DANY ET AL: "Irinotecan (CPT-11) high-dose escalation using intensive high-dose loperamide to control diarrhea" JOURNAL OF THE NATIONAL CANCER INSTITUTE (BETHESDA), vol. 86, no. 6, 1994, pages 446-449, XP009035128 ISSN: 0027-8874 page 447, column 1, paragraph 3 page 448, column 3, last paragraph	1-12

INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/IB2004/001660

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

ational Application No
.../IB2004/001660

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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